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Albumin Levels in Hispanic Dialysis Patients With and Without Type II Diabetes

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Abstract

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health Epidemiology

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Abstract

Albumin provides the vital scaffolding for growth and tissue repair and supports oncotic blood pressure and hemodynamics. In hemodialysis patients, albumin aids with fluid removal by drawing excess fluid from edematous tissues back into the blood where it can then be removed by a dialyzer. The hyperglycemia seen in dialysis patients with Type II diabetes progressively damages kidney glomeruli, which permits albumin seepage into the urine, thus lowering serum albumin. The conceptual framework underpinning this research is the van't Hoff theory of osmotic pressure. Under this framework, the solute-solvent relationship largely contributes to the osmotic movement of fluid. The purpose of this study was to determine if albumin levels differed in Hispanics on dialysis with and without diabetes and if potential differences existed over time. Differences in diabetes incidence in Hispanics suggest albumin levels may be dissimilar. Albumin physiology is abundant in the literature; how and to what magnitude albumin levels are affected in patients with diabetes is unclear. This quantitative, retrospective cohort study employed ANOVA, Repeated Measures *t* tests, Spearman Correlation, and regression analysis to evaluate potential associations between the research variables. Data were extracted from CMS-2728 forms to amass the final cohort ($N = 827$). Differences in albumin levels at the first 2 intervals were observed (Baseline 1.29 ± 0.49 mg/dL, $F = 2.28$, $p < .032$; 3 months 0.47 ±0.41 mg/dL, $F = 1.62$, $p < .004$). Covariables (hypertension, peripheral vascular disease, and infections) were controlled for but showed inconclusive results. Lower serum albumin in Hispanic dialysis patients with diabetes provides the impetus for developing ethnic-specific albumin therapies, thus promoting positive social change.

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Dedication

It is with profound admiration, love, and deepest gratitude that I dedicate this dissertation to my mother Noelia Hernandez. For most of her life she has suffered from Type II diabetes and has been my continual motivation to pursue a Ph.D. in public health to further explore this chronic disease in hopes of offering my humble contribution towards advancing understanding and therapies for people suffering from diabetes like my mom.

I also offer my gratitude and respect to those individuals that have influenced and inspired me to develop and pursue research in the field of Public Health Epidemiology and Nephrology. I am indebted to Mr. Jeffrey S. Tyer, RN, BSN, CNN and to the nursing managers from each dialysis clinic I visited. These nursing professionals were instrumental in orientating me to the dialysis facilities and who were consummate in facilitating access to patient records for data collection for this research.

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The dissertation journey requires continual guidance, encouragement, and support, not just from family and friends, but also from a dedicated dissertation committee. My committee was dedicated to potentiating my candidacy success. I offer my sincere gratitude to my Chair, Dr. Scott McDoniel, my committee member Dr. Donna White, and URR Dr. Roland Thorpe for giving of their time and energy, for imparting their wisdom, knowledge and advice, and for facilitating the dissertation process that would ensure my success with this endeavor.

I am especially grateful to Jeff and my family for their unrelenting support and understanding during the rigors of this pursuit. I look forward to spending more quality time with them.

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Chapter 1: Introduction to the Study

Background

Albumin is a ubiquitous protein found in blood plasma. Its ubiquity readily provides the body with the protein necessary for growth maintenance and tissue repair and supports oncotic blood pressure and hemodynamics (Brin & Christensen, 2006). For patients undergoing hemodialysis treatments, albumin found in the blood aids with fluid removal by drawing excess fluid from edematous tissues back into the blood, where it can then be removed by a dialyzer (Fresenius Medical Care, 2013). As a consequence of their disease, patients with a Type II diabetes mellitus diagnosis suffer from renal dysfunctions ranging from renal insufficiencies to chronic renal failure (CRF) due to the kidney's compromised ability to filter albumin. The greater the severity of the renal disease, the greater the decreases in albumin levels found in the blood plasma and hence the greater the degree of albuminuria (Haller, 2006; Stoian, Stoica, & Radulian, 2012).

As the most abundant plasma protein, albumin is largely responsible for colloid osmotic pressure. From a physiological perspective, this pulls water into the circulatory system through the capillaries, maintaining homeostatic blood pressure. A reduction of albumin in plasma, therefore, can cause a decrease in colloid osmotic pressure and subsequently tissue edema (Ahren & Burke, 2012). The physiological functions of albumin, including blood pressure regulation is abundant in the literature; what are not clear is how and to what degree albumin levels are affected in patients with a Type II diabetes diagnosis and how these potential differences might influence blood pressure and renal disease. It has not been ascertained how and to what magnitude albumin levels

are affected in patients with Type II diabetes undergoing hemodialysis therapy compared to patients with an alternative diagnosis. I aimed to pursue this research gap.

According to Chukwueke and Cordero-MacIntyre (2010), an estimated 17.5 million people in the United States were diagnosed with either Type I or Type II diabetes in 2007. In that year, it was the leading cause of blindness in people between the ages 20 and 74 years and of end-stage renal disease (ESRD) in Hispanic Americans (Chukwueke & Cordero-MacIntyre, 2010). The financial burden of diabetes is high and increasing every year.

The reasons for this burden have largely been attributed to people with diabetes having a predisposition for disease sequelae, including cardiovascular and renal disease. It is true that, while people without diabetes may never visit the hospital in a given year, people with diabetes are more likely to consult their doctor for regular diabetes check-ups (Chukwueke & Cordero-MacIntyre, 2010). These statistics establish the significance of the study and also provide the impetus and urgency to conduct the study, analyze the results and disseminate the research outcomes. The primary objective was to narrow the research gap by determining the relationship between albumin levels in Hispanic hemodialysis patients with and without Type II diabetes mellitus. Although the relationship between the dependent variable, albumin, and the independent variable, type II diabetes mellitus is well established in the literature, potential albumin level differences in these patients has not been studied to date.

Problem Statement

Decreased serum albumin levels are most notable in Hispanic American patients with diabetes. Type II diabetes prevalence is 14% in the Hispanic population (Black, 2002). This group suffers a higher risk of mortality and microvascular complications including renal disease. Albuminuria is often seen in Hispanic patients with diabetes and is strongly associated when kidney disease as a comorbidity (Choi et al., 2011; Yokoyama et al., 2011; Zakerkish et al., 2013). Albumin levels are lower in this group since the incidence of diabetes is higher in this population. The higher occurrence of renal failure and hence improper renal filtration lowers albumin levels markedly in Hispanic patients on maintenance hemodialysis (Black, 2002; Lorenzo et al., 2009; Yokoyama et al., 2011; Zakerkish et al., 2013). Consequently, the number of Hispanics requiring hemodialysis rose by 70% between 1996 and 2001 (Lash, Vijil, Gerber, & Go, 2005), correlating with observations that this population is the fastest growing demographic in the U.S. (Kanna, Fersobe, Soni, & Michelen, 2007).

Given these current statistics, which disproportionately affect this ethnic population and considering the potential long-term and sometimes catastrophic sequelae which may ensue from fluctuations in albumin levels in patients undergoing maintenance hemodialysis, there is a need to investigate if albumin level differences exist in both diabetic and non-diabetic patients undergoing maintenance hemodialysis and whether disparate patterns persist through the course of their treatment, which could incur additional risk to their maladies or even premature mortality. Although uncertain, the data on this relationship might reveal nutritional policies for dieticians and may help inform

clinical staff to design clinical therapeutic interventions regarding albumin supplementation that is tailored for Hispanic patients with a Type II diabetes diagnosis on maintenance hemodialysis.

Purpose Statement

There is a paucity of literature on differences in albumin levels of Hispanic patients with and without Type II diabetes, undergoing maintenance hemodialysis. The differences in diabetes incidence in the Hispanic population suggest albumin levels may also be different in this population. I aimed to narrow this literature paucity. The objective of this quantitative study was to examine the relationship of serum albumin levels in Hispanic patients initiating hemodialysis treatment due to renal disease associated with a Type II diabetes diagnosis and those without the disease after controlling for gender, hypertension and other covariables.

A retrospective examination of the medical records of these patients was conducted to determine if albumin levels differed in a population of adult Hispanic hemodialysis patients with and without a Type II diabetes diagnosis. I aimed to ascertain if albumin levels continued to follow trends observed from hemodialysis treatment onset. Patient medical records were analyzed at baseline, 0, 3, and 6 months post baseline to ascertain possible differences in albumin levels between those with and without Type II diabetes. According to the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines, an acceptable albumin clinical goal for patients on hemodialysis is ≥4.0g/dL (American Journal of Kidney Disease, 2007; National Kidney Foundation, 2002;

National Kidney Foundation, 2013). This was the clinical standard to which collected patient albumin values were compared to in this study.

This study entailed collecting and analyzing data on the health status and renal measures from medical records of Hispanic dialysis patients seen at Fresenius Medical Care-North America's designated renal dialysis clinics in San Antonio, Texas. These records are maintained on all patients admitted to these facilities. With appropriate permission from Fresenius' research department (Frenova Renal Research), and Walden's Institutional Review Board (Approval # 12-17-14-0298443), data were collected from Center for Medicare and Medicaid Services (CMS)-2728 forms. These forms have clinical data collected by nursing personnel, including anthropometric measures, as well as renal parameters such as BUN-serum creatinine ratios, hemoglobin A1c, lipid profiles, and serum albumin documented at the onset of treatment. Subsequent blood draws are done weekly for Hemoglobin A1c and pre and post BUN-creatinine ratios and potassium if deemed necessary by the nephrologist. Calcium, phosphorus, and albumin levels are collected monthly, peritreatment. Both weekly and monthly lab tests are documented in the patient's medical records. The primary cause of renal failure and ICD-9 codes for associated comorbidities are documented on the patient's medical records. Routine lab testing and reporting of monthly albumin levels through Spectra Laboratories were reviewed from the patient's treatment records.

Research Questions

Research Question 1. Is there a difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment?

H_O1: There is no difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment.

H_A1: Differences in serum albumin levels are observed between Hispanics with and without Type II diabetes initiating hemodialysis treatment, (H_O is false).

Research Question 2. Is there a difference in serum albumin levels over time (baseline, 3 months, and 6 months post baseline) between Hispanics with and without Type II diabetes following hemodialysis treatment?

H_O2: No albumin level differences are observed over time (baseline, 3 months, and 6 months post baseline) between Hispanics with and without Type II diabetes following hemodialysis treatment.

H_A2: Albumin level differences are observed over time (baseline, 3 months, and 6 months) between Hispanics with and without Type II diabetes following hemodialysis treatment.

Research Question 3. Is there a relationship between serum albumin, Type II diabetes, and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients?

H_O3: There is no relationship between serum albumin, Type II diabetes, and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients.

H_A3: There is a relationship between serum albumin, Type II diabetes and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients.

Conceptual Framework

This research study was framed by long-standing physiological concepts that inform and guide this inquiry. The osmosis phenomenon and the van't Hoff theory of osmotic pressure provide the pillars that ground and support this study. Osmosis is the flow of a solvent through a semi-permeable membrane that separates two volumes of liquid and disallows the passage of solute particles (Lachish, 1999; Marieb & Hoehn, 2007; Villani, Dunlop, & Damitz, 2007). The solvent flows from the volume of higher solvent concentration to the volume of lower solvent concentration. Correspondingly, when solute particles are present only in one volume, the osmotic pressure is the pressure on the solution that ceases the solvent flow (Lachish, 1999). The formula for osmotic pressure was derived by van't Hoff. The van't Hoff theory of osmotic pressure posits that π is proportional to the molar concentration (c), the absolute temperature of the system (˚K), and the gas constant (R). The van't Hoff formula $\pi = c\ R\ T$ is derived by the comparison of the pressure of an ideal gas of the same concentration and temperature. The molar concentration of solute particles *c* is proportional to the gas constant R (0.0821 L *ATM/mole*K), and the absolute temperature T in degrees Kelvin (Lachish, 2007).

This study is grounded by these two concepts; both the osmotic pressure phenomenon and the van't Hoff theory of osmotic pressure have a direct correlation to this study in that albumin is the circulating solute in blood plasma. As the osmotic

pressure theory posits, the protein is unable to cross the semipermeable plasma membrane of cells; but, the solvent or fluid can cross freely. This osmotic movement of fluids draws fluid from the plasma into the capillaries to maintain homeostatic blood pressure. These physiological concepts are well understood and described in the literature and applicable to this study.

Dialyzing patients can therefore be approached through the lens of these two axiomatic physiological concepts. The osmosis phenomenon and the van't Hoff theory of osmotic pressure are exploited in patients undergoing maintenance hemodialysis, which by the nature of their renal disease are unable to remove excess fluid from their bodies. Specifically, in hemodialysis patients the excess fluid in edematous tissues, collected during the interdialytic period, is drawn into the capillaries by osmosis and then filtered through a dialyzer using a prepared dialysate solution that can readily remove excess fluids from the patient (Fresenius Medical Care, 2013). To remove the excess fluids, an extracorporeal dialyzer is used, utilizing a dialysate solution that flows in a countercurrent direction of blood flow. This flow allows for the exchange between important electrolytes found in the dialysate and toxins that accumulate in the blood. The prescription of a certain dialysate composition is modified in order to obtain not only adequate blood purification but also optimal treatment tolerability (Fresenius Medical Care, 2013).

In hemodialysis patients, dialysate composition can be tailored in terms of the sodium, potassium, calcium and bicarbonate content; these represent the solutes (ions) in the dialysate that are essential for electrolyte balances in the body. Sodium balance

represents the cornerstone of cardiovascular stability and blood pressure control (Fresenius Medical Care, 2013). The vasoactivity of potassium increases blood flow when it is infused into the arterial supply of a vascular bed. Potassium levels can be manipulated by supplementation or during hemodialysis treatments, which can assist in regulating blood pressure (Haddy, Vanhoutte, & Feletou, 2006). Calcium is used to maintain bone density. Because patients on hemodialysis have dysfunctional kidneys, they are unable to convert vitamin D into the hormone Calcitrol. This hormone facilitates calcium absorption from the intestines into the blood. Consequently, low blood calcium levels cause calcium to be pulled from bone tissue, leading to a plethora of osteodystrophies (Davita, 2013). Lastly, bicarbonate in dialysate is personalized in order to avoid acidosis and post-dialysis alkalosis (Vigano, DiFilippo, Manzoni, & Locatelli, 2008).

The primary goal of hemodialysis for patients with chronic renal failure is to restore the composition of the body's hemodynamic environment. This is accomplished principally by formulating a dialysate whose constituent concentrations are set to approximate homeostatic values in the body (Fresenius Medical Care, 2013). Over time, by diffusional transfer and by obeying fundamental physiological osmotic principles, the concentrations of solutes that were initially increased or decreased are effectively corrected (Fresenius Medical Care, 2013). When an abnormal electrolyte concentration poses immediate adverse hemodynamic effects, the dialysate concentration of that electrolyte can be set at a nonhomeostatic level to achieve a more rapid electrolyte hemodynamic correction (Fresenius Medical Care, 2013). For chronic renal disease

patients, the composition of the dialysate can be individually adjusted in order to satisfy the specific electrolyte balances of each patient (Fresenius Medical Care, 2013). This electrolyte-blood toxin exchange between the prescribed dialysate and the bloodstream aligns with the principles of osmosis, osmotic pressure, and membrane permeability.

The intricate hemodialysis process discussed in this study is grounded by fundamental physiological principles. Both the osmotic pressure phenomenon and the van't Hoff theory of osmotic pressure provide a suitable conceptual framework for this inquiry. These concepts provide a reasonable explanation for why patients with a Type II diabetes diagnosis, receiving hemodialysis treatments show aberrant levels of albumin in their blood. The theories reflect the filtering capacity of the kidneys. In patients with a diabetes Type II diagnosis, undergoing hemodialysis because of renal disease, this filtering capacity has been compromised, therefore disobeying fundamental osmotic pressure principles.

Nature of the Study

The research design for this quantitative investigation was retrospective in nature. After receiving permission from Frenova Renal Research, the research department of Fresenius Medical Care - North America (FMC-NA), CMS-2728 forms and medical records of patients that underwent hemodialysis at designated clinics in San Antonio, Texas were examined. Patients admitted to these facilities have their blood drawn and serum albumin levels are documented on CMS-2728 forms. The records of Hispanic patients receiving hemodialysis treatments with and without a type II diabetes diagnosis on maintenance hemodialysis were examined at treatment onset, baseline (CMS), 0, 3,

and 6 months post onset. Since this was a retrospective analysis of data, a complete case analysis was conducted. A listwise deletion of patients that did not meet inclusion criteria was conducted. These criteria included hemodialysis patients with and without a type II diabetes diagnosis that remained in the dialysis facilities for at least six months and who had full hematology profiles documented on CMS-2728 forms and treatment records for that time period. Those patients who moved away, received a transplant, changed dialysis modalities, made the decision to discontinue treatment, passed away, or transferred before the six-month period were excluded from the study.

To ensure statistical power, G*Power 3 software was used to determine an appropriate sample size. SPSS analysis software was used to collect and then quantify albumin levels in this sample population to ascertain possible albumin trends and to identify if hemodialysis patients with a Type II diabetes diagnosis evidenced differences in albumin levels and hence decreased renal function compared to hemodialysis patients with a different etiologic diagnosis. Studies confirm that 3 and 6 month checks are appropriate intervals to monitor albumin levels (Black, 2002; In Control, 2007). Researchers who have collected data at 3 months, after regular hemodialysis treatments and albumin supplementation have shown significant increases in serum albumin levels from an average of 2.9± 0.4 mg/dL to 3.45 ± 0.4 mg/dL (Dalrymple et al., 2013; In Control, 2007). Higher albumin levels were maintained during this period and persisted 3 months after hemodialysis treatments and albumin supplementation. Studies showing albumin differences or improvement patterns in Hispanic, hemodialysis patients with a Type II diabetes diagnosis are nonexistent.

I aimed to identify improvement trends from hemodialysis patient schedules, from treatment onset to 6 months into the patients' treatment. The independent variable is Type II diabetes in hemodialysis patients, and the dependent variable is albumin levels in blood plasma in these patients. The null hypothesis is that no differences in albumin levels will be observed between the diabetic and nondiabetic groups and no apparent albumin level trends will be noted from treatment onset and at 3 and 6 months into the course of their treatments in both groups. Chapter 3 will present a more expansive description of the study design.

Definitions

Type II diabetes mellitus: A metabolic disorder that is characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin (Mahler & Adler, 1999).

Albumin: A simple and ubiquitous form of protein that is soluble in water and coagulable by heat, such as that found in egg white, milk, and blood serum (Alpern et al., 2013; Rozga et al., 2013).

Ultrafiltration: The process by which a pressure gradient is utilized to force fluid through a membrane (Fresenius Medical Care, 2013).

Hemodialysis: The clinical process used to achieve the extracorporeal removal of uremic wastes such as creatinine and urea and to remove fluid from the blood when the kidneys are in renal failure status (Davita, 2014; Fresenius Medical Care, 2013).

Dialyzer: A 30 centimeter long plastic device through which blood flows through a cluster of 20,000 extremely fine fibers used in hemodialysis that acts as an artificial

kidney and replaces vital functions of the natural organ (Davita, 2014; Fresenius Medical Care, 2013).

Dialysate: A chemical bath utilized in hemodialysis to draw fluids and toxins out of the bloodstream and supply electrolytes and other chemicals to the bloodstream (Davita, 2014; Fresenius Medical Care, 2013).

Countercurrent flow (exchange): The mechanism occurring in nature and mimicked in industry and engineering, in which there is a crossover of some property, usually heat or some component, between two flowing bodies flowing in opposite directions to each other. The flowing bodies can be liquids, gases, or even solid powders, or any combination of those. In hemodialysis counter current flow is used where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit or dialyzer. Counter-current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis (Davita, 2014; Fresenius Medical Care, 2013).

Selectively Permeable: The term used to describe a membrane that will allow certain molecules or ions to pass through it by diffusion **(**Marieb & Hoehn, 2007).

Interdialytic Period: The period between dialysis treatments, typically 1 or 2 days, during which fluid and uremic waste products accumulate; this fluid is removed by hemodialysis.

Assumptions

There exist some factors that can potentially influence a research study. Assumptions, for example, can be made for this study for which there is no hard data

available, a researcher might not ever satisfactorily know, and for which there is no intent to or feasibly not be able to control. The first assumption made is that the cohort of patients selected for this study was correctly diagnosed with Type II diabetes according to ICD-9 codes 25040 and 25000A by clinic nephrologists. The diagnosis assignment is assumed to be accurate and distinguishable from Type I diabetes, as this disease is not reviewed in this study. A second assumption made is that the data documented in the patient records with respect to anthropometric measurements, hematology profiles, associated comorbidities, dialysis treatment dose and modality, and dialysate prescription were correct and accurately recorded by clinical staff. It was also assumed that patients correctly self-identified themselves of Hispanic ethnicity.

Scope and Delimitations

This study was focused on determining whether albumin differences exist in Hispanic patients on maintenance hemodialysis with and without a type II diabetes diagnosis. Studies in the literature present information on albumin levels in different populations with other chronic diseases such as Type I diabetes or coronary artery disease. The studies also presented several study design models, including observational, prospective, and retrospective studies as well as case control designs. However, albumin level differences in a Hispanic population, undergoing maintenance hemodialysis have not been studied using a retrospective model.

Since medical records were examined, this study undertook a retrospective approach. Compared to a prospective model, a retrospective analysis of medical records provides readily available data, shortening the time for data collection and analysis. The

selected study population may not be generalizable to other ethnic populations; however, future research studies can expand on the population to include other ethnicities.

Limitations

As this is a records-based study, a significant limitation lies in the quality of clinical records by the dialysis facilities and the degree of thoroughness with which information was collected. Missing data on CMS-2728 forms due to hospitalization, patient transfers, noncompliance, treatment absenteeism, transplantation, allograft rejection, or death may have potentially limited data collection and analysis. In such instances, patients were excluded from the study population sample.

Generalizability to other ethnic populations may have also limited this study. The study population was Hispanics undergoing maintenance hemodialysis with and without a Type II diabetes diagnosis exclusively, and therefore may not be generalizable to other ethnic populations. The study population is restricted to patients attending weekly dialysis treatments at local dialysis clinics, and so excludes patients undergoing home hemodialysis, in-patient hospital hemodialysis, or those electing a dialysis modality not available at these clinics such as peritoneal dialysis.

Other important considerations that may have limited this study include patient phobias and demographics. Patients that for lack of insurance or that simply refuse dialysis treatment either because of disease denial or because of physician, needle, or blood phobias may not be included in the sample population. The population sample may be capturing only those that are sick that are actually attending the dialysis clinics and excluding those that are sick and not receiving necessary treatments. The clinics from

which the data were collected may represent a demographic limitation in that the community in which the clinic is located may have a higher or lower Hispanic representation than do other similar clinics in other regions of the city.

Although challenging, there are some measures that can be employed to reasonably overcome potential limitations. Secondary data, although readily available, should be reviewed to ensure instrumentation and data collection and documentation was thorough, consistent, and streamlined by trained professionals. Future studies conducted using other ethnic populations, encompassing a broader population of patients in home-health and in-patient hemodialysis venues may help control the generalizability. Selecting clinics with similar demographics may help streamline the sample population. Although limitations confer shortcomings, conditions, or influences that can be challenging to control, measures can be taken to minimize them to avoid methodological and study conclusion aberrations.

Significance

The scarcity of studies and dearth of information about albumin levels in this population opens the opportunity to make a contribution to positive social change. Because of the high incidence of Type II diabetes in the Hispanic population and considering the demographics in south central Texas, the population in this region suffers a disproportionate burden of Type II diabetes mellitus. Examinations and comparisons of albumin levels in Hispanic patients with and without a Type II diabetes diagnosis in this region may reveal information about specific albumin trends that may exist in one group and not the other. These examinations may help reveal possible albumin improvement

trends that can inform healthcare professionals about ethnic-specific nutritional supplementation or therapeutic interventions. With these supplementations and/or interventions, healthcare professionals can enhance albumin levels to achieve dialysis goals and improve overall health.

Some studies in the literature, where albumin levels have shown a significant increase with hemodialysis and albumin supplementation (In Control, 2002), provide a good basis for further investigating albumin levels in hemodialysis patients with and without a Type II diabetes diagnosis. Since there is a reasonable expectation that higher albumin levels should improve health in patients with Type II diabetes, the outcome of this study may elucidate specific trends that would inform and direct disease-specific efforts to increase albumin levels in this group. Not only does the identification of potentially modifiable factors associated with albumin levels have the potential for translational therapeutic implications, the outcomes from this study can be useful for clinical risk stratification. This study confers a clear contribution to positive social change.

This research study provides the positive social change necessary in terms of improving public health by identifying disease-specific albumin trends that could influence the course of diseases such as diabetes and renal disease so that ethnic-specific and disease-specific care can be developed for these patients. Should the albumin levels show any disparate patterns in this study population, hemodialysis patients with Type II diabetes may benefit from this research by its potential to inform and empower dialysis clinical care professionals to devote concerted efforts towards raising albumin levels in

these patients, which would help maximize their muscle mass, grip strength, and leg power (Snyder et al., 2012), thus improving the quality of life of patients afflicted with Type II diabetes and renal disease. The study's research findings can contribute to the scarce body of literature and help address diabetes health and renal disease to potentially improve diabetic and renal health outcomes in this population. The social change implications from this project are impactful, beneficial, definitive and long-term.

Summary

This chapter includes the salient features of this proposed study. Hemodialysis patients endure a rigorous treatment regimen to remove toxins from their blood and excess fluid that accumulates due to a decrease in the filtering capacity of the kidney (Fresenius Medical Care, 2013; Yokoyama et al., 2011). The gravity of this kidney filtration insufficiency may result in significant morbidity and mortality. The literature provides a robust association between albumin levels and chronic kidney disease. It is well established in the literature that patients with lower albumin clinical values correlates with poorer clinical prognoses, most notably in patients with a Type II diabetes diagnosis. There is evidence that increased albumin levels improves hemodialysis clinical outcomes and mediates overall patient health status.

Chapter 2 includes an exploration of the current literature relevant to the dependent and independent variables of this proposed study. The chapter includes an expansive discussion on the osmosis and osmotic pressure theory, seminal literature, membrane filtration and permeability, the hemodialysis process, patient fluid overload, the epidemiology, pathophysiology, and endocrinology axis of Type II diabetes, and the

salient relationships between the dependent and independent variables. Chapter 2 includes an introduction to potential confounders and limitations for this study that may influence the study outcomes. Finally, a review of the literature relevant to the epidemiological studies, which were employed to conduct this observational research, will be presented.

Chapter 3 will detail the rationale and construct of the study design. A discussion of the construct for the retrospective analysis of medical records for a population of Hispanic patients on maintenance hemodialysis with and without a Type II diabetes diagnosis will be presented. Chapter 3 will provide an explanation of the sample size, inclusion and exclusion criteria, and rationale for these criteria. An elaboration on confounding variables involved and the methods employed to control for them during the analysis phase will be presented. The data collection strategy, and the statistical methods used in the analysis will be described. The results of this study as well as an elaborative discussion, interpretation, and recommendations for dissemination and future research will be detailed in Chapters 4 and 5.

Chapter 2: Literature Review

Albumin level differences in maintenance hemodialysis patients are fundamentally based on long-standing physiological theories and concepts. The differences in diabetes incidence in the Hispanic population suggest serum albumin levels may also be different in this population (Black, 2002; McBean et al., 2005). The literature supports associations between albumin and kidney disease. However, the literature is scarce on associations between albumin and a Type II diabetes diagnosis and whether albumin level differences exist among this hemodialysis population. This literature review will present the salient facts, theories, and physiological constructs that proffer support for the hypothesis that differences in albumin levels may exist in a population of Hispanic, dialysis patients. Specifically, the relationship between serum albumin levels in Hispanic patients receiving maintenance hemodialysis due to renal disease associated with a Type II diabetes mellitus diagnosis and those without the disease were examined My primary objective was to fill this literature gap.

This literature review begins with a review of the physiological constructs, formulae, and theories guiding this study. This section includes a didactical narrative about physiological concepts, pioneering research, and historical figures and perspectives that provide the foundation for this inquiry. In the next section, the study's dependent variable will be introduced, reviewing current literature on what is known about the protein albumin found in blood plasma. This will include a summation of what is understood about albumin, its current associations, and physiological characteristics that provide the framework for the course and direction of this inquiry. The presentation of

the dependent variable will include a biological description, chemical characterization, and physiological albumin review, including its major functions, importance, and utility in the human body. Given known normoalbuminemic levels, the epidemiology and pathophysiology of albumin will be reviewed and its relationship to kidney filtration and colloid osmotic blood pressure. Specifically, this relationship will be examined in patients undergoing maintenance hemodialysis. The third section is an examination of the independent variable, Type II diabetes mellitus. I reviewed the epidemiology, pathophysiology, endocrinology axis, and its relationship to the study's dependent variable through the presentation of current research in the literature. The presentation of the independent variable will provide the rationale for possible differences in albumin levels in Hispanic patients receiving hemodialysis with a Type II diabetes diagnosis and those without one.

Literature Search Strategy

To conduct the literature search, I employed a series of key words, word combinations, and phrases related to this discipline. These included: *albumin, albuminuria, serumalbumin, albumin physiology, hypoalbuminemia, albumin pathophysiology, albumin epidemiology, biology and chemistry of albumin, van't Hoff and osmotic pressure theory, Type II diabetes mellitus, Type II diabetes and hemodialysis, Type II diabetes in Hispanics, Type II diabetes in Hispanic hemodialysis patients, hemodialysis process, albumin in hemodialysis patients, albumin in hemodialysis diabetic patients, renal failure, hemodialysis fluid overload, renal disease, chronic kidney disease, diabetic nephropathy, hemodialysis patients with diabetes,*

epidemiology of Type II diabetes, Hispanic culture and traditions, Hispanic religion, Hispanic behaviors, and *epidemiology of Type II diabetes in Hispanics*. These key words and word combinations were used to maximize response hits. I searched and obtained information from peer-reviewed journal articles from several institutions, including the Walden University Library, the John Peace Library at The University of Texas at San Antonio, the Driscoe Library at The University of Texas Health Science Center at San Antonio and the Jones Medical Library at Baylor College of Medicine in Houston, Texas. I performed searches for pertinent literature from several databases, including PubMed, MEDLINE, Science Direct and Google Scholar. Leading, reputable dialysis company websites were visited such as Fresenius Medical Care and Davita, Inc. to discuss the intricate hemodialysis process. I researched information from biology, physiology, endocrinology, and nephrology textbooks to provide a foundation for the pertinent research variables.

The references used for this study span from 1947-2015. Some references, particularly those used to present the conceptual framework, the population characterization, and the historical perspectives are considerably older; these older references, however, illustrate the long-standing constructs used to frame this study and are timeless concepts whose applicability and relevancy to this study and discipline remain unaltered through the course of time. These older references, in addition, will help underscore the deep-rooted customs and traditions that have enriched the Hispanic culture for centuries.

Conceptual Framework

The Osmosis and Osmotic Pressure Phenomena

Osmosis is defined as the diffusion of a solvent across a semipermeable membrane (Marieb & Hoehn, 2007; Villani, Dunlop, & Damitz, 2007). Lachish (1999) described the processes as the movement of solvent through a semipermeable membrane that separates two volumes of liquid and disallows the passage of solute particles. The solvent flow, according to this principle, is from a higher solvent concentration to lower solvent concentration. When solute particles are present only in one volume, the osmotic pressure is then the pressure on the solution that ceases the solvent flow (Lachish, 1999). Marieb and Hoehn (2007) proffered a concise description of this phenomenon from a solute perspective; osmosis is a process by which dissolved chemicals will move from an area of high concentration to a lower concentration area. Dissolved compounds or solutes in solution will randomly spread out until there is an equal concentration of solutes throughout the specified area.

Osmosis can describe the movement of solutes until the concentration is evenly distributed throughout the solution and it can also describe the movement of the dissolving liquid, referred to as the solvent, moving to an area of higher solute concentration, which would essentially dilute the solute. The latter description allows for an equilibration of the concentration of dissolved solutes (Marieb & Hoehn, 2010; Villani et al., 2007). Historically, this phenomenon has been conceptualized, studied, improved, and applied to a plethora of scientific inquiries and provides a suitable framework for this study and discipline.

Historical Perspective

Nollet and Dutrochet were two seminal pioneers that demonstrated the concept of osmosis and osmotic pressure. Nollet was the first to demonstrate the process by which a solvent passed selectively through a membrane. Dutrochet is credited with later coining this process osmosis. Both men made important contributions to science, which laid the groundwork for future cell theories, the elucidation of membrane structure and function, and vital physiological processes such as kidney function.

From Electrical Flow to Water Flow. In the 1750s, Nollet applied his interest in physics (Mason, 1991). Specifically, Nollet used his knowledge about electrical flow and applied it to crude experimentation in biological systems. Early experiments by Nollet entailed covering a glass tube containing sugar water with a piece of ordinary paper. He submerged the tube, paper end down, into a receptacle of water. Nollet observed that the level of liquid in the tube rose with time. The pure water crossed through the paper faster than the sugar water did. Being aware of the German experiments that observed the effects of electricity on the flow of water, where water in a thin capillary tube would simply drip from the open end, he sought to expand on that body of knowledge and investigate what would occur if electricity were applied to that tube. Nollet noted that the water in the capillary tube would flow in a constant stream instead of the continuous drip noted by his German colleagues. Armed with this new research lead, Nollet began a series of experiments in which he measured the rate of water transpiration in plants and animals both in the presence and absence of electricity, noting an increase in flow rate

when the organism was electrified (Mason, 1991). His early research opened avenues of research not yet explored in the scientific community at that time.

Nollet then carried out the first of a series experiments in which the principle of osmosis was discovered. He prepared a vessel containing alcohol, (he used "spirits of wine") and enclosed the vessel within a harvested pig bladder (Mason, 1991). Upon placing the covered vessel into a larger receptacle filled with water, Nollet observed that only the water would cross the bladder membrane. For some of his experiments, the bladder would expand until it actually ruptured. The alcohol in the vessel, however, did not cross the pig bladder membrane, suggesting that the membrane was only permeable to the solvent. In addition to this early principle of what would eventually be referred to as osmosis, Nollet had also demonstrated the semi or selective permeability properties of the bladder wall. The term *semipermeable* itself, however, would not be applied to this principle for another 150 years.

Dutrochet and Cell Membranes. Although Nollet utilized a biological membrane layer, namely a pig bladder, the conceptual discovery would not be immediately applied to cell membrane theory (Nezelof, 2003; Pickstone, 1994; Wilson, 1947). In the early 19th century, after learning about Nollet's previous success with bladder experiments, Dutrochet attempted to apply the same principle to movement of fluids across cellular membranes. Dutrochet's microscopic work with both plant and animal membranes revealed the movement of solvent (water) through the cell membranes, a process he coined osmosis. Dutrochet's studies further revealed that the

membrane itself did not determine the direction of solvent flow, but rather the nature of the solvent.

Two of Detrochet's early experiments used snails and chickens as research models. The first experiment entailed placing a snail sperm sac into water in order to examine it microscopically (Pickstone, 1977). His microscopic observations revealed that the contents were extruded from the open tip of the horn. The movement he observed was easily visible because the turbid contents (solutes) contrasted with the water (solvent) outside the snail sperm sac. Detrochet noted that the fluid movement ceased when the turbidity was observed on both sides of the snail membrane. The second early experiment by Detrochet involved constructing a sac from a portion of chicken gut. After filling the sac with milk, he immersed it in a receptacle of water and as expected the sac swelled, illustrating the osmotic movement of water into a membrane containing a lower solvent concentration (Pickstone, 1977).

To further test his ideas, Dutrochet invented an endosmometer, an early version of the osmometer, which is an instrument built in the form of a U, designed to measure the movement of water across an artificial barrier. Dutrochet described the movement of water across the barrier as endosmosis, and the reverse solvent movement exosmosis (Nezelof, 2003; Pickstone, 1977; Pickstone, 1994 Wilson, 1947). Detrochet's fascination with force vitale, the driving force that leads to tissue composition and decomposition in the chemie vivante, and the dynamic exchanges between fluids responsible for these physiological processes Detrochet described, propelled the discussion and research to

further explicate and clarify the concept of osmosis into the next century (Nezelof, 2003; Wilson, 1947).

In the mid 1800s, Graham and von Liebig sought to extend the research on osmosis commenced by their pioneering predecessors (Wisniak, 2013). Despite their efforts, Graham and von Liebig were unable to develop a suitable theory to conceptualize this phenomenon. Graham did, however, distinguished between those substances that could cross through parchment paper and those that could not; these were termed crystalloids and colloids, respectively. Graham's additional research provided the impetus for the application of the concept of osmosis principles to the process of dialysis, which is used today in dialyzers and artificial kidney machines (Wisniak, 2013). Both Graham and von Liebig set the foundation for the next series of advances towards conceptualizing osmosis principles.

The next important advance in the discipline came in 1877 when a German botanist Pfeffer studied osmotic pressure (Borg, 2003). Like Nollet, for his experiments the test protocol was also sugar water. This time, though, the sugar solution was placed in a porous clay vessel, which was submerged in a receptacle filled with pure water. Using a manometer, Pfeffer measured the osmotic pressure of the system and discovered that it was inversely proportional to the volume of a solution and directly proportional to absolute temperature or $PV = kT$, where P is pressure, V is volume, and T is absolute temperature (Borg, 2003). The constant k was subsequently used to define the universal gas constant by van't Hoff and other gas laws. van’t Hoff determined that the osmotic pressure a solute exerts is the same it would exert as a gas at the same volume and

temperature (Lachish, 2007). The formula for osmotic pressure was derived by Jacobus van't Hoff. The van't Hoff theory of osmotic pressure states that π is proportional to the molar concentration (c), the absolute temperature of the system (˚K), and the gas constant (R). The formula $\pi = c\ R\ T$, is derived by the comparison of the pressure of an ideal gas of the same concentration and temperature. *c* in the equation is the molar concentration of solute particles, *R* is the gas constant (0.0821L *ATM/mole*K), and *T* is the absolute temperature in degrees Kelvin (Lachish, 2007). The elucidation and derivation of this osmotic pressure law was fundamental to the advancement of the concept.

Another German botanist, van Mohl further advanced Pfeffer's research. In addition to describing cell division, he provided a lucid explanation for osmosis, which was the first of its kind (Ing, Rahman, & Kjellstrand, 2012). His description about the membrane having an inner protoplasm, a term used to describe the living contents of a cell surrounded by a cell membrane, provided an anatomical basis for the osmotic process in biological cells. Pfeffer's clay pot was a semipermeable membrane, which accurately represented the membranes surrounding most animal and plant cells. Mohl's research that described the protoplasm applied this concept of osmosis to living cells. These historic osmosis studies have inspired studies in various disciplines such as cell physiology, cell molecular biology, biochemistry, and further scientific inquiries investigating solution purification strategies and chemistry analysis. Nephrology studies about the hemodialysis process and application are fundamentally based on these revolutionizing concepts and are the basis for this dissertation inquiry.

The osmosis and osmotic pressure phenomena have been applied to research studies for many years. The seminal research conducted by these pioneers is didactic to numerous fields in academia as well as to healthcare protocols like the hemodialysis process used to remove blood toxins from patients with renal failure. Both the osmotic pressure theory and the van't Hoff theory describe the solute-solvent relationship. The phenomenon is based on the concentration of solute on two sides of a semipermeable membrane, which will allow for the solvent to move towards the side that is less concentrated (Lachish, 1999; 2007). In hemodialysis, the albumin protein is the primary circulating protein solute in blood plasma. As the osmotic pressure theory posits, the protein is unable to cross the semipermeable plasma membrane of cells, but the solvent, however, can cross freely. This osmotic movement of fluids draws fluid from the plasma into the capillaries to maintain homeostatic blood pressure. This concept is applied to hemodialysis treatments in which patients, by the nature of their renal disease, are unable to remove excess fluid from their tissues. Specifically, in hemodialysis patients the excess fluid in edematous tissues, collected during the interdialytic period, is drawn into the capillaries by osmosis and then filtered through a dialyzer using a prepared dialysate solution that can readily remove the excess fluids from the patient via a countercurrent flow (Fresenius Medical Care, 2013). The prescription of a certain dialysate composition changes in order to obtain not only adequate blood purification, but also optimal treatment tolerability. Dialysate composition can be tailored in terms of the sodium, potassium, calcium and bicarbonate content; these represent the solutes (ions) in the dialysate.

The specific ionic components of the dialysate prescribed by the nephrologist are vital to the osmotic movement of fluids and therefore patient clearances (Ing, Rahman, & Kjellstrand, 2012). These four ions are sodium, potassium, calcium, and bicarbonate. Sodium balance represents the cornerstone of cardiovascular stability and blood pressure control (Fresenius Medical Care, 2013). Potassium increases vasoactivity when it is infused into the arterial supply of a vascular bed. Potassium levels can be manipulated by supplementation or during hemodialysis treatments, which can assist in regulating blood pressure (Haddy, Vanhoutte, & Feletou, 2006; Ing et al., 2012). Calcium is used to maintain bone density. Because patients on hemodialysis have dysfunctional kidneys, they are unable to convert vitamin D into the hormone Calcitrol. This hormone is used to facilitate calcium absorption from the intestines into the blood. Consequently, hypocalcemic levels cause calcium to be pulled from bone tissue, which may lead to renal osteodystrophies (Davita, 2013; Ing et al., 2012). Bicarbonate concentration in dialysate is tailored to avoid acidosis and post-dialysis alkalosis (Ing et al.,2012; Vigano, DiFilippo, Manzoni, & Locatelli, 2008).

This intricate hemodialysis process is grounded by fundamental physiological concepts and theories. Both the osmotic pressure theory and the van't Hoff theory of osmotic pressure provide a suitable conceptual framework for this study. These theories provide a plausible mechanism by which patients with Type II diabetes receiving hemodialysis treatments show lower levels of albumin in their blood and consequently albuminuria. The theories, physiological concepts, and dialyzer membranes used for maintenance hemodialysis reflect the filtering capacity of the kidneys. In patients with

Type II diabetes and renal disease, this filtering capacity has been compromised, therefore disobeying fundamental osmotic pressure principles and membrane filtration processes.

At that time, the novel concept of the cell membrane as a barrier capable of regulating osmosis was initially inimical to cell theory and thus beyond immediate application by Nollet (Mason, 1991). Nollet's discovery nevertheless represented one of the first of its kind in the developing discipline of experimental physics and physiology. Furthermore, when a similar phenomenon was found to occur in biological membranes, the inception of several scientific disciplines began to arise. Pfeffer, for example, explained a role for osmotic pressure in the action of fluids within plant vessels (Borg, 2003). The significant contribution to the mathematics of osmosis and chemical equilibrium was derived by van't Hoff. van't Hoff is credited with referring to the principle behind Nollet's pig bladder membrane as semipermeable, which was the first use of that term in describing cellular membrane physiology. The salient history behind the fundamental principles of osmosis and osmotic pressure theories provides the foundation for the intricate hemodialysis process that patients with renal failure endure to filter their blood.

The Hemodialysis Process

The Dialysis Machine

The first dialysis machine was constructed by Dutch physician, Dr. Willem Kolff, in 1941 (Fresenius Medical Care, n. d.; Ing, et al., 2012; Kidney Dialysis Information Centre, n. d.). His crude machine was constructed from the cooling system of an old

Ford, cellophane wrapped sausage skin, parts from an old downed German airplane and a porcelain bathtub. Kolff's early work on dialysis machine construction was seemingly a junkyard challenge. Modern kidney dialysis machines, however, are much more sophisticated, with digital displays and state-of-the-art dialyzers and web-based monitoring and data storage systems. The basic principle behind Kolff's original machines, however, still remains today; the machines remove a small amount of blood from the body at a time and filter out waste products from the blood through fundamental osmotic principles. Today's machines and dialyzers, though, are capable of removing a broader range of uremic wastes products from the blood and can effectively balance essential ion concentrations (Fresenius Medical Care, n. d.; Ing, et al., 2012; Kidney Dialysis Information Centre, n. d.).

Kidney Function

When the kidneys have become damaged and are no longer functioning properly, kidney dialysis is used to replace normal kidney function (Davita, 2014). Physiologically, the kidneys aid in controlling the levels of dissolved minerals called electrolytes and filter out waste products or metabolites created by cells using energy. These functions help in the maintenance of homeostatic amounts of compounds such as sodium, potassium and calcium in the blood as well as the removal of potentially toxic compounds. These toxic compounds are filtered, concentrated and collected by the kidneys into urine, which allows them to be excreted from the body. When the kidneys fail, the dialysis process can be used to take over that function (Davita, 2014).

The hemodialysis process aligns with the principles of osmosis, solution

permeability, and membrane structure and function (Fresenius Medical Care, 2013). The process involves removing blood from the body via an access, usually an arteriovenous graft in the forearm, and circulated and filtered through an extracorporeal fluid circuit, then returned to the patient through the same access. The circuit includes a hemodialyzer, which is a device that is used to filter the blood. The hemodialyzer contains a selectively permeable membrane, similar to the membranes that Nollet, Dutrochet, Pfeffer and Kolff used, with a filtration capacity that allows fluids and uremic waste products to cross through, but prevents the exchange of blood components and proteins such as albumin. The countercurrent movement of the dialysate fluid that is used to clean and detoxify the blood, flows on the opposite side of the dialyzer membrane and draws waste and extra fluid from the blood, which can then be discarded (Fresenius Medical Care, 2013).

Osmosis and Hemodialysis

Kidney dialysis machines exploit osmotic principles to take over the filtering capacity of the kidneys (Sakai, 2000). Like those original membranes first introduced by Nollet and Detrochet capable of filtering substances from a given solution, dialysis machines employ a sophisticated semipermeable membrane, which is capable of allowing small molecules, such as water, salts, and metabolites to pass, but disallows larger components such as proteins (albumin) and blood cells from filtering through. Dialysis machines direct the blood alongside a semi-permeable membrane while circulating a large volume of a liquid called the dialysate along the opposite side of the membrane. The countercurrent flow between the blood and the dialysate causes the metabolites to flow out of the blood, through the membrane, and into the dialysate via osmosis. The

membrane, furthermore, also allows electrolytes to seep through the membrane as well so that the blood can remove electrolytes that are in excess, thereby maintaining electrolyte homeostasis. It is through the principles of osmosis that dialysis machines and dialyzers effectively remove toxins from the blood and essentially take over the filtration function from the kidneys (Ing et al., 2012; Sakai, 2000).

Diffusion, Osmosis, and Ultrafiltration

Three fundamental concepts frame the elaborate hemodialysis process. The process by which the albumin protein provides the mechanism by which colloid pressure is maintained is due in large part to these physiological processes. These three processes are: (a) diffusion; (b) osmosis; and (c) ultrafiltration. Each process plays a vital role in human physiology and is directly related to the process by which homeostatic blood pressure is maintained in order to dialyze patients suffering from renal failure. The dialysis process and the effective filtration of metabolites and other toxins from albumin protein in the circulatory system to hemodialyze patients is a direct application of these concepts. Furthermore, as discussed by Iseki et al. (1993), albumin levels in patients with a type II diabetes mellitus diagnosis serve as predictors for death, providing the reasoning and justification for this research inquiry.

Diffusion. Diffusion is a fundamental driving force in many biological processes, and is an example describing how the living world is regulated by the same physical laws as the nonliving world (Villani, Dunlop, & Damitz, 2007). Diffusion, therefore, applies to the process of hemodialysis. Diffusion is defined as the exchange of solutes dissolved in fluid across a semipermeable membrane because of differences in the concentration

gradient on both sides of the membrane (Fresenius Medical Care, 2013). When there is a higher concentration of a given solute on one side of a membrane relative to the other, the diffusion randomly occurs to try and achieve equal solute concentrations on both sides of the membrane. In hemodialysis, the dialysis machine controls this transfer of solutes by controlling the chemicals in the dialysate according to the doctor's prescription. Hemodialysis machines control the chemicals in the dialysate by mixing dialysis fluid concentrates such as acetate or sodium bicarbonate plus acetic acid based solutions with purified water. Each of the solutes in the dialysate can be manipulated to improve the amount of solute removed by diffusion to adequately dialyze patients (Fresenius Medical Care, 2013).

Osmosis. Whereas diffusion describes the random movement of solutes across membranes, osmosis describes the diffusion of a solvent, usually water, across a biological membrane from areas of high to low concentration (Villani et al., 2007). This phenomenon is the net movement of the solvent across a semipermeable membrane driven by a difference in the amounts of solute on the two sides of the membrane (Fresenius Medical Care, 2013). In hemodialysis, this refers to the movement of a solvent across cell membranes within the body such as the movement of solvent within erythrocytes to the blood plasma, or from within cells of the various tissues in the body to interstitial fluid, and not to water movement across the hemodialyzer membrane. Manipulating sodium, referred to as sodium profiling, can be used to increase the rate of osmosis early in the hemodialysis treatment by increasing the sodium concentration of the plasma (Fresenius Medical Care, 2013).

Ultrafiltration. Lastly, ultrafiltration utilizes a pressure gradient to force fluid through a membrane (Fresenius Medical Care, 2013). This phenomenon is useful because it controls the patient's weight loss over the course of the treatment. Modern dialysis machines are referred to as volumetric, which means they control the volume of fluid removed from the patient directly, allowing dialysate pressure to change naturally in order to achieve the prescribed fluid removal goal. To achieve volumetric control, the flow rate of dialysate into and out of the dialyzer is controlled using two flow controllers, or by having equal dialysate flow rates into and out of the dialyzer and removing fluid between these two equal flows. Employing volumetric control allows the physician to exploit the effective "high flux" dialyzers, which allow a great deal of fluid movement with minimal pressure differences (Fresenius Medical Care, 2013; Ing et al., 2012).

Fluid Overload and Ultrafiltration

There exists a wide array of current studies that are a direct application of the principles of osmosis, membrane function, fluid movement, and filtration. These concepts are common denominators that guide and inform this study's research questions. When any of these processes go awry, it illustrates the pathophysiology of kidney function and filtering capacity. As a consequence, hemodialysis patients experience fluid overload. Patients with end-stage renal disease are exposed to extreme shifts in body volume and thereby cardiovascular strain as a result of interdialytic weight gain, fluid removal during hemodialysis, and also chronic fluid overload (Ismael et al., 2014). Fluid overload, either because the semipermeable membranes of nephron glomeruli are compromised or because of inadequate dialyzer and/or dialysate prescription, may lead to abnormal

hemodynamic conditions and higher risk for cardiovascular morbidity. Even subtle fluctuations in fluid balances may have dire clinical outcomes and poor prognoses (Antlanger et al., 2013; Kim et al., 2012), underscoring the importance of and the direct application to the principles of osmosis, membrane filtration, and the intricate hemodialysis process.

It is well understood that fluid accumulation in hemodialysis patients is associated with adverse outcomes in critically ill patients. Bouchard et al. (2009) sought to ascertain if fluid accumulation is associated with mortality and non-recovery of kidney function in critically ill adults with acute kidney failure. The authors defined fluid overload as having more than a 10% increase in body weight relative to normal baseline weight recordings. Of the 618 patients enrolled in their prospective, multicenter observational study, the authors found that patients with fluid overload experienced significantly higher mortality within 60 days of maintenance hemodialysis. Among patients that were dialyzed, survivors had significantly lower fluid accumulation at the start of dialysis treatment compared to non-survivors. The authors also noted that 31% of the population selected for their study had Type II diabetes as a comorbidity; this may or may not have influenced fluid accumulation in their study, but is a noteworthy factor to consider when making conclusive assessments about fluid accumulation in this population (Bouchard et al., 2009).

Fluid accumulation and overload was also investigated by Hecking et al. (2012). In their prospective, multicenter, randomized, controlled clinical trial, the authors recruited 60 hemodialysis patients with fluid overload and sought to determine if

ultrafiltration was the superior method to control fluid overload over conventional hemodialysis. The patients were randomized into three groups: (a) an ultrafiltration and dialysate conductivity group; (b) an ultrafiltration and temperature regulation group; and (c) a conventional hemodialysis group. The authors found that the ultrafiltration and dialysate conductivity group showed significantly fewer intra and post dialytic complications. The prescribed dialysate recipe has shown to improve the diffusion of toxins from the blood into the dialysate and osmotically draws fluids from the extracellular spaces into the circulatory system, while simultaneously ridding of excess fluid accumulation for cardiovascular fluid homeostasis. The ultrafiltration process utilizes a pressure gradient to force fluid through the dialyzer membrane (Fresenius Medical Care, 2013). This hemodialysis strategy is useful because it controls the patient's weight loss over the course of the treatment, which can translate into improved dialysis clearances and better overall dialysis hemodynamic outcomes (Hecking et al., 2012).

Fluid overload was further investigated by Antlanger et al. (2013). Like previous studies, the authors assert that chronic fluid overload is closely associated with higher mortality (Antlanger et al., 2013; Bouchard et al., 2009; Hecking et al., 2012). For their prospective study, 144 hemodialysis patients at three Fresenius dialysis facilities in Austria were recruited. The authors found that of the recruited population, 39% had predialysis fluid overload. Those patients with higher BMI's had lower fluid overload, suggesting that patient dry weights were inadequately prescribed and/or difficult to achieve when they were overweight (Antlanger et al., 2013). Additionally, and perhaps correspondingly, the albumin levels in the fluid overloaded patients were significantly

lower. The authors concluded that cardiovascular parameters and volume measurements, including albumin levels, when compromised or abnormal, might suggest that fluid overload is a biomarker for cardiovascular risk (Antlanger et al., 2013). Bouchard et al. (2009), Hecking et al. (2012), and Antlanger et al. (2013) shared an important methodological population recruitment strategy. The population for these studies was recruited from multiple dialysis centers with a wide ethnic representation of hemodialysis patients, proffering increased generalizability of study outcomes to populations beyond Hispanic Americans.

Lindberg, Prutz, Lindberg and Wikstrom (2009) agree with Bouchard et al. (2009), Hecking et al. (2012), and Antlanger et al. (2013) that excessive interdialyitc weight gain and ultrafiltration rates above 10ml/h/kg body weight suggest higher morbidity and mortality. In their study, the authors retrospectively examined cohorts of patients on maintenance hemodialysis from The Swedish Dialysis DataBase and The Swedish Renal Registry of Active Treatment of Uremia from 2002-2006. A cohort of 9,693 hemodialysis sessions in 4,498 patients were examined. The study aimed to estimate the prevalence of fluid consumers, identify ultrafiltration patterns, and attempt to explicate interdialytic weight gain. The authors concluded that there are potentials for continuing improvements in the care of hemodialysis patients with fluid overload, including more frequent dialysis, such as nocturnal or daily dialysis to all patients (Lindberg et al., 2009). This study's design was a retrospective analysis of both a Swedish database and registry, which qualifies as secondary data analysis. This study aimed to utilize a similar data analysis strategy to elucidate the albumin levels of patients

on hemodialysis in the selected population. This study also provided a model option for possible population size requirements that would satisfy statistical power during data analysis.

A multicenter, interventional trial that was based on several observational studies was conducted by Kim et al. (2012) to determine hemodynamic and biochemical benefits of measuring fluid status is hemodialysis patients. The authors enrolled 120 patients and divided them into two groups: (a) the hyperhydrated group, and (b) the dehydrated group. After reducing the patients body weight in the hyperhydrated group and raising the body weight in the dehydrated group for sixteen weeks, the results showed that despite enrolling all euvolemic patients for their study, the hyperhydrated patients contributed over one-third of the participants. Of the 120 enrollees, 44 were in the hyperhydrated group and 18 were in the dehydrated group. Furthermore, the authors found that after sixteen weeks systolic blood pressure and pulse pressure decreased in the hyperhydrated group, while there was no change in blood pressure in the dehydrated group post intervention. The study underscored the importance of accurately assessing fluid status in hemodialysis patients so as to regulate blood pressure (Cigarran et al., 2007; Kim et al., 2012). Since blood pressure is largely maintained by albumin levels, the authors measured albumin levels at week 0, 8, and 16 and found that compared to the dehydrated group, the hyperhydrated group showed an albumin drop from 3.89mg/dL, 3.89mg/dL, 3.79mg/dL in weeks 0, 8, and 16, respectively. These results correlate with an expected reduction in kidney filtering capacity. Additionally, the results align with osmotic pressure principles. Since some albumin is lost during the filtration process, a

hemodynamic change occurs whereby the fluid moves from the capillary lumen through the selectively permeable membranes into the interstitial fluids, causing fluid overload tissue edema.

Cigarron et al. (2007) followed suit with a cross-sectional study that aimed to evaluate the relationship between serum albumin concentration and hydration state. The study investigated 108 non-selected patients that were put into three groups based on their serum albumin levels. Seventy-five healthy individuals comprised the control group for comparisons. The authors concluded that hypoalbuminemia is a marker of fluid overload (Artlanger et al., 2013; Cigarran et al., 2007). There exists a direct relationship between albumin levels and fluid excess as a consequence of albumin level differences in patients on maintenance hemodialysis (Cigarran et al, 2007; Kim et al., 2012). The physiological importance and clinical significance of albumin in patients undergoing maintenance hemodialysis is formidable and worthy of further exploration.

Hispanic Population

Minority populations are rapidly growing in the United States. This is especially evident in the Hispanic population (Lopez, 2008). In 2002, Hispanics became the largest minority group in this country, accounting for 14.5% of the U.S. population by 2005. Consequently, the demand for health care among this population is growing as well. According to Lopez et al. (2008), Hispanic individuals in the U.S. have a high prevalence of Type II diabetes mellitus, which is a known risk factor for the development of chronic kidney disease. This, in turn, places the Hispanic population at high risk to develop stage 5 chronic kidney disease, which often requires maintenance hemodialysis. Therefore, the

importance of recognizing the needs of this growing population segment by health care providers, including physicians, nurses, social workers and dieticians is imperative. For this research, a retrospective examination of the treatment records of a sample Hispanic population that received hemodialysis at local dialysis clinics in San Antonio, Texas was conducted. Both diabetic and nondiabetic patients on maintenance hemodialysis that received treatments at these clinics were reviewed to determine if albumin level differences existed between hemodialysis patients with a Type II diabetes mellitus diagnosis and those without one. The medical records were analyzed at baseline, 0, 3, and 6 months post baseline. An acceptable goal level for albumin, according to the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines is ≥4.0g/dL (American Journal of Kidney Disease, 2007; National Kidney Foundation, 2002; National Kidney Foundation, 2013). This level was also used in this research as the acceptable level for comparing albumin levels in the sample population.

The study consisted of collecting and analyzing data on the health status and renal measures from medical records of Hispanic dialysis patients seen at Fresenius Medical Care-NA's designated renal dialysis clinics in San Antonio, Texas. These records are maintained on all patients admitted to these facilities. After obtaining permission from Frenova Renal Research and Walden's Institutional Review Board (Approval # 12-17-14-0298443), data were collected from Centers for Medicare and Medicaid Services (CMS)-2728 forms. The CMS-2728 government form is a validated data collection instrument that is completed for all new patients who are initiated on dialysis (Appendix A). Data arising from this form have been published in numerous studies. It records data on

sociodemographic characteristics and captures information on a many comorbidities, hematology profiles, and clinical indicators (Murthy, Malony, & Stack, 2005). The clinical data are collected by nursing personnel, including anthropometric measurements of age, weight, and height, as well as renal parameters such as BUN-serum creatinine ratios, hemoglobin $A1_C$, lipid profiles, and serum albumin documented at the onset of treatment. Subsequent blood draws are done weekly for Hemoglobin $A1_C$ and pre and post BUN-creatinine ratios and potassium if deemed necessary by the nephrologist. Calcium, phosphorus, and albumin levels are collected monthly peritreatment. Both weekly and monthly lab tests are documented in the patient's medical records. Additionally, the primary cause of renal failure and ICD-9 codes for associated comorbidities are documented on the patient's medical records. Routine lab testing and reporting of monthly albumin levels through Spectra Laboratories were reviewed from the patient's medical records.

Retrospective analysis of medical records in end-state renal disease (ESRD) patients who underwent maintenance hemodialysis were examined by Ricks et al. (2012). The authors reviewed records in any 1 of the 580 outpatient dialysis facilities of Davita, Inc. from July 2001 through June 2006. Cohort inclusion criteria consisted of patients that were on dialysis for at least 90 days, were being treated with maintenance hemodialysis at study onset, had a history of diabetes, and had at least one $A1_C$ measurement. Medical Evidence CMS-2728 forms of the U.S. Renal Data System were examined for preexisting comorbid conditions. The patient records were reviewed from July 2001 to June 2006 and followed up for one year. Over the five-year period, 164,789

adult subjects received dialysis treatment in Davita clinics. Of these, 141,762 patients were undergoing maintenance hemodialysis at the time of entry into the cohort. 54,757 diabetic, maintenance hemodialysis were identified. The authors aimed to determine mortality predictability of $A1_C$ and random serum glucose over time. Cox proportional hazards regression were used to examine whether glycemic control predicted survival for up to 6 years of follow up. Exploratory analysis among patient subgroups, including a serum albumin based subgroup was conducted. Logistic regression was performed to analyze the predictive value of $A1_C$ and to assess the association between different laboratory and clinical parameters and $A1_C$ levels. The authors found that poor glycemic control appeared to be associated with decreased survival in the general population of diabetic, maintenance hemodialysis patients. In the serum albumin subgroup in particular, the results showed that even with moderate glycemic increases, this group revealed a marked increase risk for all-cause or cardiovascular mortality (Ricks et al., 2012).

A retrospective, secondary data analysis from 2000 through 2008 on a multiethnic group of participants (N = 122,716) from the Kidney Early Evaluation Program (KEEP) was also conducted by Jolly et al. (2011). KEEP is a free, community-based voluntary screening program designed to detect chronic kidney disease, aimed at identifying individuals with risk of kidney disease. Participants were screened based on blood and urine specimen to assess serum creatinine, fasting blood glucose, and urine albumin levels. The authors included patients with a known diabetes diagnosis, hypertension, kidney disease, and a family history of diabetes. For this study, patients that were on hemodialysis or had undergone a kidney transplant were excluded from the study. After

exclusionary criteria, *n* = 19,205 constituted the final population for this study. The authors divided the population into five groups based on ethnicity: (a) Non-Hispanic White, (b) African American, (c) Asian, (d) American Indian/Alaska Native, and (e) Hispanic. The authors conducted multivariate Cox proportional hazards regression analyses to determine the association of race/ethnicity with all-cause mortality among all participants with chronic kidney disease. The authors showed that the risk was similar among African Americans, higher for American Indian/Alaska Natives, and lower in Hispanics compared to their White counterparts. The latter result is consistent with the literature on the existence of the "Hispanic Paradox," describing a high chronic disease risk factor profile with a lower mortality compared to their white counterparts. The authors concluded that significant differences in mortality exist among persons with chronic kidney disease (Jolly et al., 2011).

The Hispanic Paradox was further confirmed in another study conducted by Ricks et al. (2011). For their retrospective, cohort study, the authors examined a 6-year cohort of *N* = 109,605 maintenance hemodialysis patients including *n* = 39,090 Blacks, *n* = 17,417 Hispanics, and *n* = 53,098 non-Hispanic white outpatients from DaVita dialysis clinics between 2001 and 2007. Cox proportional hazards models and Kaplan-Meier log-rank tests examined the association between BMI and the six-year survival among these race/ethnic groups. Of the 109,605 patients selected for the study, 45% of the population was diagnosed with Type II diabetes. The authors reviewed the Davita database and Medical Evidence Form CMS-2728 to determine presence or absence of diabetes and associated comorbidities. The authors showed that a higher BMI had a protective quality

and therefore higher survival rate among African Americans and Hispanics compared to their white counterparts. Although obesity is associated with deleterious outcomes in the general population, in maintenance hemodialysis patients this association is reversed, confirming the "reverse epidemiology" phenomenon. For the Rick's et al. (2011) study, both the reverse epidemiology phenomenon and the Hispanic paradox were important population considerations (Ricks et al., 2011) and were equally important considerations for this investigation.

Hispanic, hemodialysis population studies were also conducted by Yan et al. (2013). A retrospective analysis of a cohort of Caucasian, Black and Hispanic patients from the United States Renal Data System was identified. A cohort of $N = 1,282,201$ patients were included in the study. Medical Evidence Forms CMS-2728 were reviewed to ascertain patient ethnicities and specific patient comorbidities. The authors sought to investigate if survival in hemodialysis patients is modified by age, ethnicity, and race. Cox regression analysis was used to determine survival differences for the entire study cohort. The authors found that mortality risk was lowest in Hispanics, intermediate in non-Hispanic Blacks, and highest in non-Hispanic Whites. This trend held true for the overall dialysis population and most age groups (Yan et al., 2013).

Murthy et al. (2005) confirmed this survival advantage in Hispanic patients on maintenance hemodialysis. In their historical, prospective cohort study of new ESRD patients, the authors identified $N = 158,685$ adult patients who initiated hemodialysis between 1995 and 1997. Patients were identified from the Medical Evidence Form CMS-2728. Descriptive statistics of patient characteristics were performed for the entire cohort

and for the six combined race subgroups. Chi square tests were used to compare categorical variables and means of variables were compared using ANOVA. Multivariate logistic regression was performed to examine the association of ethnicity and race with three comorbid indicators, including diabetes and hypoalbuminemia. Additionally, multivariate Cox regression models examined the relationship of ethnicity-race with mortality risk in new ESRD patients. After exclusion criteria, the study cohort consisted of n = 100,618 patients. 10,393 (10.3%) were identified as Hispanic. The authors concluded that survival of new ESRD Hispanic dialysis patients was significantly higher, with a 17% lower adjusted mortality risk among those without diabetes and 30% lower adjusted mortality risk among those with a diabetes diagnosis (Murthy et al., 2005).

To further assess patterns and predictors of mortality in hemodialysis patients, Lukowsky et al. (2012) examined a large (N = 82,566) cohort of incident hemodialysis patients from Davita clinics from 2001 to 2006. After exclusion criteria, n = 18,707 incident dialysis patients constituted the study population. Descriptive analysis was performed on the population. Kaplan-Meier estimation, mortality ratios, and survival curves were produced. Multivariate logistic regression models were conducted to estimate standardized mortality ratios. Cox proportional hazard models were used to calculate hazard ratios for the 5-year survival for the patient characteristics such as demographics, comorbidities, and laboratory values. The patients were selected from The United States Renal Data System databases. The authors divided the cohort into a priori groups to estimate survival at 3, 6, 12, and 24 months. Serum albumin as well as other clinical values were collected at treatment onset and documented on CMS-2728 forms

and subsequently during treatments. The authors found that incident hemodialysis patients exhibit the highest mortality during the first six months of dialysis treatment, particularly in the first two months. Of these, hypoalbuminemia accounted for one third of all deaths in the first 90 days (Lukowsky et al., 2012).

Dalrymple et al. (2013) sought to measure serum albumin and prealbumin concentrations in incident dialysis patients to evaluate protein-energy wasting (PEW). The authors reported that low albumin and prealbumin levels are important biochemical indicators of PEW and are powerful predictors of mortality risk in patients undergoing maintenance hemodialysis (Dalrymple et al., 2013). The authors recruited participants from the Comprehensive Dialysis Study (CDS) for a prospective cohort study of adults with end-stage renal disease (ESRD) in whom maintenance hemodialysis was newly initiated. Participants were enrolled between 2005 and 2007. A cohort of $N = 1,678$ incident dialysis patients from 297 facilities consented to participate in the surveys and/or laboratory component of the CDS. Of these, 35 patients donated serum for the laboratory research component.

The authors collected baseline data from the Medical Evidence Form from the Department of Health and Human Services and the Centers for Medicare and Medicaid Services (CMS 2728 Form). They classified participants as having diabetes if diabetes was the primary cause of ESRD or if diabetes was listed among the comorbidities. For the laboratory chemistry, blood was drawn at enrollment and thereafter every three months for the first year of the study by participating dialysis units. The authors measured albumin and prealbumin twice on each serum sample and used the mean

concentration of the duplicate serum albumin and prealbumin values in the statistical analyses.

For their study, the dependent variables of interest were longitudinal changes in serum albumin and prealbumin levels, measured at 0, 3, 6, 9, and 12 months. A total of *n* = 266 CDS Nutrition substudy participants with laboratory measures were included in the study of which 35 enrolled in the laboratory research component. These participants were from 56 participating dialysis facilities. The mean age of the participants was 62 years. 55% were male, 71% were white, 68% were on hemodialysis, and 8% were on peritoneal dialysis. The study cohort was characterized by a high prevalence of Type II diabetes. The authors found that serum albumin concentration increased, whereas prealbumin concentration remained relatively stable over time. After testing individually for diabetes, atherosclerotic vascular disease, heart failure, and higher C-reactive protein, the concentrations were associated with lower serum prealbumin concentrations. From their results, the authors concluded that further understanding of the mechanisms underlying differences between albumin and prealbumin kinetics in dialysis patients may lead to improved approaches to the management of PEW.

This study aimed to employ a similar study design as Dalrymple et al. (2013). The study intended to examine albumin levels at baseline, 0, 3 and 6 months from CMS-2728 forms and patient records to ascertain possible differences in serum albumin levels. Whereas Dalrymple et al. (2013) measured albumin levels in a large multi-ethnic cohort of hemodialysis patients, most with a diabetes diagnosis, this study aimed to evaluate albumin levels in a cohort of Hispanic hemodialysis patients with the same chronic

disease diagnosis.

Numerous studies have investigated large cohorts of hemodialysis patients to address a myriad of research questions regarding treatment outcomes, albumin improvement patterns, mortality, as well as comorbidity comparisons among various ethnicities. Some studies have examined hematology profiles of specific ethnic populations receiving maintenance hemodialysis treatments. As discussed above, several have reviewed and compared Hispanic survival analysis, dialysis modalities, glycemic/$A1_C$ control, race/ethnicity and age, renal disease risk, and associations between dialysis outcomes with a Type II diabetes mellitus diagnosis. None, however, have investigated if a Type II diabetes diagnosis in dialysis patients might influence albumin levels or whether albumin level differences or improvement patterns exist from treatment onset through the course of their dialysis treatments. It is apparent from the studies presented in this literature review that the protein albumin is a key research indicator from which to monitor dialysis treatment progress and to gauge patient prognosis.

Albumin Characterization and Physiological Roles

Albumin is characterized as a globular protein with a molecular weight of 69,000 daltons (Alpern, Caplan, & Moe, 2013). It has a negative charge at physiological pH, is synthesized in the rough endoplasmic reticulum in liver hepatocytes, and catabolized by all metabolically active tissues (Alpern et al., 2013; Rozga et al., 2013). The molecule is a single peptide chain composed of 585 amino acids with a polypeptide arrangement in folded alpha helices, held together by disulfide bridges. Because of this flexible arrangement, albumin may change shape, facilitating its ability to bind many endogenous

and exogenous ligands (Rozga et al., 2013).

This ubiquitous plasma protein largely contributes to plasma colloid osmotic pressure (COP) due to both its small size and abundance. Compared to other globular proteins in the blood, albumin accounts for 55-60% of total plasma proteins by weight, which is why it plays such a significant role in blood pressure regulation (Rozga et al., 2013). Its synthesis is regulated primarily by a change in interstitial colloid osmotic pressure. The normal range of human serum albumin in adults is 3.5–5.0 g/dL. In tissue spaces, however, the concentration is much lower at 1.4 g/dL. In addition to this major physiological function, albumin also serves as a carrier protein for many insoluble organic substances, is recruited for binding and transporting drugs, is a prolific free radical scavenger, is useful in acid-base balances, plays a major role in anticoagulatory and antithrombotic regulation, and is vital for vascular permeability (Alpern et al., 2013; Rozga et al., 2013). Considering these vital roles in the human body and because albumin protein levels have shown to fluctuate in pathomechanistic incidences, each of these roles are explicated further to provide a comprehensive characterization of the protein's physiological utility and therefore relevance to this study.

Colloid Osmotic Pressure

Colloid osmotic pressure (COP) is the force opposing hydrostatic pressure (Rozga et al., 2013). It is created by the presence of large non-diffusible molecules, such as plasma proteins, which cannot cross the capillary wall. These molecules draw water to themselves because the water concentration in their immediate surroundings is lower than it is on the opposite side of the capillary wall (Marieb, & Hoehn, 2010). According to

Alpern et al. (2013), hydrostatic pressure that is created by the presence of albumin accounts for 75 - 80% of the COP. Blood pressure regulation can be explicated by the Starling's equation as well as fundamental osmotic pressure theories and principles (Alpern et al., 2013). According to the equation, the flow of fluid out of capillaries is determined by a filtration constant multiplied by the net force driving fluid out of the capillary (hydrostatic pressure minus oncotic pressure) minus the osmotic gradient pulling the fluid out. Altogether, the Starling's equation for blood pressure regulation can be quantified using the equation: Transcapillary Flow = k [(Pcap + Pi) - (Pi + Pcap)] (Janecek & Sigler, 1996; Rozga et al., 2013).

The salient concepts of blood pressure maintenance and regulation are fundamentally based on the principles of osmosis and the osmotic pressure theory. According to these principles, the movement of water draws fluid into the cells away from the tissues to maintain homeostatic blood pressure, accurately reflecting the process of osmosis by which solvent moves down its concentration gradient (Fresenius Medical Care, 2013; Lachish, 2007). Each cell membrane serves as the semipermeable membrane that will allow for this osmotic fluid movement that regulates COP.

Binding and Transport

Albumin possesses binding and transport properties (Alpern et al., 2013; Roszga et al., 2013). The binding and transport functions include circulating ligands, metabolite and drug delivery to tissue sites, detoxification, drug inactivation, various molecule stabilization, metabolism of endogenous and exogenous substances, and antioxidant protection. The protein is capable of binding drugs and other ligands, therefore reducing

the circulating serum concentration of these compounds. Albumin's morphology consists of four binding sites with varying specificity for different compounds. Because of this unique structure, competitive binding of drugs may occur at either the same or entirely different structural sites. For instance, the drugs that are important for albumin binding include Warfarin (Coumadin), Digoxin, NSAIDS, Midazolam, and Thiopental. Some of these, like Warfarin and Diazepam, compete for the same binding site. It is therefore important to consider that hypoalbuminemia is related to higher free drug levels and vice versa (Alpern et al., 2013; Rozga et al., 2013).

Free Radical Scavenging

Albumin contributes to antioxidant and free radical scavenging (Alpern et al., 2013; Rozga et al., 2013). Albumin is a major source of sulphydryl groups; these "thiols" scavenge free radicals, specifically those with a nitrogen and oxygen species, whose cumulative effects wreak havoc on tissues and overall physiological function (Alpern et al., 2013; Rozga et al., 2013). Albumin is known to inhibit oxygen free radical production by polymorphonuclear leukocytes. It is capable of binding iron and copper, making them less likely to form reactive oxygen species. The protein's antioxidant properties are demonstrated in the inflammatory response, carbon tetrachloride poisoning, and uremia (Rozga et al., 2013).

Acid-Base Homeostasis

Albumin is known to play a role in plasma buffering due to the presence of many positively and negatively charged residues on the albumin molecule (Rozga et al., 2013). Chemically, albumin is a negatively charged protein, contributing heavily to the "anion

gap." This concept posits that the concentration of anions and cations in plasma should be equal. The anion gap is calculated as AG = (Na + K)- (Cl) in (mEq/l). The remaining anions that are added to this equation come mostly from albumin, inorganic phosphate and hemoglobin. Therefore, in hypoalbuminemic states, the anion gap is narrowed (Alpern et al., 2013).

Anticoagulant and Antithrombotic Effects

Although the anticoagulant and antithrombotic effects of albumin are poorly understood, it does play a role in preventing coagulation and dissolving existing coagulants in a Heparin-like manner by binding nitric oxide radicals, inhibiting inactivation, and permitting a more prolonged antiaggregatory effect (Alpern et al., 2013; Rozga et al., 2013). Additionally, albumin may inhibit platelet function through platelet activating factor and the cyclo-oxygenase pathway. In diabetes specifically, glycosylated albumin may increase thrombotic event and atherosclerosis incidences (Alpern, et al., 2013; Rozga et al., 2013).

Vascular Permeability

Evidence shows that albumin may play a role in limiting the capillary bed leakage during stress-induced increases in capillary permeability (Alpern et al., 2013; Rozga et al., 2013). This is directly related to endothelial cell's ability to control the permeability of their walls and to the interstitial spaces between them. Albumin is thought to play a role in plugging this gap or may have a repelling effect because of its overall net negative charge (Alpern et al., 2013; Rozga et al., 2013). Rozga et al. listed albumin's vascular permeability functions as increasing microvascular permeability during inflammation,

sepsis, and trauma, minimizing microvascular permeability to large molecules by repelling negatively charged molecules or by narrowing the channels by binding to the endothelial cells, and reducing vascular permeability by exploiting its antioxidant and anti-inflammatory properties.

There is a marked relationship between albumin and patients with a Type II diabetes diagnosis. Folsom, Eckfeldt, Nieto, Metcalf, & Barnes (1995) confirm this assertion. In their study, the authors reviewed data from the Atherosclerosis Risk in Communities Study to determine if there was a relationship between Type II diabetes mellitus and albumin levels. The authors found that of the adult population recruited for their study, the mean albumin concentration was .04 to .12 g/L lower in participants with a Type II diabetes diagnosis compared to those without the disease (Folsom et al., 1995). What is not known, however, is if similar decreases in albumin is seen in adult, Hispanic patients on maintenance hemodialysis with the same chronic disease diagnosis. Considering the prevalence of Type II diabetes in this population, and the number of Hispanics that are currently receiving maintenance hemodialysis treatments due to renal failure, a study to ascertain if a Type II diabetes diagnosis influences albumin levels in this hemodialysis population provokes intrigue and warrants further investigation.

Type II Diabetes Mellitus

The study investigated albumin levels in the Hispanic population with a Type II diabetes diagnosis undergoing maintenance hemodialysis. This section will briefly describe the epidemiology, pathophysiology and endocrinology implications of this disease to highlight the role it plays in its relationship to albumin levels and to provide

justification for the population selected for this study. Additionally, this section will elaborate on the population used for this study. Because the Hispanic population is deep-rooted in long-standing culture and customs, behavioral, cultural, religious, and psychosocial dimensions will be briefly presented to provide a comprehensive profile of the Hispanic community, its culture, influences, customs, and traditions which can broaden the understanding of and provide ample evidence for the higher prevalence of this disease in this population.

Type II diabetes mellitus has become a serious public health epidemic in the United States and across the globe. According to Rosal et al. (2009), by 2050 approximately 29 million Americans will be diagnosed with Type II diabetes mellitus. The evidence exists of the impact this disease will have on population health. This disease is especially prevalent in the Hispanic community. It is estimated that more than 20% of the U.S. Hispanic population will develop Type II diabetes by 2030 (Rosal et al., 2009). The diabetes health issue in the Hispanic community is serious and omnipresent. The prevalence rates of Hispanic adults with diabetes are about twice that of their white counterparts (Centers for Disease Control and Prevention, 2005) and rapidly growing with every passing decade. In fact, this population suffers higher rates of morbidity and mortality related to diabetes than any other ethnicity. The unique social determinants of health that are significant factors in the health status of this community, including behavioral, psychosocial, and cultural aspects, are, for the most part, the underlying culprit for this serious health issue in this community. Additionally, the strong religious traditions, rooted in Mexican influences exacerbate this health dilemma.

Type II Diabetes Endocrinology and Pathophysiology

Type II diabetes is a chronic metabolic disease characterized by high glucose levels in the blood (Mahler & Adler, 1999). This occurs because of impaired regulation of liver glucose synthesis and β-cell dysfunction and failure. The primary etiology of diabetes is an initial deficit in insulin secretion by the pancreatic β islets of Langerhans and insulin deficiency associated with peripheral insulin resistance. In patients with diabetes, the absence or insufficient secretion of insulin causes hyperglycemia, which causes numerous abnormal physiological effects and disease sequelae (Campbell, 2000; Mahler & Adler, 1999).

A person with diabetes is defined as someone with a fasting blood sugar of 140mg/dL or higher (Mahler & Adler, 1999). Typical signs and symptoms of this disease include polydipsia and polyuria. As excess sugar accumulates in the bloodstream, fluid is pulled from the tissues, which can cause dehydration and producing an unusual thirst. As a result of the increased fluid intake, urine synthesis increases and polyruria subsequently occurs. Diabetes mellitus also triggers polyphagia since a depletion of insulin prevents sugars from being adequately transported into cells. This endocytotic dysfunction causes muscular and organ energy depletion, triggering the insatiable appetite. Despite eating more than usual to try and satiate hunger, people who suffer from diabetes may lose weight and may experience cachexia. Without the ability to metabolize glucose, the body uses alternative fuels stored in muscle and fat (lipolysis) instead. The inordinate glucose concentration that accumulates in the blood, therefore, exhausts and eventually compromises glomerular filtration capacity, which allows excess glucose to seep into the

urine. Glucosuria, therefore, is common in patients with a Type II diabetes diagnosis (Figure 1). Additional symptoms typically seen in these patients include chronic fatigue, irritability, frequent infections, retarded wound healing, blurred vision, retinopathy, neuropathy, and scleroderma diabeticorum (Campbell, 2000; Mahler & Adler, 1999).

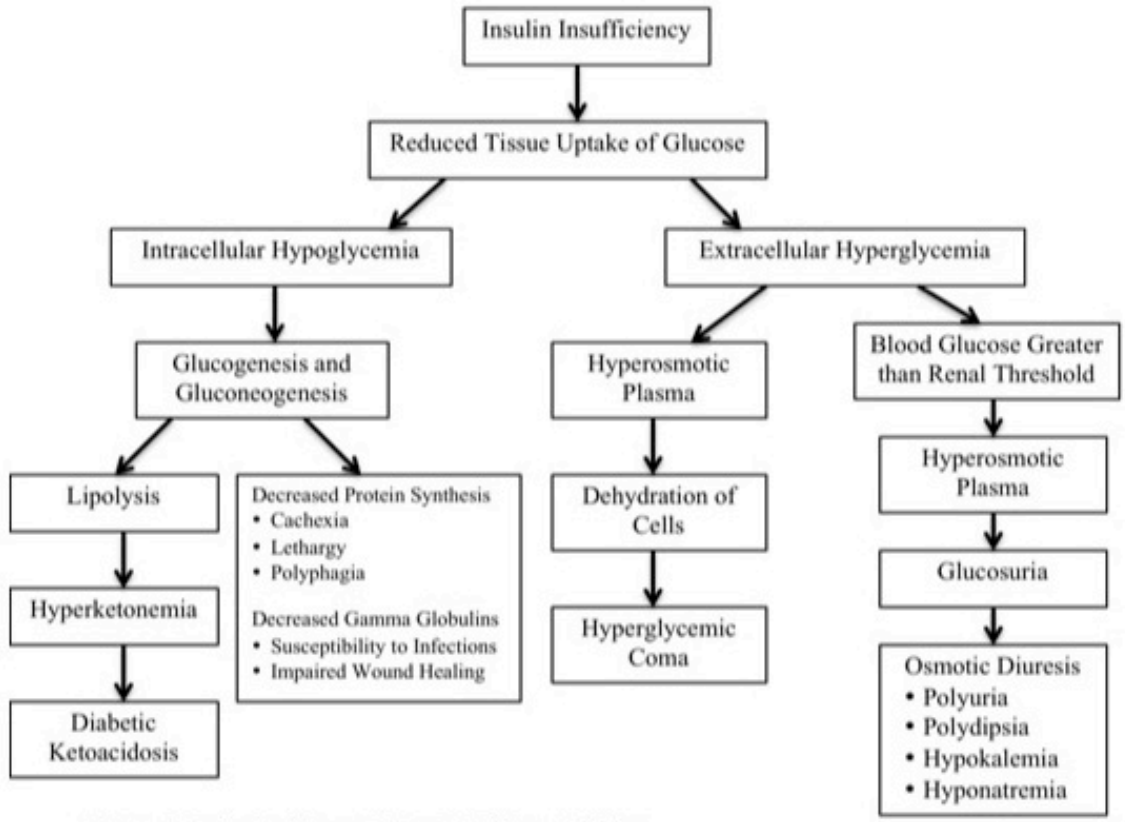


Figure 1. Pathophysiology of Type II Diabetes Mellitus.

Albumin and Type II Diabetes

Global prevalence of Type II diabetes mellitus has increased dramatically over the past two decades. According to Zakerkish, Shahbazian, Shahbazian, Latifi and Aleali (2013), the prevalence grew from about 30 million cases in 1985 to 177 million in 2000 and 285 million in 2010. If this trend continues, by 2030 more than 360 million people will be diagnosed with Type II diabetes mellitus. In the U.S., Type II diabetes is the

primary cause of end-stage renal disease, non-traumatic limb amputations, and blindness in adults. With the increasing prevalence of Type II diabetes worldwide, it is expected that this chronic disease will remain among the primary causes of human mortality (Zakerkish et al., 2013).

Uncontrolled Type II diabetes may gradually progress towards renal failure. One of the first clinical symptoms of diabetic nephropathy is microalbuminuria, which progresses to macroalbuminuria soon thereafter. This continual loss of albumin in the urine due to kidney dysfunction is noted by a progressive loss in glomerular filtration rate. The loss of filtration rate finally leads to end-stage renal disease, requiring hemodialysis (Yokoyama et al., 2011; Zakerkish et al., 2013). The relationship between albumin and Type II diabetes is clear and finite and warrants further exploration.

Zakerkish et al. (2013) sought to investigate the correlation between urine albumin and a Type II diabetes diagnosis in a sample population ($N = 350$) of patients in Iran. In their cross-sectional study, the authors examined diabetic patients attending the Diabetes Clinic at Golestan Hospital from 2010 to 2011. Chi Square, 1-way ANOVA, multiple logistic regression, t tests, and linear regression analyses were conducting on study variables. The authors found that of the 350 participants, $n = 72$ patients (20.6%) had microalbuminemia and $n = 18$ (5.1%) had macroalbuminemia and hence albuminuria, suggesting that diabetic patients had higher prevalence rates of renal failure. Additionally, the authors found that duration of diabetes mellitus was extended with albuminuria (Zakerkish et al., 2013).

Hsu et al. (2011) enrolled $N = 738$ normoalbuminuric Type II diabetic subjects for

a prospective cohort study. The authors aimed to reassess the association between insulin resistance and microalbuminuria in these patients by following the patients from 2005-2009. Kaplan-Meier analyses and univariate Cox proportional hazards models were used to explore associations between insulin resistance. The authors found that insulin resistance is a strong predictor in determining the development of microalbuminuria within 5 years for Type II diabetic patients (Hsu et al., 2011). The study demonstrates the intimate relationship between albumin levels and type II diabetes mellitus.

Locatelli, Cavalli, Manzoni, and Pontoriero, (2011) investigated the impact of membrane permeability on survival in incident hemodialysis patients who were hypoalbuminemic (≤4 g/dL) and normoalbuminemic (>4 g/dL) as separate randomization groups. In their prospective, randomized Membrane Permeability Outcome (MPO) study the authors enrolled $N = 738$ hemodialysis patients from 59 European countries. Hypoalbuminemic patients accounted for $n = 567$ of the study population and 171 enrollees had albumin levels greater that 4 g/dL. Statistical analyses included Kaplan Meier and Cox proportional hazards models. After exclusion criteria, $n = 647$ patients were included in the survival analysis. Patients in both groups had similar baseline characteristics. The authors found that patients with serum albumin ≤4 g/dL had significantly better survival rates in the high-flux membrane permeability group compared with the low-flux group. The authors additionally considered the diabetic patients in their population ($n = 157$). A post-hoc secondary analysis of the diabetic subpopulation showed that high-flux membranes might significantly improve survival in diabetic patients. A relative risk reduction in mortality in patients with albumin levels ≤4

g/dL was 18.9% and 53.3% in diabetic and non-diabetic patients, respectively with high flux membrane use. No difference was found in patients with normal albumin levels (Locatelli et al., 2011). The comparative analysis between diabetic and nondiabetic groups based on baseline albumin levels informed the study design for this investigation.

Yokoyama et al. (2011) conducted an observational four-year cohort study to investigate the annual rate of glomerular filtration rate decline in association with albuminuria progression in Type II diabetes. The authors enrolled $N = 1002$ subjects of whom 699 were normoalbuminuric between 2004 and 2006. Inclusion criteria consisted of those patients that had been treated for diabetes or hypertension. Patients who visited the Jiyugaoka Internal Medicine clinic for at least 1 year, had more than three measurements of serum creatinine after 2004, and who had three measurements of urinary albumin to creatinine ratio at baseline and at follow up were eligible for inclusion. Patients with a serum concentration of greater than 132.6 μmol/L were excluded. Statistical analyses included linear regression model of time on glomerular filtration rate, chi square tests to determine significance of differences between groups, and multiple linear regression for the analysis of associations of variables with glomerular filtration slope values. The authors reported that patients with a Type II diabetes diagnosis and normoalbuminruria exhibited a steeper slope decline in glomerular filtration rate compared to those without Type II diabetes (Yokoyama et al., 2011). The methodology employed by Yokoyama et al. (2011) is noteworthy. The authors compared diabetic and nondiabetic patients to ascertain possible glomerular filtration rate declines and albuminuria in a Japanese population. This study similarly examined patient records

with and without a Type II diabetes diagnosis to identify possible albumin level differences but in a different population.

Lorenzo et al. (2009) also examined a cohort of 333 patients with chronic kidney disease of which 46% were diabetic. In their retrospective, longitudinal, observational study, patients that were referred to a nephrology clinic at the University Hospital of Canary Islands were examined for 7.5 years to clarify whether diabetes is a predictor of more rapid decline of renal function, in patients with moderate to severe chronic renal disease. During this period, baseline and follow up data were collected for $N = 407$ patients. After exclusion criteria, $n = 333$ patients who had more than three serum creatinine tests sufficient to calculate the rate of decline in kidney function were included in the study. Patient characteristics were collected from electronic medical records, including anthropometric values, demographics, BMI, comorbidities, and smoking status. Patients were followed until dialysis initiation, death, or loss to follow up. Baseline laboratory tests included creatinine ratios, serum albumin, and hemoglobin. Statistical analyses included, univariate analyses, the Chi Square test, t tests, Kaplan-Meier, and Cox proportional hazard regression. Confirmed using a time-dependent Cox model, of the 333 patients in the study, the results showed that at comparable levels of albuminuria, chronic kidney disease development was similar in patients with and without diabetes (Lorenzo et al., 2009), in stark contrast to Yokoyama et al. (2011) study outcomes and counter to what might be reasonably expected from the research hypothesis proposed by this study. Unlike Yokoyama et al. (2011), who's study outcomes showed that a Type II diabetes significantly influenced albuminuria because of decline in glomerular filtration

rate, Lorenzo et al. (2009) found conflicting results. For their study, the results showed that in both the diabetic and nondiabetic groups, chronic kidney disease evolved in a similar manner. The results, however, reveal a literature chasm that this research aimed to narrow.

The study design employed by Lorenzo et al. (2009) aligns with the proposed study design for this research inquiry. The authors retrospectively analyzed medical records for their population. This proposed study extends the research protocol used by Lorenzo et al. (2009), using the same retrospective approach, the same diabetic and nondiabetic groups, but with a different and larger sample population. The author's comparison of both diabetic and nondiabetic groups reflects the methodology that was employed for this study. Data collection and analysis also reflected study protocols employed by Lorenzo et al. (2009). For their study, serum albumin levels were examined both at baseline and through the follow up period. Similarly, this study examined serum albumin levels at 3 and 6 months post baseline to identify possible albumin level differences in the study's sample population.

Albumin and chronic kidney disease.

The relationship between albumin levels and chronic kidney disease (CKD) is remarkable. Equally remarkable is the importance of monitoring and maintaining normoalbuminemic levels in these patients with this chronic disease. CKD describes abnormal kidney function and/or morphology. The definition of CKD is based on the presence of kidney damage manifested by albuminuria or decreased kidney function based on glomerular filtration rates. Therefore, serum albumin levels in dialysis patients

are strong predictors of CKD and risk of mortality (Iseki, Kawazoe, & Fukiyama, 1993). Numerous studies have studied the relationship between albumin and CKD. The following section presents selected studies investigating this association.

Goldwasser, Kaldas and Barth (1999) investigated albumin and creatinine as mortality predictors of survival in dialysis patients. The authors recruited 195 patients undergoing maintenance hemodialysis. The cohort was comprised of African American, Caucasian, and Hispanic patients all of whom had a Type II diabetes mellitus diagnosis. The authors found that the first half-year on hemodialysis showed a 13% increase in serum albumin levels, but showed a slow, progressive decline in albumin levels in long-term patients, correlating with patient mortality. The authors found that newly diagnosed patients that initiated hemodialysis showed some albumin improvements within months 1-6, but long-term dialysis patients showed a progressive serum albumin level decline (Goldwasser et al., 1999).

Leavey, Strawderman, Young, Saran, Roys, Agodoa, Wolfe and Port (2000) also demonstrated that low serum albumin concentrations predict increased mortality in hemodialysis patients. For this study, the authors measured cross-sectional and longitudinal predictors of serum albumin and found that among the various predictors serum albumin levels were significantly lower in patients with diabetes. The authors found that various predictors such as a diabetes diagnosis were associated with serum albumin. The Goldwasser et al. (1999) and Leavey et al. (2000) studies support the assertion that serum albumin levels are strong predictors of mortality and are closely associated with several exposures and chronic disease diagnoses such as diabetes. This

underscores the reason why serum albumin should be frequently and aggressively monitored in order to make necessary adjustments to dialysis dose, diabetic hemodialysis diet, as well as for other therapeutic strategies. The Goldwasser and Leavey studies were particularly informative to this investigation because the recruited populations were Type II diabetes mellitus patients on hemodialysis and because the studies examined albumin levels over time.

Considering the known vital functions of albumin previously discussed and the importance of maintaining adequate levels in the blood, there are differences in serum albumin levels amongst various ethnicities. Noori et al. (2011) assert that higher serum albumin and creatinine and various other indices are seen in African Americans versus Caucasians. $N = 1300$ patients on maintenance hemodialysis were recruited for their prospective cohort study. Inclusion criteria included outpatients on hemodialysis from eight Davita clinics in Los Angeles. Of these, 893 signed the IRB consent form. After, exclusion of Asians, Indians, and those of unknown racial/ethnic background, the authors compiled 799 total participants. Among these were $n = 520$ whites, of which $n = 457$ were Hispanics and 279 African Americans. The authors followed these patients for 6 years and found the African American group had leaner muscle mass indices, but had higher BMI, lean body mass and mid-arm muscle circumference when compared to their white counterparts of mostly Hispanic descent. Furthermore, this group showed higher albumin, prealbumin, creatinine and homocysteine levels. Intriguingly, and perhaps paradoxically, despite having poor survival indicators, the results also showed a 2.4 and 4.1 death risk in African Americans and Whites respectively, suggesting that albumin as

well as interleukin-6 may have a protective, mitigating role in the patient's survival in African Americans (Noori et al. 2011).

Choi, Karter, Liu, Young, Go, and Schillinger (2011) disagree with Noori et al. (2011). In their prospective survey study, the authors recruited diabetic patients from a health care system in Northern California from the DISTANCE study. A large sample of $N = 20,030$ subjects responded to the survey of which 3,629 individuals were excluded. Ethnic minorities were well represented, with a larger proportion of Hispanics, Filipinos, Asians, and African Americans. The authors found that there were 981 confirmed incident albuminuria events in three years, with Hispanics and Asians only showing 8% albuminuria incidence and hence a higher mortality risk. In comparison, African Americans, Filipinos, and Asians, showed an albuminuria incidence of 11%, 10%, and 9%, respectively (Choi et al., 2011), contradicting the death risk outcomes from the Noori et al. (2011) research findings. Both studies, although contradictory in the result outcomes, do reflect possible differences in albumin levels across various ethnicities.

Chronic dialysis patients show significantly lower levels of serum albumin. This is especially formidable in hemodialysis patients with a Type II diabetes mellitus diagnosis (Iseki, Kawazoe, & Kukiyama, 1993). Iseki et al. (1993) assert that serum albumin is a strong predictor of death in dialysis patients. In their prospective study, the authors recruited $N = 1,982$ patients that had survived at least 1 year of maintenance hemodialysis. Those that did not satisfy the inclusion criteria were removed. A cohort of 1,243 participants were recruited. Of these, 104 had died, 16 underwent renal transplantation and 5 had been transferred. The remaining 1,222 patients were used for

analysis. The authors reviewed the medical records and compiled a treatment profile for each participant, including serum albumin laboratory values. In both the deceased group and the participant group serum albumin levels were significantly lower and therefore a strong predictor of death in maintenance hemodialysis (Iseki et al., 1993).

Similarly, Liu, Peng, Liu, Xiao, Chen, Huang, and Liu (2008) conducted a clinical study by analyzing the clinical records of $N = 514$ end-state renal disease Chinese patients. The authors sought to ascertain the level of renal function and the relationship of renal function and serum albumin at the start of maintenance hemodialysis. The authors retrospectively examined these records from 2001 to 2007 and found that a wide variation existed in renal function at the initiation of hemodialysis in this population (Liu et al., 2008). Comparably, Sridhar and Josyula (2013) also retrospectively analyzed 57 end-state renal disease hemodialysis patients. For their study, serum albumin levels were analyzed against several independent variables. Demographic and other clinical data were reviewed. The authors found that serum albumin had a significant correlation with serum albumin levels. Additionally, patients with Type II diabetes also showed significant correlations with the plasma protein. The authors confirmed that serum albumin is an effective marker of nutrition and inflammation and can consistently predict patient mortality. A serum albumin level of less that 3.8 g/dL confers a greater mortality risk in end-stage renal disease hemodialysis patients and is therefore an adequate indicator of patient prognosis and patient death (Sridhar et al., 2013).

Both the Iseki et al. (1993) and the Liu et al. (2008) studies were particularly informative to this study. In both, the authors reviewed clinical medical records, which

was the methodological approach used in this study. The Sridhar et al. (2013) study demonstrates a retrospective analysis of medical records, which aligns with the type of design used in this research study. The Iseki et al., (1993) and Liu et al., (2008) studies demonstrate the significance of analyzing serum albumin levels in hemodialysis patients and the impact albumin level fluctuations have, not only on subsequent hemodialysis treatments in terms of treatment dose, duration, and frequency, but also on patient hemodynamics and blood pressure maintenance, and muscle composition, tone and strength. For patients with diabetes, the serum albumin levels were especially affected in these studies and consequently the albumin clinical targets were not adequately achieved (Sridhar, et al. 2013).

To further establish correlations and potential differences between albumin levels among hemodialysis patients, Peacock et al. (2008) recruited $N = 307$ diabetic participants of whom 258 were on maintenance hemodialysis and 49 of whom did not have renal disease, which served as the control group. Blood samples were collected and serum albumin levels were analyzed for all participants. Among the diabetic group with renal disease, glycated albumin concentrations were significantly higher than those without renal disease. The author's prospective cohort study found that serum albumin, compared to other measurements, more accurately reflected glycemic control in diabetic hemodialysis patients (Peacock et al., 2008). This provides further evidence for the association between serum albumin concentration, CKD, and Type II diabetes in hemodialysis patients, and provided further justification for this research inquiry.

Type II Diabetes and Chronic Renal Failure

Mahbub et al. (2013) assert that diabetes is the most common cause of kidney failure. Approximately 180,000 people suffer from kidney failure as a consequence of diabetes. Renal failure cases resulting from diabetes account for nearly 44% of new cases. And, even when diabetes is controlled, the disease can lead to chronic kidney disease and kidney dysfunction. In the U.S., about 24 million people have diabetes and each year more than 100,000 people are diagnosed with renal failure (Mahbub, 2013). Several studies have found an association between Type II diabetes mellitus and chronic hemodialysis patients. The following are salient studies in the literature describing those relationships.

Marimoto et al. (2010) reveals a relationship between Type II diabetes and chronic hemodialysis. In their study, the authors investigated the characteristics of 43 hemodialysis patients that had survived more than 20 years of maintenance hemodialysis in terms of their blood chemistry, chronic disease, complications, blood pressure, body mass index, and the existence of chronic diseases such as diabetes. The participant's hemodialysis start dates were between 1974 and 1985 and they were followed prospectively until they died or were still alive as of 2005. The patients were divided into the survivor group and the deceased group. The results showed that long-term survivors shared five common characteristics: (a) initiating hemodialysis at a young age; (b) being diabetes mellitus free; (c) controlled cardiothoracic ratio; (d) a small decrease in weight during the long course of treatment; and (e) being hypercholesterolemia and hypertryglyceridemia free (Morimoto et al., 2010). Furthermore, the authors found that

serum albumin levels were lower in the deceased group with higher incidence of diabetes mellitus compared to the survivor group. The study demonstrated the strong relationship between diabetes mellitus and chronic hemodialysis. Additionally, the study also showed a slight correlation between diabetes and albumin level decreases. This provides some evidence that, at least in this Japanese population, a Type II diabetes mellitus diagnosis might adversely influence albumin levels, potentially affecting patient prognosis and mortality risk compared to their nondiabetic, hemodialysis patient counterparts.

Mahbub et al. (2013) recruited 118 patients to participate in cross sectional study that would determine the primary etiology of their renal disease. For 9 months, the patients were monitored and the authors found that 44.1% of the patients suffering from renal failure was due to a Type II diabetes diagnosis. The authors concluded, even though they had a relatively small population and was limited to a single center dialysis unit, that diabetes is the leading cause of renal failure in hemodialysis patients (Mahbub et al., 2013). Sattar et al. (2012) conducted a similar study, expanding on the population size and dialysis centers used by Mahbub et al. (2013). In their HEMO Study, $N = 883$ diabetic patients were recruited to ascertain risk of death of these patients. The authors found the hazard ratio for diabetes increased with each year, suggesting that risk of death associated with diabetes in ESRD increases over time and this relationship is underappreciated using statistical survival methods. The studies by Mahybub et al. (2013) and Sattar et al. (2012) establish a positive correlation between renal disease and Type II diabetes mellitus.

Girman, Brodovics, Alexander, O'Neill, Engel, Williams-Herman, and Katz (2011) further examined studies on patients with Type II diabetes. The authors reviewed the Full Feature General Practitioner Research Database. This database contains current electronic health records collected from 590 general medicine practices. A cohort of Type II diabetes patients (n = 119, 966) and those without the disease (n = 1, 794, 516) were sampled from the large database. The authors found, that from 2003 to 2007, acute renal failure was 198 per 100,000 person-years in patients with Type II diabetes and only 27 per 100,000 person-years among patients without the disease. The authors concluded that patients with a Type II diabetes diagnosis were at higher risk for renal failure compared with patients without diabetes. This study, in particular investigated a cohort of patients with and without a Type II diabetes diagnosis in a large population, similar to the design that was employed in this study. To achieve statistical power, Girman et al. (2011) established a significant relationship between Type II diabetes, renal disease, and hemodialysis patients but with a larger population size than that employed by Mahbub et al. (2013) and Sattar et al. (2012). The Girman et al. (2011) study, in particular informed this proposed study about an appropriate population sample size.

The relationship between Type II diabetes and renal failure is well described in the literature (Mihaescu et al., 2012). Renal disease is one of the most serious complications of Type II diabetes mellitus and is the leading cause of end-stage renal disease in the United States, requiring renal replacement therapy via various modalities including hemodialysis. As the population of patients with a Type II diabetes diagnosis

continues to grow, the diabetic nephropathy burden increases correspondingly (Mihaescu et al., 2012), providing the impetus to further investigate these relationships.

Hispanic Population Dimensions

Hispanic Biological Dimensions

Biological variations are those diverse, phenotypic manifestations that exist between people with respect to physical appearance such as skin and hair color and other visible physical characteristics, enzymatic and genotypic variations, electrocardiographic patterns, susceptibility to disease, nutritional preferences and deficiencies, and psychological characteristics (Tienda & Mitchell, 2006). While it is accepted that individuals may differ culturally, the biological differences evident among people in various ethnic groups are rarely considered, especially for the administration of medical care.

Comprehensive efforts to provide a description of the health and health behaviors of Hispanics are complicated by numerous factors (Tienda & Mitchell, 2006). Hispanics living in the United States represent an increasing diversity of national origin subgroups. Newer groups, such as Dominicans, Salvadorans, Guatemalans, and Colombians, have grown rapidly, adding their numbers to well-established populations of Mexican, Puerto Rican, and Cuban origin groups. The information that is available about origin subgroups suggests that health status differs across these subgroups. Additionally, the health of U.S. Hispanics differs by generational status. On numerous dimensions, foreign-born Hispanics have better health indicators than their U.S.-born counterparts. Moreover, among the foreign-born, health status and health behaviors may differ by degree of

American acculturation.

From this perspective, the gaps in the available data on the health and health behaviors of Hispanics impose significant limitations. One frequent and noteworthy issue is the lack of specific data for subgroups of Hispanics defined by national origin and generation in the United States. Most studies categorized Hispanics into a single group or they focus solely on Hispanics of Mexican decent, who are by far the most numerous. The relative lack of detailed epidemiological data on the incidence and prevalence of common and important diseases such as cardiovascular disease or Type II diabetes is yet another important problem. Moreover, for many such conditions, data are unavailable to assess incidence or prevalence according to immigrant status or, among the foreign-born, by length of residence in the United States and degree of acculturation (Tienda & Mitchell, 2006). These biological factors that exist among Hispanic subgroups are important considerations for the diabetic and renal health statuses in patients receiving maintenance hemodialysis.

Hispanic Behavioral Dimensions

Although a genetic etiology has been established, for some Hispanics eating behaviors is known to trigger Type II diabetes (Tuomilehto, 2001). Poor nutritional choices by this population exacerbate diabetes and are also linked to other related conditions such as hypertension and renal failure. There is also strong evidence supporting the fact that risk factors such as obesity and a sedentary lifestyle are primary, nongenetic factors of this disease. Other behavioral risk factors include cigarette smoking and excessive alcohol consumption (Schneiderman, 2004).

Evidence shows that a diet high in saturated fats and low fiber content may increase the risk of Type II diabetes (Bazzano, Serdula, & Liu, 2005). Typical Hispanic cuisine is high in saturated fats and low in fiber content, especially those residing in communities bordering Mexico (Ritchie, Calloway, Murphy, Receveur, Lamp, & Ikeda, 1995). Monounsaturated or polyunsaturated fats, however, appear to have a beneficial effect on insulin activity by increasing insulin sensitivity. Another dietary factor in developing Type II diabetes is whole grain consumption. According to Bazzano et al. (2005), whole grain consumption provided a protective quality towards significantly lowering the risk of developing Type II diabetes. The author showed that there was a 27% decrease risk of developing diabetes when 33 servings of whole grain foods were consumed per week.

A sedentary lifestyle is a known risk factor for Type II diabetes (Bazzano et al., 2005; Tuomilehto et al., 2001). The protective effects of physical activity, even if infrequent, for the diabetic cannot be overemphasized. This physical inactivity is especially pervasive in the Hispanic community. Increased physical activity amplifies tissue sensitivity to insulin. Improvements in cardiorespiratory fitness and muscle strength by engaging in at least four hours of exercise per week was found to have a significant reduction in the risk of developing Type II diabetes (Tuomilehto et al., 2001), and this included any type of sports, household work, gardening, or work-related physical activity which showed similar reduction in risk. Hispanics that participated in diabetic studies involving increased physical activity reported that having a disability, back pain, or ankle or foot injuries limited their ability to engage in or maximize physical activity.

Others reported that inclement weather, unsafe neighborhoods, and insufficient time were also factors that influenced their opportunities to engage in exercise (Castillo et al., 2010). Nevertheless, any amount of modified physical activity confirmatively showed a reduction in both diabetic risk and Type II diabetes complications.

In the Hispanic community behavioral expression is based on customs and Latin traditions. Young men are influenced to drink and smoke at an early age (Ritchie et al., 1995). According to Bazzano et al. (2005), smoking may increase risk of diabetes by causing elevated blood glucose levels, increased insulin resistance, and higher levels of glycosylated hemoglobin than do non-smokers (Bazzano et al., 2005). Additionally, excessive alcohol consumption contributes to excess energy intake and obesity, disturbance of carbohydrate and glucose metabolism, and liver dysfunction. Hispanic diet is influenced by deep-rooted customs and traditions and may often be inadequate and deleterious to health. This is an important consideration for this study; examining hematology profiles for this population, might identify differences in albumin levels based on Type II diabetes.

Not only does the traditional Hispanic diet consist primarily of high fat content and low fiber food dishes (Bazzano et al., 2005), Hispanic desserts are largely influenced by traditional Mexican sweat bread, which largely is high in sugar content that may potentially elevate blood glucose levels. “Panaderias,” or Mexican sweet bread businesses, abound in Hispanic communities, making it difficult for diabetics to resist temptation and make healthier food choices. Additionally, dietary fiber has been shown to delay absorption of carbohydrates after a meal and thereby decreases the response to

other dietary carbohydrates. Coupled with a low fiber diet, a diet high in sugar content exacerbates Type II diabetes mellitus. Studies show that people who have diabetes tend to lack enough fiber in their diet (Chaufan, Davis & Constantino, 2011). Because dietary fiber helps slow down the rate of glucose that enters the bloodstream, it is considered a protective agent that helps prevent diabetes. Hispanics, however, albeit erroneous, perceive fiber consumption as mostly used for medicinal reasons, such as impaction or other digestive complications. Access to healthy foods in Hispanic communities, as well as access to recreational areas such as gyms or parks is limited in these communities which makes reducing or preventing diabetes incidence in this community a challenging endeavor (Chaufan et al., 2011).

Hispanics express their eating habits based on traditional Mexican customs (Noble, 1991). Alimentation for Hispanics consists largely of the following regimen. First, a light “desayuno,” or breaksfast, is served. This is followed by a lunch, or “el almuerzo,” consisting of traditional staple foods like eggs, beans, and tortillas, which is usually the main meal of the day. According to Mexican tradition, it is customary for adult family members and children to come home from work or school for about two hours to be together for this meal. “La siesta,” which is a rest period taken after lunch, is known to be a common practice among adult Hispanics. In the early evening, “la merienda,” a light snack of coffee and rolls or sandwiches is served. This meal is often informal. Finally, in the evening, often as late as 9:00 p.m., “la cena,” a small supper, concludes the day's meals (Noble, 1991). This eating regimen is not conducive of a healthy lifestyle and reflects some of the primary risk factors that trigger Type II

diabetes. First, the number of meals is more than the typical three-meal system adopted by non-Hispanic individuals. Also, “la siesta” contributes to the sedentary lifestyle that studies show leads to increased risk of diabetes (Bazzano et al., 2005; Tuomilehto et al., 2001). Lastly, eating supper at such a late hour allows for dietary fats to be stored viscerally while sleeping (Yurugi et al., 2012). Hispanic dietary behaviors must therefore be considered as potentially influential when investigating this chronic disease in this population.

Behavioral social determinants of health are largely centered on dietary issues. Dietary behaviors are closely aligned with culture and customs in this community. Studies show that a diabetics’ primary barrier to trying to maintain and adhere to a proper diet is being in the presence of friends or relatives that are non-supportive; when they indulge in foods with little or no nutritional value in the presence of the diabetic, this can be deconstructive in their efforts to prevent weight gain (Wen, Parchman, & Shepherd, 2004). Other important dietary behaviors, influencing the health of this population are access to healthy foods and recreational areas. The accessibility of farmers markets, healthy food stores, parks and other recreational areas are scarce, which only exacerbates the health issue in this population (Chaufan et al., 2011).

Hispanic Cultural and Religious Dimensions

Barriers that exist to address the health issue among Hispanics are not restricted to behavioral dietary factors. Cultural and religious barriers also exist. For example, Hatcher and Whittemore (2007) address the concept of “susto” as a cultural cause of diabetes. Occurring during a specific startling event, “susto” literally means ‘‘fright of

surprise." Hispanic adults believe that diabetes already exists in their body, and the strong emotional response to a startling event triggers the body's susceptibility to diabetes. Erroneously, to them, being overweight is protective against "susto." In terms of religious aspects, Hispanics' strong affiliation and dedication to the Catholic Church and their dutiful connection to God through prayer influences their daily life in a significant way. Hispanics strongly believe that their priest or prayer could help with their diabetes and therefore removes the need for subsequent doctor consultations. They believe that prayer and religious guidance prevents stress and anxiety and allows them to adhere to their initial treatment regimens. This, in turn, helps better cope with "susto," which may lead to improved diabetes outcomes (Zaldivar & Smolowitz, 1994).

Hispanic Psychosocial Dimensions

Depression is two times more prevalent among Hispanics with Type II diabetes (Fortmann, Gallo, Walker, & Philis-Tsimikas, 2010). It is an important factor to consider when investigating and addressing diabetes health disparities in this population. Hispanics express the highest incidence of depression than any other ethnicity. Diabetes and depression only intensifies adverse effects and complications such as poorer compliance with treatment recommendations, worse glycemic control, increased diabetes complications, and higher overall mortality rates (Fortmann et al., 2010). According to Fortmann et al., participants in her study who reported greater self and neighborhood support expressed less depressive episodes than those that did not have similar support systems. Furthermore, of those that reported less depression, improved diabetes self-management was seen. The authors further assert, that individuals with Type II diabetes

who experience comorbid depression manage their diabetes less effectively, are less socially and physically active, and are more likely to express feelings of hopelessness and despair. These individuals report an overall dismal perception of life and their future than their non-depressed counterparts. The impact that depression has on glycemic control and health outcomes and the impact support systems have on disease management and depression in this population is significant because it represents a possible direction by which depression and health outcomes can be prevented, reduced or eliminated (Fortmann et al., 2010).

A diabetes diagnosis provokes a grieving process with characteristic rejection or anger responses that are typically seen in chronic illnesses. The progressive nature of the disorder compounded by secondary complications, may add further psychological stress (Zambanini, McIntosh, Mitchell, & Catalan, 1999). Stress hormones are released in respond to daily work or living working conditions. Cortisol and the catecholamines epinephrine and norepinephrine are secreted in response to these stressors. Although these hormones provide protective effects, including maximizing muscular exertions, sustained long term secretion of these hormones because of persistent stress can lead to a chronic health condition such as Type II diabetes. Increased and prolonged levels of these hormones have been correlated with increased risk of developing diabetes (Schneiderman, 2004). Increased levels of cortisol causes adipocyte deposition deep in the abdomen and in the coronary arteries. Visceral fat accumulation is correlated with increase diabetes risk and fat deposition in the coronary arteries may lead to atherosclerosis (Yurugi et al., 2012). In the Hispanic population, abdominal fat

accumulation is expressed with larger, pear-shaped physiques. The magnitude of this expression is evidenced by increases in angioplasty and stent procedures and other heart related complications requiring drug interventions or surgery (Schneiderman, 2004).

Hispanic External Dimensions

The socioeconomic status of Hispanics is comparable to that of African Americans and significantly lower than that of non-Hispanic Whites (Morales, Lara, Kingston, Valdez, & Escarce, 2002). This is reflected in most measures of socioeconomic status, including personal and family income, poverty rates, educational attainment, and occupation. In 1997, for example, 26% of Hispanic and African American families lived in poverty, compared with 7% of White families. While the median family income for all Americans was $42,299, the median income for Hispanic families was $26,178. Among Hispanic subgroups, socioeconomic status varies significantly. Generally, Mexicans and Puerto Ricans are the worst off, while Cubans and South and Central Americans are the best off. In 1997, the median family income was highest for Cubans, followed by Mexicans and Puerto Ricans; the poverty rate was greatest among Puerto Rican families (33%), followed by Mexican families (28%), South and Central American families (19%), and Cuban families (13%). Educational attainment, as the proportion of the population to go beyond high school, was greatest among Cubans (65%), followed by South and Central Americans (63%), Puerto Ricans (61%), and Mexican Americans (49%). Rates of occupation in high-risk/low-status occupations were highest among Mexicans (77%), Puerto Ricans (68%), and South and Central Americans (68%), and lowest among Cubans (53%) (Morales et al., 2002). The socioeconomic status of this

population may influence the ability of patients to adequately manage their diabetes and may therefore influence albumin levels.

Summary

The ubiquity of albumin provides the body with the protein needed for growth maintenance and tissue repair and supports the oncotic blood pressure and hemodynamics (Brin & Christensen, 2006). For patients undergoing maintenance hemodialysis, albumin found in the blood aids with fluid removal by drawing extra fluid from edematous tissues back into the blood, where it can then be removed by a dialyzer (Fresenius Medical Care, 2013). Seminal research conducted by Dutrochet and Nollet laid the foundation for filtration system dialyzers currently used for hemodialysis patients. Furthermore, Pfeffer and van't Hoff elucidated osmotic pressure principles that not only frame physiological chemical and biological processes, but also govern the way dialyzers and kidney dialysis machines filter a dialysis patient's blood from toxins and waste products that accumulate during the interdialytic period. As a consequence of their disease, patients with Type II diabetes suffer renal dysfunctions ranging from renal insufficiencies to chronic kidney disease due to the kidney's compromised ability to filter albumin. The greater the severity of the renal disease, the greater the decreases in albumin levels found in the blood plasma and hence the greater the degree of albuminuria (Stoian et al., 2012). The decreased serum albumin levels are most extraordinary in Hispanic American hemodialysis patients with diabetes. Type II diabetes prevalence is 14% in the Hispanic population (Black, 2002). This group suffers a higher risk of mortality and microvascular complications including renal disease. Because of the hyperglycemic filtration strain imposed on the

kidneys and eventual glomerular destruction, albuminuria is often seen in Hispanic patients with Type II diabetes (Choi, Karter, Liu, Young, Go, & Schillinger, 2011). As presented in this literature review, numerous studies confirm these clinical indices and disease trends in the Hispanic population.

This literature review has elucidated information about albumin levels in the Hispanic population on maintenance hemodialysis. Albumin levels are lower in this group since the incidence of diabetes is higher in this population. The higher occurrence of renal failure and hence improper renal filtration lowers albumin levels markedly in Hispanic, hemodialysis patients (Black, 2002). The number of Hispanics requiring hemodialysis has consequently risen by 70% between 1996 and 2001 (Lash, Vijil, Gerber, & Go, 2005), correlating with observations that this population is the fastest growing demographic in the U.S. (Kanna, Fersobe, Soni, & Michelen, 2007). There exists a paucity of literature on differences in albumin levels of Hispanic patients with and without a Type II diabetes mellitus undergoing maintenance hemodialysis. The differences in diabetes incidence in the Hispanic population suggest albumin levels may also be different in this population. This literature review reveals a clear literature gap, which this research study aimed to fill. Furthermore, not only does the identification of potentially modifiable factors associated with albumin levels have the potential for translational therapeutic implications, the outcomes from this study can be useful for clinical risk stratification. Hence, this provides the opportunity to make an impactful contribution to positive social change.

This quantitative, cohort study employed a retrospective approach, analyzing medical records collected and compiled at seven dialysis clinics in San Antonio, Texas. The study evaluated possible differences in serum albumin levels in a population of Hispanic patients receiving maintenance hemodialysis with and without a Type II diabetes diagnosis for comparative analysis. Data were extracted and analyzed from CMS-2728 forms on the health status and renal measures from medical records of Hispanic patients on hemodialysis treated at Fresenius Medical Care-NA's designated renal dialysis clinics. The study examined associations between the outcome variable albumin and the independent variable Type II diabetes. Chapter 3 will discuss the methodology of this research study.

Chapter 3: Research Method

Introduction

It is well understood that hypoalbuminemia manifests in a plethora of different diseases and disorders (Haller, 2006; Kaysen et al., 1995). It is therefore a reliable blood chemistry value used in a variety of settings to help diagnose disease, to monitor changes in health status with treatment or with disease progression, and as a screen that may indicate the need for subsequent laboratory testing. Hence, low albumin levels can reflect diseases in which the kidneys cannot prevent a depletion in albumin in the blood due to its leakage from the bloodstream into the urine (Girman et al., 2011).

One of the earliest signs of kidney damage is albuminuria. Albumin's utility in fluid dynamic maintenance in the body is well established in the literature (Haller, 2006; Stoian, Stoica, & Radulian, 2012). Through fundamental osmotic principles and pressure theories, the kidneys filter toxins from the blood, while glomerular membranes disallow proteins from permeating through in order to maintain normal fluid dynamics and homeostatic oncotic blood pressure. Physiologically, proteins should be reabsorbed in the blood and not be allowed to escape into the urine. However, if the kidneys are damaged or diseased, renal filtration capacity is compromised and albumin may seep into the urine (Haller, 2006; Stoian et al., 2012).

Type II diabetes is a chronic disease that exposes the kidneys to an inordinate amount of glucose that can damage the filtration system of the kidneys (Fukuoka et al., 2007). The hyperglycemia exhausts the glomerular membranes, allowing albumin to seep into the urine and thus lowering albumin levels in the blood. The disease is characterized

by increased plasma glucose levels, which modify blood plasma proteins by a non-enzymatic reaction referred to as glycation. Protein glycation leads to formation of toxic molecules. In diabetes, the accumulation of these toxic end products is accelerated and contributes to pathogenesis of diabetic sequelea (Fukuoka et al., 2007).

Blood plasma proteins are the first to get modified as they are directly exposed to higher glucose concentrations (Peakcock et al., 2008). A number of plasma proteins have been identified. Human serum albumin, as one of most abundant plasma proteins, is heavily glycated in diabetes. Since albumin constitutes more than 50% of plasma proteins, any variation in levels of albumin may change the stoichiometry of glycation of other plasma proteins' glycation. In patients with a Type II diabetes diagnosis, albumin synthesis and secretion is therefore decreased due to insulin deficiency. Consequently, it can be reasonably expected that albumin levels decrease in diabetes and may affect plasma protein glycation.

I investigated if a difference in serum albumin levels exists between adult Hispanic patients undergoing hemodialysis treatments due to renal disease associated with and without Type II diabetes. To test the hypothesis of possible albumin level differences, a review of the medical records of this cohort of patients to quantify pre, post, and peritreatment serum albumin levels was conducted. Furthermore, the study aimed to ascertain if albumin levels continue to follow any patterns observed from hemodialysis treatment onset to 3 and 6 months post onset.

This chapter includes an outline of the selection of study design for this investigation, the study population and sampling decisions, data collection procedures

and methods, and the statistical analysis planned to test the hypothesis concerning the potential albumin level differences in adult, Hispanic patients with and without a Type II diabetes diagnosis, undergoing maintenance hemodialysis, possible albumin level differences that may exist within these groups, and to determine if there is an association between serum albumin, Type II diabetes, and known predictors that may modulate albumin levels in this sample population.

Research Design

The intent of this investigation was to ascertain potential albumin level differences and patterns in a population of Hispanic patients undergoing maintenance hemodialysis with and without a Type II diabetes diagnosis, and to determine if an association between albumin levels, Type II diabetes, and known predictors exists. The conceptual framework that underpins this study was elucidated in Chapter 1, and the literature review presented in Chapter 2 provides further substantiation to the merit of this study. The quantitative design of this study undertook a deductive, systematic approach, employing statistical and computational methods of measurement to test the hypothesis that may reveal and quantify possible differences in albumin levels (dependent variable) in hemodialysis patients with and without a Type II diabetes diagnosis (independent variable) (Creswell, 2009). This study was observational in nature in that there were no interventions or manipulations of the conditions under study. The selected population was merely observed and exposures or interventions occurred based upon their own choice (Aschengrau & Seage, 2008).

A cohort study is one of the most common observational and epidemiological research designs (Thiese, 2014). Cohort studies are used to evaluate two groups from within a defined population, one with a known exposure and the other without. These groups are then followed prospectively for an established time period to ascertain whether a disease occurs at a greater frequency and/or magnitude when compared to the non-exposed group. For this study, the exposure is Type II diabetes mellitus. Cohort studies, although common and powerful, however, cannot determine causality, but can suggest an association or correlation (Thiese, 2014).

The research questions for this proposed research are:

Research Question 1. Is there a difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment?

H_O1: There is no difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment.

H_A1: Differences in serum albumin levels are observed between Hispanics with and without Type II diabetes initiating hemodialysis treatment, (H_O is false).

Research Question 2. Is there a difference in serum albumin levels over time (baseline, 3 months, and 6 months post baseline) between Hispanics with and without Type II diabetes following hemodialysis treatment?

H_O2: No albumin level differences are observed over time (baseline, 3 months, and 6 months post baseline) between Hispanics with and without Type II diabetes following hemodialysis treatment.

H_A2: Albumin level differences are observed over time (baseline, 3 months, and 6 months) between Hispanics with and without Type II diabetes following hemodialysis treatment.

Research Question 3. Is there a relationship between serum albumin, Type II diabetes and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients?

H_O3: There is no relationship between serum albumin, Type II diabetes and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients.

H_A3: There is a relationship between serum albumin, Type II diabetes and known predictors (e.g., hypertension, peripheral vascular disease, and infection/inflammation) that may modulate albumin levels in Hispanic dialysis patients.

A historical, retrospective analysis of Center for Medicare and Medicaid Services (CMS)-2728 forms and treatment records of hemodialysis patients was conducted to address the research questions for this study. The design is consistent with the state of knowledge in this field, as numerous studies employ a similar design and analysis model (Dalrymple et al., 2013; Jolly et al., 2011; Lukowsky et al., 2012; Murthy et al., 2005; Ricks et al., 2011; Ricks et al., 2012; Yan et al., 2013). Since all relevant events have already occurred, retrospective cohort designs are generally conducted within a small time frame at a minimal cost (Thiese, 2014). They are powerful to study rare exposures and offer the most unambiguous determination of a temporal sequence. However, for

historical designs, although time and cost efficient, data reliability may be compromised since they were recorded in the past. Information about confounders may be unavailable because they were not considered when the study was initiated. Although these factors may pose some research challenges, the nature of a retrospective cohort design minimizes time and resource constraints (Thiese, 2014).

Population Setting and Sample

Fresenius Medical Care-North America (FMC-NA) is the world's largest integrated provider of products and services for individuals undergoing dialysis due to chronic kidney failure, a condition that affects more than 2.1 million individuals globally (Fresenius Medical Care, 2013). FMC-NA provides renal services to people throughout the United States, Mexico, and Canada through an expansive network of more than 2,100 dialysis facilities in North America. Vascular access centers, laboratory, pharmacy and affiliated hospitals, and nephrology practices provide individualized renal supplementation therapies for patients. FMC-NA is also the continent's leading producer of dialysis equipment, dialyzers and related disposable products, and is a major supplier of renal pharmaceuticals (Fresenius Medical Care, 2013).

With appropriate permission from FMC-NA's research department (Frenova Renal Research) and Walden's Internal Review Board, a request was submitted for permission to access patient medical records at Village Oaks Dialysis Center (#8856), Southeast Dialysis Center (#1664), Northwest Bexar County Dialysis Center (#1648), Alamo City Dialysis Center (#8861), Central San Antonio Dialysis Center (#8855), West Bexar Dialysis Center (#6618), and Ingram Dialysis Center (#8868) in San Antonio,

Texas, to review the medical records of patients attending these facilities. The numbers in parentheses are the official clinic facility numbers that will be used for identification and reference in this study. These seven facilities are FMC-NA's largest dialysis centers in the San Antonio region. Patients attend these facilities triweekly for dialysis treatments. To gain access to patient records, Frenova Renal Research required an application to be completed. These forms included the Clinical Research Approval application and the Governing Body Memorandum (Appendices B and C).

There are n = 125, n = 159, n =140, n = 106, n = 104, n = 97, and n = 106 patients attending #8856, #1664, #1648, #8861, #8855, #6618, and #8868, respectively. Between the seven facilities, there are approximately 837 cumulative patients, undergoing weekly dialysis therapies. Of these patients, Hispanics account for approximately 65%, 75%, 75%, 95%, 95%, 98%, 85% attending #8856, #1664, #1648, #8861, #8855, #6618, and #8868, respectively. Approximately, 75% of the Hispanic, hemodialysis facilities receiving treatments at these facilities have a Type II diabetes diagnosis. Clinic #8856 currently has 70 diabetic patients (56%). #1664 has 115 (72%), #1648 has 92 diabetic patients (66%), #8861 has 74 diabetic patients (70%), #8855 has 66 (63%), #6618 has 65 (67%) and #8868 has 70 (66%) diabetic patients currently on the clinics' dialysis schedules. While the number of diabetic patients at each facility does fluctuate slightly over the years, overall the large Hispanic, diabetic and nondiabetic population in these facilities at any given year provided a suitable number of medical records to access for review.

The study population consisted of a cohort of adult, hemodialysis patients attending seven local dialysis facilities in San Antonio, Texas. Each facility follows the exact dialysis treatment protocols and utilizes the same documentation system and instrumentation provided by the clinical services department. Protocols implemented by the clinical services department follow the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, which are recognized throughout the world for improving diagnosis and treatment of kidney disease (National Kidney Foundation, 2013).

The same data for both diabetic and nondiabetic patients were collected for each patient from CMS-2728 forms at treatment onset and subsequently from medical records based on their treatment schedules. For older patient records, those prior to 2012, data were extracted from paper records. After 2012, the data were collected and amassed from electronic medical records; the same data were extracted from both paper and electronic records and information about how the transition between paper and electronic records was implemented and whether there were any differences in data uniformity in terms of the type of data collected, data documentation and entry, data compilation, and data storage was also be presented. To ensure data collection quality control, duplicate entry or spot checks of a small population sample (10%) at each clinic was conducted. The sample population was randomly selected and then divided into two groups, those with a Type II diabetes diagnosis and those without one. Stratified random sampling was considered in this study. Statistical stratification of the data was conducted to identify possible serum albumin patterns per individual clinic to assess possible regional

differences in albumin levels and by gender to identify possible differences in albumin levels between diabetic and nondiabetic men and women on maintenance hemodialysis.

Random samples are commonly used in population sampling situations when reviewing historical data (Stat Trek, 2014). For this study, the samples that were selected for review were assigned random sequential numbers to keep records organized and more importantly to maintain patient confidentiality. These numbers were used solely to keep an accurate count of records being amassed per clinic and for categorization of diabetic and nondiabetic groups. The key feature to a random sampling strategy is that each unit in the population has an equal probability of being selected in the sample. Random sampling minimizes selection bias, and hence ensures obtaining a valid representative sample (Stat Trek, 2014). A stratified random sampling will help increase the study's validity and veracity. By isolating strata with shared attributes or characteristics, key population characteristics in the sample can be captured (Stat Trek, 2014). Stratified random sampling, therefore, was a suitable strategy for obtaining and amassing samples for this study.

As this was a retrospective analysis of data, the sampling frame consisted of a complete case analysis for all patients that were attending the dialysis facilities. This included those patients currently on the dialysis schedules and those that passed away, transferred, received a transplant, and for other reasons with complete data. A listwise deletion of patients that did not meet inclusion criteria was conducted. Inclusion criteria consisted of hemodialysis patients with and without a Type II diabetes diagnosis that remained in the dialysis facilities for at least six months and who had their albumin levels

documented on CMS-2728 forms at treatment onset and subsequently in medical records. Patients who moved away, received a transplant, changed dialysis modalities, discontinued treatment, were transients, had an allograft rejection, or passed away before the 6-month period were excluded from the proposed study.

The estimated sample size for this study was determined by G*Power 3.1 software. G*Power is a free, downloadable statistical analysis program commonly used in social, behavioral and biomedical research (Faul, Erdfelder, Lang, & Buchner, 2007). The software runs on most computer platforms, covering a wide variety of statistical tests, power analyses, effect size calculations, and graphic options. Because this is a quantitative, epidemiological study, G*Power 3.1 was appropriate to determine an adequate sample size.

A small effect size of 0.2 was selected based, in part, on personal interviews with clinical managers of each facility, which through their numerous years of experience assert that patients with a Type II diabetes diagnosis exhibit remarkable differences in achieving hemodialysis albumin goals compared to their nondiabetic counterparts. Additionally, the selected effect size corresponds to KDOQI guidelines, which report both normal and abnormal albumin clinical values. KDOQI guidelines suggest an albumin value goal of ≥4.0 mg/dL. Furthermore, the guidelines report that a mere 0.2% drop in albumin levels warrants albumin supplementation therapies. Additionally, KDOQI guidelines caution that a 0.5% drop from standard normoalbuminemic values hinders the patients from achieving prescribed hemodialysis goals and renders unfavorable patient prognoses and overt, deleterious signs and disease sequelea

(American Journal of Kidney Disease, 2007; National Kidney Foundation, 2002; National Kidney Foundation, 2013a; National Kidney Foundation, 2013b), further justifying the selected effect size. A 0.2 effect size was the most conservative estimate that lead to larger sample size requirement.

To quantify albumin levels at two different time intervals, the absolute and relative change was computed to compare potential albumin level changes among patients in both groups. The intervals used to quantify albumin levels were baseline CMS to 0 months, 0 to 3 months, 3 to 6 months, and 0 to 6 months. To compute the absolute change in albumin levels, the albumin level value at time Interval 1 was subtracted from the albumin level value at time Interval 2 to obtain the difference. For example, if a patient initiated hemodialysis with an albumin level of 2.3mg/dL and after 3 months the albumin level rose to 3.7mg/dL, then the absolute change was computed as 3.7mg/dL – 2.3mg//dL = 1.4mg/dL. The relative change was then the absolute change divided by the albumin level value at time Interval 1 times 100. Therefore, the relative change would be 1.4mg/dL ÷ 2.3mg/dL X 100% = 60.9%. For this quantitative study, an average was taken for all interval values and then plugged into the formulae to quantify the absolute and relative changes for the entire sample population used for this proposed study.

By convention, an alpha level of .05, power of .80, and small effect size of 0.2 was entered in the G*Power 3.1 software. Since an ANOVA was the planned statistical test to address Research Question 1, drop down menu settings on G*Power included the test family, which was set to *t* test, the statistical test, which was set to difference between two independent means (two groups), and type of power analysis, which was set to a

priori computation of required sample size given α, power, and effect size. The generated sample size for each group according to G*Power was 394, which yielded a cumulative cohort of 788 patient records. In accordance with the G*Power results, a cohort of 788 CMS-2728 forms and treatment records was the projected sample size to address Research Question 1. The longitudinal power analysis, which addressed Research Question 2, was also conducted using G*Power 3.1. To address Research Question 2, the same alpha, effect size, and power values will be inputted into G*Power. Since a repeated measures t-test was the planned statistical test to address Research Question 2, drop down menu settings on G*Power included the test family, which was set to *t* test, the statistical test, which was set to difference between two independent means (two groups), and type of power analysis, which was set to a priori computation of required sample size given α, power, and effect size. The generated sample size for each group according to G*Power was 394, which yielded a cumulative cohort of 788 patient records. In accordance with the G*Power results, a cohort of 788 CMS-2728 forms and treatment records was amassed to address Research Question 2. The summative cohorts, estimated by G*Power 3.1 yielded 788 cohorts to address both research questions. These calculated cohorts provided adequate sample sizes for this study.

The intent of this research was to ascertain possible albumin level differences or patterns in a cohort of Hispanic patients on maintenance hemodialysis. Given the rapid growth in minority populations in the United States, particularly the Hispanic population (Lopez, 2008), the selection of the study population was justified (Lopez, 2008). In 2002, Hispanics became the largest minority group in this country, accounting for 14.5% of the

U.S. population by 2005. According to the United States Census Bureau, Hispanics in Bexar County accounted for 63.2% of the total population in 2010 (United States Census Bureau, 2014). Furthermore, in the same year, 137,009, or 11.8% of the population, were diagnosed with diabetes, correlating with epidemiological evidence that it is the fourth leading cause of mortality in Bexar County (Texas Diabetes Institute, 2014). The diabetes health disparity in this region of Texas is a grave, widespread, and omnipresent public health issue.

The demand for health care among this population parallels its rapid growth. Lopez et al. (2008) asserts that Hispanics in the U.S. show a higher prevalence of Type II diabetes mellitus. The chronic nature of this disease increases the risk for developing renal disease. As a known risk factor for renal disease, Type II diabetes incurs a higher risk of Stage 5 chronic kidney disease on the Hispanic population, which often requires dialysis therapy (Table 2). For this quantitative research, a retrospective examination of CMS-2728 forms and the treatment records of a cohort of Hispanic patients on hemodialysis that received treatments at local dialysis clinics in San Antonio, Texas was conducted. Both diabetic and nondiabetic patients on maintenance hemodialysis that received treatments at these clinics were reviewed to test the hypothesis that potential albumin level differences or patterns exist between hemodialysis patients with a Type II diabetes mellitus diagnosis and those without one. Additionally, known predictors, albumin levels, and Type II diabetes were compared to identify possible associations that may reveal if serum albumin is modulated by these covariables.

Instrumentation

Upon receiving official permission from Frenova Renal Research, data were collected from Centers of Medicare and Medicaid Services (CMS)-2728 forms (Appendix A). The CMS-2728 government form is a validated data collection instrument that is completed for all new patients who are initiated on dialysis. Data arising from this form have been published in numerous studies (Dalrymple et al., 2013; Lukowsky et al., 2012; Murthy et al., 2005; Ricks et al., 2011; Ricks et al., 2012; Yan et al., 2013). The form captures data on sociodemographic characteristics, anthropometric measurements, as well as comorbidities, hematology, and clinical indicators (Murthy et al., 2005).

For this study, IBM Statistical Package for the Social Sciences (SPSS) was used for data collection and analysis. SPSS is a widely used and powerful statistical analysis software suite that facilitates data collection and analysis (Faul et al., 2007). It is used extensively in the social sciences for quantitative, epidemiological studies. The software contains several modules, which provide the researcher the ability to create databases for analysis. SPSS creates a database from which statistical treatments can be conducted using simple drop down menu options. The analysis module capabilities include reading and analyzing the entered data using statistical treatments such as descriptive statistics, including cross tabulation and frequencies, and bivariate statistics, including means, t-test, ANOVA, correlation, and nonparametric tests. Additionally, SPSS generates linear regression, multiple regression, and factor and cluster analyses. The generated data analyses are represented via tabular and/or graphical forms (Faul et al., 2007).

Data Collection and Management

The data for this study were extracted from both electronic and paper patient medical records located securely at each dialysis facility. The clinical data and patient treatment records are collected and documented by nursing personnel and patient care technicians (PCT), including anthropometric measurements of age, weight, and height, as well as renal indices such as BUN-serum creatinine ratios, hemoglobin $A1_C$, lipid profiles, and serum albumin documented at the onset of treatment. Peritreatment, in addition to monitoring blood pressures, PCT's draw blood to conduct complete blood counts. Subsequent blood draws are conducted weekly by nursing personnel for hemoglobin $A1_C$ and pre and post BUN-creatinine ratios and potassium if deemed necessary by the nephrologist. Calcium, phosphorus, and albumin levels are collected monthly, peritreatment. Both weekly and monthly lab tests are documented in the patient's medical records. Routine lab testing and reporting of monthly albumin levels through Spectra Laboratories were reviewed from the patient's medical records.

The primary cause of renal failure and ICD-9 codes for associated comorbidities are documented on CMS-2728 forms and the patient's medical records. ICD-9 codes for the primary chronic disease and associated comorbidities (covariables) were collected to streamline data collection and analysis. Table 1 lists the ICD-9 codes that were used for this study. In addition to ICD-9 codes and comorbidities, this study collected data on therapeutic management of diabetes; the data included whether the patients were on insulin, oral medications, or both.

Table 1

ICD-9 Codes For Independent Variable and Covariables (Comorbidities)

ICD-9 Code Ranges	Covariable (Comorbidity)	Description
250.40 250.42 25000A	Type II Diabetes	Type II Diabetes with Renal Manifestations Type II Diabetes or unspecified type, uncontrolled
401-405	Hypertension	Essential Hypertension, Hypertensive heart disease, Hypertensive chronic kidney disease, Hypertensive heart and chronic kidney disease, and Secondary hypertension
440-449	Peripheral Vascular Disease	Atherosclerosis, aortic aneurysm and destruction, peripheral vascular disease, arteriole embolism and thrombosis, atheroembolism, polyarteritis nodosa allied conditions, disorders of arteries and arterioles, disease of capillaries, septic arteriole embolism
Codes with root 686, 038, 040-041, 996.62, 999.31	Infection/Inflammation	Unspecified local infection skin and subcutaneous tissue; wound infection, septicemia, bacterial diseases, bacterial infection, infection and inflammatory reaction due to internal prosthetic device and graft, central venous catheter infection

During data collection, each CMS-2728 form was screened to ensure that all data were complete. CMS-2728 forms with missing data such as gender, age, albumin levels, cause of renal failure, and associated comorbidities were excluded from the data analysis sample. Hence, a listwise deletion of the data minimized data cleaning prior to the data analysis phase. Additionally, an Excel spreadsheet was used to compile the data extracted from CMS-2827 forms and patient treatment records. The spreadsheet employed a formula whereby it would flag inaccurate or erroneous data that were keyed incorrectly during data entry. For example, normoalbuminemic range, according to KDOQI guidlines, is 3.4 - 5.4 mg/dL (American Journal of Kidney Disease, 2007; National Kidney Foundation, 2002; National Kidney Foundation, 2013). When an albumin value

was keyed into the spreadsheet that was not within these parameters and therefore incompatible with life, the value box on the spreadsheet would automatically flag the entry in red for immediate correction. This strategy prevented the inclusion of corrupt, truncated, or inaccurate data that were erroneous or incompatible with life. The same procedure was applied to other variables such as gender, age, Type II diabetes diagnosis, hypertension, peripheral vascular disease, and infection/inflammation, thus minimizing data cleaning during data analysis. Furthermore, for quality assurance, duplicate entries or spot checks were randomly collected on a separate spreadsheet from electronic records for 10% of the population sample from each clinic and then further verified on treatment record hard copies.

In order to compile comparable amounts of follow-up data for both groups, hospital labs or clinic labs were used from CMS-2728 forms to qualify patients as End State Renal Disease (ESRD) patients (Table 2), depending if the patient initiated treatment at the hospital or the dialysis clinic. These labs include hemoglobin $A1_{c,}$ creatinine clearances, and serum albumin levels. These documented labs were used as baseline values to which subsequent labs were compared. Comorbidities documented on these records were also used as baseline data. The retrospective review of medical records captured all patient data currently attending the facilities. Patients were followed prospectively from their treatment initiation date to 6 months into their treatment. Between 7 clinics, approximately 15 patients are admitted each month as new hemodialysis patients. Therefore, an approximate pool of 900 CMS-2728 forms and treatment records were available for review. This available pool estimation amply

satisfied the proposed cohort of 788 records (394 per group) to address Research Questions 1 and 2 generated by G*Power.

Data collection also captured mortality rates as well as anthropometric information (e.g. age and height) on those records that were excluded from the sample population. For example, patient records with missing data entries either because they passed away, moved away, withdrew from dialysis, or that simply had no documented reasons for treatment discontinuation, were also collected to create a comprehensive profile of the exclusion criteria used to compile the final sample population.

Table 2

KDOQI – Chronic Kidney Disease Stages

Stage	Glomerular Filtration Rate (GFR) mL/min/1.73m^2	Description
1	≥90	Kidney damage with normal or ↑GFR
2	60-89	Kidney damage with mild ↓GFR
3	30-59	Moderate Kidney damage with ↓GFR
4	15-29	Severe Kidney damage with ↓GFR
5	<15 or on dialysis	Very severe damage; End Stage Renal Disease

Source: National Kidney Foundation

Study Variables

Dependent Variable

The dependent variable in this study is albumin levels for each patient as documented on CMS-2728 forms at treatment onset and subsequently in their treatment

records. Albumin levels are documented at treatment onset and monitored peri and post treatment as deemed necessary by the clinic nephrologists. Decreased albumin levels may cause numerous symptoms that can affect hemodialysis treatment goals and overall patient prognosis. Furthermore, a chronic disease process, such as Type II diabetes, may influence albumin levels. Acutely, a drop in normoalbuminemic levels produces a plethora of maladies including ascites or bloating in abdominal area, cramps, fatigue, loss of appetite, pleural effusions, localized swelling, muscle weakness, and weight loss. As the hypoalbuminemia worsens, chronic symptoms include liver problems, heart conditions, digestive ailments, respiratory infections, and kidney dysfunction. Therefore, measured albumin levels for each patient is the outcome variable for this study (Davita, 2014; Fresenius Medical Care, 2013). The level of measurement for this variable was operationalized on SPSS as 0 for albumin levels <4.0 mg/dL and 1 for albumin levels ≥4.0mg/dL (Table 3).

Independent Variable

The independent variable in this study is a Type II diabetes mellitus diagnosis with ICD-9 code 25040 and 25000A in patients undergoing maintenance hemodialysis. Individuals with this disease can synthesize the hormone insulin normally (Campbell, 2000; Mahler & Adler, 1999). Their pancreas, however, either does not secrete enough insulin or the body's cells are incapable of recognizing the insulin receptor. For the latter, the insulin resistance prevents glucose endocytosis into the body's cells. This endocytotic failure allows the sugar to accumulate in the bloodstream, which over time causes cellular dysfunctions, damaging nerves and small blood vessels of the kidneys (Figure 1).

Additionally, the hyperglycemia can cause polyuria, which can lead to severe dehydration (Campbell, 2000; Mahler & Adler, 1999). For this study, a person with Type II diabetes was defined as someone with a fasting blood sugar of 140 mg/dL or higher (Mahler & Adler, 1999) and identified from the record review and final diagnosis of the case as being Type II diabetes with renal manifestations per ICD-9 code 25040 and 25000A, documented on CMS-2728 forms (Table 1). The level of measurement was operationalized on SPSS as Yes or No (Table 3).

Potential Confounders

There were potential confounders that were considered in this study that may have influenced study outcomes. First, hypertension may be a potential confounder in hemodialysis patients with Type II diabetes. Malliara (2007) asserts that the prevalence of hypertension in hemodialysis patients is about 86%. Isolating possible differences in albumin levels in hemodialysis patients with and without a Type II diabetes diagnosis may be challenging in terms of determining whether the differences are due to serum albumin differences, hypertension, or both. This extraneous variable may have influenced study outcomes, either positively or negatively, and therefore may have resulted in erroneous study conclusions. Hypertension was defined using ICD-9 root codes 401-405 (Table 1). These codes included: Essential hypertension (401), Hypertensive heart disease (402), Hypertensive chronic kidney disease (403), Hypertensive heart and chronic kidney disease (404), and Secondary hypertension (405). As this is a chronic condition, this covariable was defined as physician diagnosed at time of initiation of hemodialysis. It was operationalized on SPSS as, Yes = 1 and No = 0.

A second potential confounder is peripheral vascular disease (PVD). PVD is common in the US population. Recent prevalence estimates show 4%-12%, depending on age and diabetes status. PVD prevalence in the dialysis population is significantly higher. According to Plantinga et al. (2009), global and US prevalence estimates in this population account for 25% and 28%, respectively. Consequently, PVD is a known predictor that can influence albumin levels in patients receiving maintenance hemodialysis. O'Hare, et al. (2002) found a negative association between serum albumin and PVD. It is reasonable to expect that serum albumin levels may be lower as a consequence of PVD and not because of a Type II diabetes diagnosis. Furthermore, PVD may also lower serum albumin levels in the non-diabetic hemodialysis group, which may skew result outcomes towards the null. PVD was defined using ICD-9 codes 440-449 (Table 1). These codes include: Atherosclerosis, aortic aneurysm and destruction, peripheral vascular disease, arteriole embolism and thrombosis, atheroembolism, polyarteritis nodosa allied conditions, disorders of arteries and arterioles, disease of capillaries, and septic arteriole. This chronic disease was also defined as physician diagnosed. It was documented as present at hemodialysis initiation and operationalized on SPSS as, Yes = 1 and No = 0.

Another potential confounder to consider in this study is inflammation due to infection. Inflammation is the body's response to either physical injury and/or the invasion of foreign bodies such as bacteria or viruses (Don & Kaysen, 2004). The inflammatory response occurs when the immune system activates white blood cells and other immune chemicals, which sends them to the invasion or injury site. In some cases,

the response may be acute, which manifests rapidly and may last for minutes or days. Chronic inflammation, however, persists long-term. Because it is continually reinforced by the release of immune system chemicals, this type of inflammation is often omnipresent.

Inflammation is known to lower albumin levels by forcing the liver to divert albumin synthesis towards making proteins that are necessary for the immune response (Don et al., 2004). Furthermore, when the fractional catabolic rate is extreme, the transfer of albumin out of the vascular compartment is increased leading to hypoalbuminemia. Abnormally low serum albumin levels develop during an acute or chronic inflammatory response. Acute sources of low serum albumin include bladder and gingival infections. Potential chronic sources leading to hypoalbuminemia include lupus, inflammatory bowel disease, arthritis, MRSA, and chronic kidney disease (Don et al., 2004).

Acutely, the study identified when and if a patient was diagnosed with an infection. These infections were primarily skin and subcutaneous tissue infections. Other infections included, wound infection, septicemia, bacterial diseases, bacterial infection, infection and inflammatory reaction due to internal prosthetic device and graft, and central venous catheter infection (Table 1). These infections may be present at hemodialysis initiation or may manifest subsequently peritreatment and were documented accordingly. Chronically, the infections were defined as physician diagnosed, present at time of hemodialysis initiation, and documented on CMS-2728 forms and or treatment records. On treatment records, this covariable was identified based on hematology results showing a white blood cell count greater than 10.80mg/dL confirming the infection and

with a physician diagnosis.

The "Healthy Migrant Effect" may confound the study population used for this study. According to Fennelly (2005), first generation immigrants are often healthier than U.S.-born residents who share similar ethnic or racial backgrounds. Over time, however, the migrant health advantage drastically dwindles. This "paradoxical assimilation" phenomenon has to do with the length of time that an immigrant spends in the U.S. and correlates with increases in low birth weight infants, adolescent risk behaviors, cancer, anxiety and depression, and general mortality (Fennelly, 2005).

Intriguingly, though, the Hispanic paradox may confound the results in an entirely different way. For the past twenty years there has been widespread evidence of a Hispanic paradox in the United States, in which most Hispanic groups are characterized by low socioeconomic status, but better than expected health and mortality outcomes. Franzini, Ribble, & Keddie (2001) assert that the paradox may be due to possible underreporting of Hispanic deaths, the "healthy migrant effect," and/or unique risk profiles in this population group, including the "reverse epidemiology" phenomenon. These factors, according to the authors, may contribute to, but do not explain, this paradox. The reasons for this paradox, although speculative, are likely multifactorial and social in origin (Franzini et al., 2001).

The term "reverse epidemiology" refers to associations between traditional and nontraditional risk factors and clinical outcomes that are the opposite of those expected from studies in the general population (Balakrishnan & Rao, 2007). A reversal in the association is often encountered in patients with chronic illness, including those with

advanced chronic kidney disease on maintenance hemodialysis. For this study, there is a reasonable expectation that this phenomenon may confound study outcomes, considering the ethnicity of the sample population and associated comorbidities. Table 3 summarizes the variable types, variable names, potential responses, and corresponding level of measurements for this study.

Table 3

Variables – Potential Responses and Level of Measurements

Variable Type	Variable Name	Potential Responses	Level of Measurement
Dependent	Albumin	<4.0mg/dL = 0 ≥4.0mg/dL = 1	Nominal with a dichotomous response
Independent	Type II Diabetes	Yes/No	Dichotomous
Covariable	Hypertension	Yes/No	Dichotomous
Covariable	Peripheral Vascular Disease	Yes/No	Dichotomous
Covariable	Infection/Inflammation	Yes/No	Dichotomous

Study Limitations

The proposed study may have some potential limitations that warrant explication. First, the data analyzed were secondary data. Although the medical records reviewed were compiled, stored and maintained by medical professionals, the data may be incomplete due to patient hospitalizations, patient referrals, and/or patient treatment absenteeism. Secondary data analysis, however, can be quite advantageous in that it saves time and money and provides access to large quantities of data at once. The data, however, are collected by third party entities and may have been collected for reasons not directly related to the specific study aims or research hypothesis. With permission from

Frenova Renal Research and with Internal Review Board approval, access to patient medical records was attained, and data were extracted and amassed to address the specific research questions for this study.

Generalizability to other ethnic populations may also limit this study. The study population consists of adult, Hispanics undergoing maintenance hemodialysis with and without a Type II diabetes diagnosis. The study outcomes, therefore, may not be generalizable to other ethnic populations. Additionally, the population is restricted to patients attending weekly dialysis treatments at local dialysis clinics, and so excludes patients undergoing home hemodialysis, in-patient hospital hemodialysis, or those electing a dialysis modality not available at these clinics such as peritoneal dialysis. In addition to this population restriction, a population sample limitation may also limit the proposed study. To ensure internal validity, a complete data analysis at all seven clinics was conducted with strict exclusion criteria. To ensure external generalizability, basic anthropometric information, mortality, and hematology on patient medical records that were excluded from the study were collected. Generalizability and sample population restrictions are two important factors that may limit the study.

Other important considerations that may limit this study include patient phobias and demographics. Patients lacking health insurance or that simply refuse dialysis treatment either because of disease denial or because of doctor, needle or blood phobias may not be included in the sample population. Therefore, the population sample may be capturing only those that are sick that are actually attending the dialysis clinics and excluding those that are sick and not receiving necessary treatments. Additionally, the

clinics from which the data are collected may represent a demographic limitation in that the community in which the clinic is located may have a higher or lower Hispanic representation than do other similar clinics in other regions of the city. Both of these potential limitations are considerations for this investigation.

Review of the Study Design

Research in the field of nephrology and hemodialysis primarily employs experimental and observational study designs. This study employed an observational approach to address the research questions. Observational studies in general can be used to investigate the effects of a wide range of exposures, including preventions, treatments, and possible causes of disease. This study is a cohort study, which is one of the most common types of observational and epidemiological research models. Advantages of observational studies such as a cohort study include providing information that explains the causes of disease incidence and the determinants of disease progression, to predict the future health care needs of a population, and to control disease by studying ways to prevent disease and prolong life with disease. A strong limitation to observational studies is the inability of the investigators to have complete control over disturbing influences or extraneous factors. This is because a key feature of observational cohort studies is that the investigator is disconnected from direct patient contact and instead passively collects data without patient contact (Aschengrau & Seage, 2008), as was the case in this study. Another important characteristic of cohort observational research designs is that they cannot determine causality but can suggest variable associations and/or correlations; this study aimed to show potential associations between serum albumin and Type II diabetes,

but did not aim to show that Type II diabetes causes serum albumin differences between diabetics and nondiabetics.

Well-designed cohort studies can provide powerful outcomes (Song & Chung, 2010). In a cohort study, an outcome or disease-free population is initially identified by the exposure or event of interest and followed until the disease or outcome of interest occurs. This design has the potential to provide the strongest scientific evidence because exposure is identified before the outcome. This temporal framework, consequently, can assess causality (Song & Chung, 2010). Cohort study designs have advantages and disadvantages. Cohort studies are particularly advantageous for examining rare exposures since subjects are chosen based on their exposure status. Additionally, the researcher can examine multiple outcomes simultaneously. The need for a large sample size, the potentially long follow-up duration, and the cost to conduct the study, are all definite disadvantages of this design model (Song & Chung, 2010).

Cohort study frameworks can be either prospective or retrospective (Song & Chung, 2010). Whereas prospective studies are carried out from the present time into the future retrospective or historical studies are carried out at the present time and examine past events. Often times this study design examines medical events or past outcomes, as was the case for this study. For this design approach, a cohort of subjects selected based on exposure status is chosen at the present time, and outcome data, which was measured in the past, are reconstructed for examination. Researchers have limited control over data collection, since the data were previously collected. Therefore, existing data may be incomplete, inaccurate, or inconsistently measured between subjects. However, because

the data is immediately available, this study design is comparatively less costly and shorter in duration than prospective cohort designs (Song & Chung, 2010). A retrospective, cohort design is therefore the most appropriate approach to answer the research questions of this study and to test the hypotheses of potential differences in albumin levels in hemodialysis patients with and without Type II diabetes.

A retrospective cohort study was an adequate design model to investigate the hypothesis of whether albumin levels in two homogeneous populations of Hispanic patients receiving hemodialysis show differences or are influenced by a Type II diabetes diagnosis. This design type would allow the selection of a Hispanic population of hemodialysis patients from a specific treatment start date and then examined 3 and 6 months into the course of their treatment. The patient population can therefore be carefully selected from those that remained on maintenance hemodialysis for the full study period in order to control missing data due to loss to follow up, transplant, death or other inevitable reasons. Additionally, the study population size can be controlled, and patient confidentiality can be maintained by randomly listing each patient record in sequential order. This numbering system would be different from the 6-digit medical records identification numbers (MRI) assigned by the clinics.

Data Analysis

After collecting the necessary data from the dialysis facilities, the compiled data spreadsheet was uploaded into SPSS to conduct a comparison of means for all patients in both groups. The collected data included anthropometric measurements of age, gender, and ethnicity, associated comorbidities, including diabetes, hypertension, PVD, and

presence of infections/inflammation, and hematology profiles, including creatinine values and albumin levels. Descriptive univariate analysis included frequency tables for all variables. Mean values for albumin levels at diagnosis, treatment onset, and 3 and 6 months post onset were also presented.

Research Question 1 aimed to investigate if albumin level differences existed in Hispanics patients with and without a Type II diabetes diagnosis that are initiated on hemodialysis. The null hypothesis (N_O) is that there will be no difference in albumin levels between both groups. The alternative hypothesis (H_A) is that there will be a difference in albumin levels between both groups. Depending on the data a simple linear regression analysis or an ANOVA was proposed to address Research Question 1. If the data fit the simple linear regression model, then the days that each patient came in for dialysis treatment and had their blood drawn for albumin analysis would be the independent variable (X-axis), and the dependent variable would be albumin level values (Y-axis). Data permitting, linear regression analysis would allow a comparison of slopes between both groups to determine if a difference in albumin levels exists between both groups within a period of 6 months. The data, however, did not fit the linear regression model; therefore, an ANOVA was conducted instead. The data met the assumptions for the ANOVA and therefore qualified as a suitable model to test for significant differences in means. For this study, the ANOVA was used to determine if a difference exists in mean albumin levels between the diabetic and nondiabetic group. An alpha level of .05, power of .80, and a small effect size of 0.1 was entered into G*Power 3.1 software. Drop down menu settings on G*Power included the test family, which was set to *t* test, the

statistical test, which was set to difference between two independent means (two groups), and type of power analysis, which was set to a priori computation of required sample size given α, power, and effect size. The generated sample size for each group according to G*Power was 394, which yielded a cumulative cohort of 788 patient records. This was the projected sample size to address Research Question 1.

For Research Question 2, the data were analyzed at 3 and 6 months post baseline; repeated measures *t* tests were conducted to determine if potential differences existed in albumin levels at these time intervals in both the diabetic and nondiabetic, hemodialysis groups. Repeated measures designs allow the detection of within-person change over time and typically exhibit higher statistical power (Guo et al., 2013). Repeated measures designs are advantageous; for this study, collection of repeated measurements of key variables can provide a more definitive evaluation of changes in albumin levels over time. Furthermore, collecting repeated measurements can simultaneously increase statistical power for detecting albumin level changes while minimizing the costs of conducting the study. Research Question 2 aimed to determine if Hispanic patients on hemodialysis, both with and without a Type II diabetes diagnosis, showed differences in albumin levels at 3 and 6 months post initiation of hemodialysis. The null hypothesis (H_O) is that there will be no albumin level differences observed between both groups at these intervals. The alternative hypothesis (H_A) is that albumin level differences are observed between both groups at these intervals. A repeated measures *t* test was a suitable test to compare means between four time intervals in this sample population. The intervals will be baseline CMS-0 months, 0-3 months, 3-6 months, 0-6 months. G*Power

determined that a cumulative cohort of 788 (394 per group) medical records was required to achieve statistical power. This statistical test and corresponding power analysis was repeated for the nondiabetic group during the same intervals for comparative analysis.

Research Question 3 aimed to determine if there is a relationship between known predictors hypertension, peripheral vascular disease, and infection/inflammation, serum albumin levels, and Type II diabetes in Hispanic, hemodialysis patients that might modulate albumin levels. The null hypothesis (H_O) is that there will be no relationship between these predictors, serum albumin, and Type II diabetes in these patients. The alternative hypothesis (H_A) is that there is a relationship between known predictors, serum albumin levels, and Type II diabetes in both groups. In this study, co-variables such as hypertension, PVD, and inflammation/infection are known to influence albumin levels and were dealt with during the analysis phase. To address this research question, a Pearson's correlation test was selected to establish an association between the known predictors and serum albumin levels. This decision assumed the data met the strict linear assumption of this test. Since the data did not meet this linear assumption for this parametric test, a nonparametric Spearman correlation was conducted instead. For this test, the variables must be ordinal, interval, or ratio. A Pearson correlation on interval or ratio data would be the preferred parametric test to conduct; however a Spearman correlation can be used when the assumptions of the Pearson correlation are markedly violated. A second assumption of the Spearman Correlation is that there is a monotonic relationship between the variables. A monotonic relationship is an important underlying assumption of the Spearman correlation, which is less restrictive than a linear

relationship. All variables were modeled together using logistic regression analysis to determine the relative contribution of each covariable in addition to the study's independent variable and to identify their individual relationship to the dependent variable of albumin levels. Multiple logistic regression is the appropriate multivariate statistical test to address this research question since the independent variable, the covariables, and the dependent variable are all dichotomous.

Seven hundred and eighty eight medical records (394 records for each group) were randomly selected and amassed until the final cohort was completed. The data were extracted from the same CMS-2728 forms and patient medical records at each facility. Data from these records included anthropometric measurements of age, weight, gender and ethnicity, cause of renal failure, albumin levels, a Type II diabetes diagnosis, and the presence of associated comorbidities. The collected data were transformed into dichotomous responses for each variable of interest. Albumin levels were operationalized as <4.0 mg/dL = 0 and ≥40 mg/dL = 1. For covariables it was Yes = 1 and No = 0, and for Type II diabetes it was Yes = 0 and No = 1. The transformed data were uploaded into SPSS for analysis. Univariate, bivariate and multivariate analysis were used to address each research question.

Threats to Study Validity

There are several potential threats to validity that can impact the veracity of this study. First, selection bias poses a serious problem in retrospective cohort studies (Aschengrau & Seage, 2008). This occurs when the method by which subjects are chosen is erroneous, leading to a distortion of the statistical analyses, resulting from the method

by which samples were collected. This distortion may either underrepresent or overrepresent an association, incorrectly favoring the null or alternative hypothesis. This may lead to inaccurate study conclusions. The patient records selected for this study came from a large cohort of hemodialysis patients from whom samples were randomly selected and then grouped according to the presence or absence of a Type II diabetes diagnosis. The selection process for this study, therefore, minimized internal validity.

Second, information bias also constitutes a threat to validity to this study (Aschengrau & Seage, 2008). Nondifferential misclassification bias resulting from a lack of documented information in the patient records can pose a data collection and analysis challenge. For example, if there are missing albumin values on CMS-2728 forms or on patient medical records either because they were missed or because they were inaccurately recorded, then this would reflect an under representation of those data favoring the null hypothesis. Missing data may occur if patients are hospitalized for an extended period of time or if they are transients, in which case their travel schedules would necessitate them attending facilities outside the regional scope of this study. Unfortunately, this bias may not be entirely resolved except by increasing the sample size so as to minimize the effect. The proposed sample size for this study should likely reduce the impact of nondifferential misclassification bias.

Aschengrau & Seage (2008) assert that confounding by extraneous variables may influence study outcomes. Covariates, such as hypertension, peripheral vascular disease, or inflammation/infection, may lower albumin levels in hemodialysis patients in a similar manner as would Type II diabetes mellitus. These variables cannot be excluded from

analysis and must be dealt with to prevent erroneous statistical outcomes such as Type 1 or Type 2 errors. When comparing two means, concluding that the means were different when in reality they were not different would constitute a Type 1 error; concluding the means were not different when in reality they were different would constitute a Type 2 error (Banerjee et al., 2009). An effective way to deal with these covariates is through multiple logistic regression, which will identify contributions to the outcome and relationship to the dependent variable albumin.

Protection of Participants Rights

Data were collected from confidential patient treatment records. According to FMC-NA's clinical services department, new patient admissions are offered the opportunity to permit the use of their personal health information in any future research studies, having been informed that no personal identifiers will be included in the research and that the nature of such research would report aggregate data outcomes only. Additionally, the clinical services department follows HIPPA rules to ensure patient rights. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule aims to protect individually identifiable health information from uses and disclosures that may compromise patient privacy. The HIPAA Privacy Rule provides federal protections for personal health information that is stored by health care entities. The rule does, however, permit the disclosure of personal health information needed for patient care and for research purposes upon a special approval process (Fresenius Medical Care, 2013b). The patients sign a consent form upon admission to the facility. The patients are given the option to accept or decline the offer upon admission and are

advised that should they decline the offer, they may at any point during their clinic tenure reverse their declination. These forms are stored in the patient's treatment records. For newer patients, the medical records are in electronic form. For older patients, the records are in paper form. In addition to being stored on one laptop that was password protected, the data extracted from these records were compiled and stored on a flash drive and external drive, both of which were password protected and encrypted. The laptop flash drive and external drive containing the data were kept in a locked cabinet with restricted access. The data will be retained and securely stored for a minimum of five years from the end of the study, after which the data will be permanently deleted.

Summary

The purpose of the study was to explore the possibility that albumin levels in hemodialysis patients may be mediated by a Type II diabetes diagnosis. The null hypotheses are that there will be no differences in albumin levels between Hispanic patients with and without a Type II diagnosis on hemodialysis, that there will be no significant disparate differences post treatment onset, and that known predictors do not significantly modulate serum albumin in both groups. The study design was a retrospective cohort study conducted on a sampling of a large cohort drawn from hemodialysis patient medical records that attended local dialysis clinics for renal therapy in seven of FMC-NA's largest dialysis facilities in San Antonio, Texas. A sample size of 788 patient records (394 diabetics and 394 nondiabetics) was generated by G*Power. These records were selected randomly until a complete cohort was amassed. Data collected from each record included anthropometric measurements, hematology profiles

(including serum albumin levels), predictors, and whether a Type II diabetes mellitus diagnosis was present. These data were uploaded into SPSS for analysis.

This study aimed to fill a literature gap on possible differences and patterns in albumin levels between patients with and without a Type II diabetes diagnosis. Hemodialysis patients are treated as a homogenous group from a clinical perspective. All hemodialysis patients currently receive standardized hemodialysis treatments. Hispanic patients, however, are unique in terms of behavioral, psychosocial, cultural and religious dimensions. Neither the literature nor the clinical operating procedures implemented at the dialysis facilities consider these nuances, so specific strategies to improve and maintain albumin levels are nonexistent for this population. This is the gap this research attempted to fill.

The positive social change from this endeavor is significant. In addition to contributing knowledge and understanding to the discipline, examinations and comparisons of albumin levels in Hispanic patients with and without a Type II diabetes diagnosis may reveal information about specific serum albumin level patterns that may exist in one group and not the other. These examinations may help elucidate possible albumin improvement trends that might inform healthcare professionals about ethnic-specific nutritional supplementation or therapeutic interventions. These supplementations and/or interventions may inform and assist dialysis healthcare professionals in improving albumin levels to achieve dialysis goals and overall health. Chapter 4 will present the results of this research study.

Chapter 4: Results

Introduction

The purpose of this quantitative, retrospective cohort study was to investigate if differences existed between albumin levels in a cohort of patients, both with and without Type II diabetes receiving maintenance hemodialysis. The null hypotheses for this study are that there are no differences in albumin levels in both groups and albumin patterns will not show similar improvement clinical trends towards normoalbuminemic restoration through the course of their hemodialysis treatments. Known predictors such as a history of hypertension, peripheral vascular disease, and the occurrence of an infection or inflammatory immunological response were also examined to ascertain what effect, if any, these covariables might have towards modifying albumin levels in this population. This chapter includes the results of this investigation.

Eight hundred and twenty-seven CMS-2728 forms and patient treatment records of patients evaluated and treated at Fresenius Medical Care – North America were reviewed to amass the final cohort. Records that were incomplete were excluded from this sample. This left $N = 582$ records (males = 299 and females = 283) with complete data over 6 months. Of these, the final Hispanic cohort of $N = 405$ patient records, ($n = 281$ diabetic and $n = 124$ nondiabetic) met the inclusion criteria for this study. A summary of all records amassed by clinic and key variables collected for this study is shown on Table 4.

Table 4

Summary of Participant Characteristics by Clinic Based on Medical Records Review

Clinic #	**1648 N = 113**	**1664 N = 125**	**6618 N = 61**	**8855 N = 79**	**8856 N = 139**	**8861 N = 79**	**8868 N = 80**
Age	*M*=65.3 *SD*=13.4	*M*=63.8 *SD*=12.6	*M*=64.1 *SD*=12.2	*M*=63.7 *SD*=12.9	*M*=66.9 *SD*=12.3	*M*=64.2 *SD*=12.5	*M*=64.8 *SD*=12.3
Gender							
Male	(*n*=48) 53.9%	(*n*=53) 45.3%	(*n*=36) 60.0%	(*n*=36) 48.0%	(*n*=54) 54.5%	(*n*=40) 55.6%	(*n*=32) 45.7%
Female	(*n*=41) 46.1%	(*n*=64) 54.7%	(*n*=24) 40.0%	(*n*=39) 52.0%	(*n*=45) 45.5%	(*n*=32) 44.4%	(*n*=38) 54.3%
Weight (Kg)	89	86.3	76.8	77.1	85.5	84.7	88.5
Height (cm)	162.0	164.5	163.5	161.5	163.7	164.9	161.0
Ethnicity							
Hispanic or Latino	(*n*=56) 62.9%	(*n*=72) 61.5%	(*n*=52) 86.7%	(*n*=68) 90.7%	(*n*=41) 41.4%	(*n*=59) 81.9%	(*n*=57) 81.4%
NonHispanic or Latino	(*n*=33) 37.1%	(*n*=45) 38.5%	(*n*=8) 13.3%	(*n*=7) 9.3%	(*n*=58) 58.6%	(*n*=13) 18.1%	(*n*=13) 18.6%
Race							
White	(*n*=86) 96.6%	(*n*=94) 80.3%	(*n*=56) 93.3%	(*n*=72) 96.0%	(*n*=79) 79.8%	(*n*=65) 90.3%	(*n*=62) 88.6%
Black/African American	(*n*=1) 1.1%	(*n*=23) 19.7%	(*n*=3) 5.0%	(*n*=3) 4.0%	(*n*=19) 19.2%	(*n*=7) 9.7%	(*n*=8) 11.4%
Asian	(*n*=2) 2.2%	(*n*=0) 0.0%	(*n*=1) 1.7%	(*n*=0) 0.0%	(*n*=0) 0.0%	(*n*=0) 0.0%	(*n*=0) 0.0%
Native Hawaiian or Other Pacific Islander	(*n*=0) 0.0%	(*n*=0) 0.0%	(*n*=0) 0.0%	(*n*=0) 0.0%	(*n*=1) 1.0%	(*n*=0) 0.0%	(*n*=0) 0.0%
CMS Baseline Albumin	*M*=3.1 *SD*=.69	*M*=3.0 *SD*=.70	*M*=2.8 *SD*=.73	*M*=3.2 *SD*=.70	*M*=3.3 *SD*=.66	*M*=3.0 *SD*=.73	*M*=3.2 *SD*=.79
Diabetic	(*n*=54) 60.7%	(*n*=75) 64.1%	(*n*=43) 71.7%	(*n*=50) 66.7%	(*n*=66) 66.7%	(*n*=42) 58.3%	(*n*=51) 72.9%
Nondiabetic	(*n*=35) 39.3%	(*n*=42) 35.9%	(*n*=17) 28.3%	(*n*=25) 33.3%	(*n*=33) 33.3%	(*n*=30) 41.7%	(*n*=19) 27.1%
Hypertension	(*n*=77) 86.5%	(*n*=113) 96.6%	(*n*=45) 75.0%	(*n*=71) 94.7%	(*n*=91) 91.9%	(*n*=68) 94.4%	(*n*=63) 90.0%
Peripheral Vascular Disease	(*n*=8) 9.0%	(*n*=17) 14.5%	(*n*=7) 11.7%	(*n*=8) 10.7%	(*n*=8) 8.1%	(*n*=7) 9.7%	(*n*=6) 8.6%
Infection/Inflammation	(*n*=18) 20.2 %	(*n*=26) 22.2%	(*n*=0) 0.0%	(*n*=15) 20.0%	(*n*=19) 19.2%	(*n*=11) 15.3%	(*n*=18) 25.7%

Note. Table reflects all records that met inclusion criteria over six months. *N*= 582 (males *n* = 299, females *n* = 283); CMS is Centers for Medicare and Medicaid Services

The study population was drawn from a large cohort of records, which were amassed from all patients ($N = 827$) currently attending seven dialysis clinics in San Antonio, TX. Prior to 2014, the electronic data were collected from Proton; this was the computer software used to collect, monitor, and store patient treatment records at these facilities. Beginning in 2014, the electronic records were collected from eCube Clinicals. This is the newest web-based data collection and storage software currently used by Fresenius Medical Care – North America. All data from CMS-2728 forms were extracted from paper treatment records. Patient data that were collected and stored prior to Proton and eCube Clinicals integration were extracted from paper treatment records. All records were randomly selected from each clinic by shift without replacement and then operationalized according to age, sex, diabetic status, comorbidities, and clinic locale until both groups were identified. The diabetic group was defined as those hemodialysis patients with a nephrologist diagnosis on record of Type II diabetes, with a blood glucose level at or exceeding 140mg/dL (Mahler & Adler, 1999) and with ICD-9 codes 250.40, 250.42, and 25000A (Table 1). Patients identified for the nondiabetic group were attending hemodialysis treatments for alternative diagnoses.

Selected data elements were extracted from each record. These included anthropometric measurements of age, race, gender, height, body weight, hematology levels, including hemoglobin, white blood cell count, transferrin saturation, ferritin, and serum albumin, and renal parameters, including creatinine, potassium, phosphorus, and calcium. Data collection also included medications, comorbidities such as peripheral vascular disease, hypertension, and infection, as well as other relevant data that would

help address the research questions, meet study inclusion criteria, satisfy statistical power, and allow for future research expansion opportunities.

Power Analysis

The original proposed sample size for this study was determined using G*Power 3.1 analysis software using an alpha of .05, a power of .80, and a small effect size of .20. This was a two-sided test and these values were based upon previous study estimates and KDOQI guidelines (National Kidney Foundation, 2002; National Kidney Foundation, 2013a; National Kidney Foundation, 2013b). These guidelines are followed by each dialysis facility and are the standard operating guidelines that each facility uses to properly and uniformly dialyze patients on their treatment schedules. After the data collection and analysis phases were complete, the proposed cohort of $N = 788$ (394 per group) was not met for two reasons. First, the hemodialysis clinics are required to "thin out" patient treatment records as the compilation of treatment records prevents the binders from closing. These older records are sent to Iron Mountain, an off-site data storage location, where they are stored for a negotiated period of time. Access to Iron Mountain records is restricted to clinical managers and medical directors seeking to verify historic patient records that exceed those stored at the facilities. Iron Mountain charges a per record fee to the dialysis facilities interested in acquiring historic patient treatment records stored at their facility.

Frenova Renal Research stipulated in their Research Project Approval Application (Appendix B) that the principle investigator should not incur any additional research-related costs to the facility because of this study. Second, continually fluctuating

censuses at each dialysis facility, due to patients lost to follow up (n = 4), patient transfers/transient status (n = 110), hospitalizations (n = 6), allograft rejection (n = 16), transplantation (n = 6), or patient withdrawal/death (n = 4), placed a limitation as to amassing the originally proposed population sample. The population sample was, therefore, restricted to all current patients on the treatment schedule at each facility, all deceased patients who currently had treatment records stored in the dialysis facilities, all patients that had not received a cadaver kidney, had an allograft rejection or that had not previously transferred in from or out to another facility beyond the scope of this research study.

To verify power on the final population sample, a post-hoc power analysis was conducted using G*Power software to achieve statistical power with the final cohort of N = 405 (281 diabetics and 124 nondiabetics). On the G*Power main menu, t tests was selected from the drop down menu under test family. The statistical test was set at Means: Difference between two independent means (two groups). Since this was a power analysis conducted after the analysis phase, the type of power analysis selected from the drop down menu was Post hoc: Compute achieved power – given $\propto$, sample size, and effect size. Under input parameters, a two-tailed test with a medium effect size of 0.5, $\propto$ = 0.05 and sample size groups of 281 and 124 were inputted, which was more suitable for the collected data. The achieved statistical power, generated by G*Power software, was greater than 0.99, amply satisfying the power for a medium effect size for this study cohort.

As outlined in Table 4, the variables were transformed into dichotomous or binary variables. The variable gender was categorized as Male = 0 and Female = 1. Race was operationalized as White = 1, Black/African American = 2, American Indian/Alaskan Native = 3, Asian = 4, and Native Hawaiian or other Pacific Islander = 5. Ethnicity was further operationalized as Hispanic = 0 and NonHispanic = 1. Patients with ICD-9 codes 25040 and 25000A, Type II diabetes mellitus with renal manifestations as their cause of renal failure were operationalized as Yes = 0 and No = 1. Comorbidities documented on CMS-2728 forms were operationalized as HBP_Comorbidity_Num and PVD_Comorbidity_Num; if present at treatment initiation, then Yes = 1 and No = 0. The comorbidity of Infection/Inflammation was defined as exceeding normal white blood cell hematology counts of >10.80mg/dL, according to CMS-2728 forms; this comorbidity was then operationalized as Yes = 1 and No = 0. Quantitative analysis of the absolute and relative albumin level changes at four different intervals was operationalized as Abs_change and Rel_change, respectively, for each of the four intervals (Table 5). Following these conversions, the transformed data were entered into SPSS Version 21 for analysis.

Table 5

Variables and Covariables – SPSS Measurement Level

Variable	Operationalized	Measurement
Sex	Sex_Num	Male 0 Female 1
Ethnicity	Ethnicity_Num	Hispanic or Latino 0 NonHispanic or Latino 1

Race	Race_Num	White 1 Black/African American 2 American Indian/Alaskan Native 3 Asian 4 Native Hawaiian or other Pacific Islander 5
Renal Failure ICD-9	Diabetic_Num	Diabetes Y/N: Yes 0 No 1
Hypertension	HBP_Comorbidity_Num	Hypertension Y/N: Yes 1 No 0
Peripheral Vascular Disease	PVD_Comorbidity_Num	PVD Y/N: Yes 1 No 0
Infection/Inflammation	Infect_Num	Infection /Inflammation Y/N: Yes 1 No 0
Albumin (CMS)	Alb_CMS_Num	<4.0mg/dL = 0 ≥4.0mg/dL = 1
Albumin (0 months)	Alb_0mos_Num	<4.0mg/dL = 0 ≥4.0mg/dL = 1
Albumin (3 months)	Alb_3mos_Num	<4.0mg/dL = 0 ≥4.0mg/dL = 1
Albumin (6 months)	Alb_3mos_Num	<4.0mg/dL = 0 ≥4.0mg/dL = 1
Albumin Absolute Change	Abs_change (3mos-CMS)	Interval: CMS - 0 months
Albumin Absolute Change	Abs_change (3mos-0mos)	Interval: 0 months - 3 months
Albumin Absolute Change	Abs_change (6mos-3mos)	Interval: 3 months - 6 months
Albumin Absolute Change	Abs_change (6mos-0mos)	Interval: 0 months - 6 months
Albumin Relative Change	Rel_change (3mos-CMS)	Interval: CMS - 0 months
Albumin Relative Change	Rel_change (3mos-0mos)	Interval: 0 months - 3 months
Albumin Relative Change	Rel_change (6mos-3mos)	Interval: 3 months - 6 months
Albumin Relative Change	Rel_change (6mos-0mos)	Interval: 0 months - 6 months

Note. Num was used as a categorical variable on SPSS; CMS is Centers for Medicare and Medicaid Services; HBP is high blood pressure; PVD is peripheral vascular disease; Infect is infection/inflammation

Analysis

Descriptive Univariate Analysis

For the entire study cohort, the ages ranged from 22 to 96 years with a mean age of 62.4 years and a mode of 67 years. There were 301 (53.5%) males and 262 (46.5%) females. The vast majority of the population, 706 (85.4%) were White and of those 562 (68.0%) were of Hispanic or Latino ethnicity. Anthropometric measurements included weight and height mean values of 82.0 Kg and 162.1 cm, mode values of 83.0 Kg and 160.0 cm, and median values of 80.1 Kg and 163.0 cm, respectively. The final study population that met inclusion criteria was comprised of $n = 281$ (69.4%) diabetic patients and $n = 124$ (30.6%) nondiabetic patients. Of those, $n = 366$ (90.4%) patients had a history of hypertension and $n = 43$ (10.6%) patients were diagnosed with peripheral vascular disease as comorbidities. Additionally, $n = 74$ patients (17.8%) were diagnosed with an infection or inflammatory condition present at treatment initiation. Amongst the Hispanics with diabetes, $n = 256$ (91.1%) had a history of hypertension, $n = 38$ (13.5%) had PVD, and $n = 45$ (16.0%) developed an infection or inflammatory condition pre- and/or peritreatment. These findings are summarized on Figure 2. Descriptive statistics for albumin levels at four different time intervals are listed in Table 6.

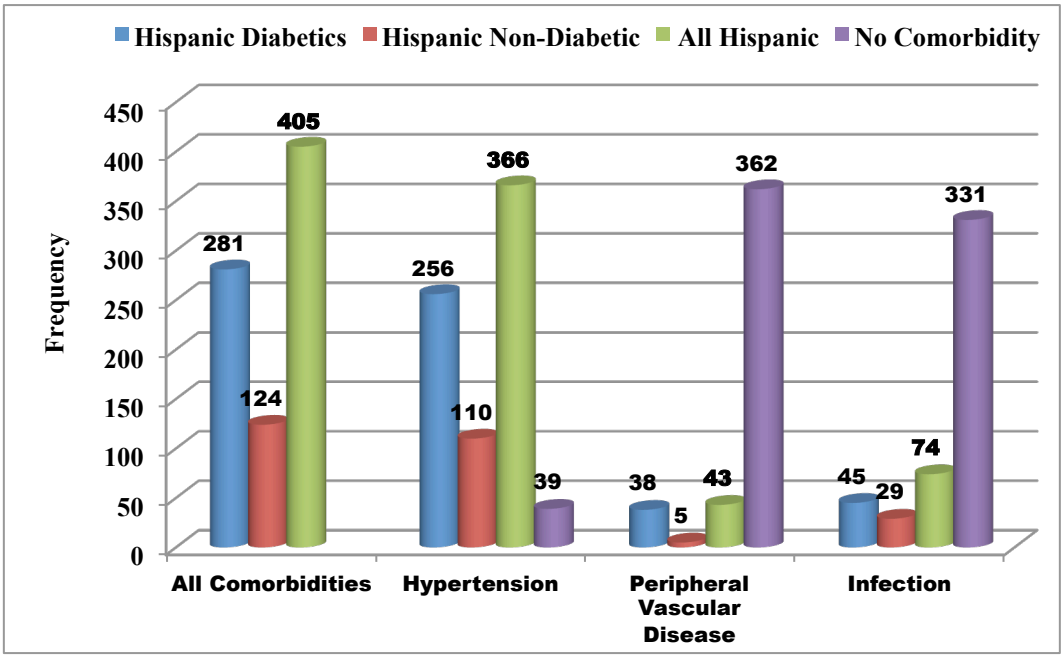


Figure 2. Frequency of Comorbidities in Hispanic Population

Table 6

Descriptive Statistics of Albumin Levels Over Time

Time Interval	*N*	Albumin Level Minimum (mg/dL)	Albumin Level Maximum (mg/dL)	Mean	Std. Error	Std. Deviation	Variance
CMS baseline	405	1.1	4.9	3.0243	0.03743	0.75334	0.568
0 months	405	1.7	4.5	3.4149	0.02677	0.53884	0.290
3 months	405	1.5	4.7	3.7017	0.02107	0.42406	0.180
6 months	405	2.0	4.8	3.8121	0.01981	0.39861	0.159

Note. CMS is Centers for Medicare and Medicaid Services

One-Way ANOVA

Research Question 1 seeks to determine if a difference exists in albumin levels between diabetic and nondiabetic, hemodialysis patients. To address this research question, a one-way ANOVA statistical test was selected to compare means between four albumin levels at four different time intervals. An ANOVA puts all the data into one number (F) and gives one p value for the null hypothesis. This test has several important assumptions that must be met, two of which were used to assess the suitability to address Research Question 1. First, there is an assumption of normality. The groups must be

normally distributed on the dependent variable. To assess a deviation from normality, a histogram was generated on SPSS after data collection was complete and cleaned; the generated results did not indicate evidence of skewness, or light or heavy-tailedness (Data not shown). Second, the inequality of the population variances was assessed by examination of the relative size of the sample variances using a robust Levene's test (Data not shown). Since both the normal distribution and equal population variances assumptions were met, the ANOVA was suitable to address Research Question 1. The generated results between both groups are presented in Table 7.

Table 7

Statistical Analysis of Variance of Albumin Levels Between Diabetic and Nondiabetic Patients

		Sum of Squares	*df*	Mean Square	*F*	Sig.
CMS baseline	Between Groups	1.292	1	1.292	2.283	0.032
	Within Groups	227.984	403	0.566		
	Total	229.276	404			
0 months	Between Groups	0.469	1	0.469	1.619	0.004
	Within Groups	116.83	403	0.29		
	Total	117.299	404			
3 months	Between Groups	0.029	1	0.029	0.162	0.687
	Within Groups	72.62	403	0.18		
	Total	72.649	404			
6 months	Between Groups	0.034	1	0.034	0.211	0.646
	Within Groups	64.157	403	0.159		
	Total	64.191	404			

Note. CMS is Centers for Medicare and Medicaid Services; Underline indicates significance ($p < .05$)

The analysis of the data shows that the albumin levels at CMS baseline and 0 month intervals were statistically significant, 95% CI [2.9, 3.1], $p < .032$ and 95% CI [3.3, 3.5], $p < .004$, respectively. The *F* statistic for the CMS baseline and 0 month

intervals were statistically significant (CMS baseline: $F = 2.283$ and, 0 month: $F = 1.619$). The intervals at 3 and 6 months, however, were not statistically significant as each have p values greater than 0.05 at 0.69 and 0.65 and F statistics of .162 and .211, respectively. Hence, the albumin level mean differences at 3 and 6 months are most likely due to chance. This demonstrates that peritreatment hemodialysis patients with and without Type II diabetes showed a significant difference in albumin levels at time interval CMS and 0 months. However, the patients did not continue to show similar albumin patterns through the course of their treatment. Confirmation of the statistical insignificance of these intervals is seen in Table 8. The upper and lower bounds 95% CI [2.90, 3.07 and 2.96, 3.26] and 95% CI [3.33, 3.45 and 3.36, 3.57] in the CMS and 0 month intervals between both diabetic and nondiabetic groups do not overlap, thus confirming this conclusion.

Table 8

Between Group Differences of Albumin Levels According to Diabetes Status Over Time

		N	Mean	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
CMS baseline	Diabetic	281	2.9868	2.9022	3.0714	1.30	4.60
	Nondiabetic	124	3.1094	2.9637	3.2550	1.10	4.90
	Total	405	3.0243	2.9508	3.0979	1.10	4.90
0 months	Diabetic	281	3.3923	3.3318	3.4528	1.90	4.50
	Nondiabetic	124	3.4661	3.3616	3.5706	1.70	4.40
	Total	405	3.4149	3.3623	3.4675	1.70	4.50
3 months	Diabetic	281	3.6961	3.6508	3.7414	1.70	4.70
	Nondiabetic	124	3.7145	3.6254	3.8036	1.50	4.50
	Total	405	3.7017	3.6603	3.7432	1.50	4.70
6 months	Diabetic	281	3.8060	3.7619	3.8502	2.00	4.80
	Nondiabetic	124	3.8258	3.7463	3.9053	2.00	4.50
	Total	405	3.8121	3.7732	3.8510	2.00	4.80

Note. CMS is Centers for Medicare and Medicaid Services

Absolute and Relative Change

Research Question 2 seeks to ascertain if a difference in serum albumin levels exists at four different time intervals between Hispanics with and without Type II diabetes post treatment initiation. To address this question, the absolute and relative changes in albumin levels were computed and a Spearman's Correlation of albumin levels at these time intervals and Type II diabetes was conducted. A repeated measures *t* test was also conducted to further assess differences in albumin levels over time. The repeated *t* test was selected over a repeated ANOVA in order to clearly see effects across all four intervals (CMS baseline, 0, 3, and 6 months). Additionally, the repeated *t* test was used to generate information for future larger studies; for these larger studies a repeated ANOVA test would be ideal, as it would account for more information in variance over all time points and would control error rate. The absolute and relative albumin level computations for both the diabetic and nondiabetic groups and the entire Hispanic sample population are shown in Table 9. Figures 3 and 4 illustrate these findings.

Table 9

Average Absolute and Relative Albumin Level Changes at Four Time Intervals of Hispanic Cohort

Groups	Absolute Change	Relative Change (%)
Diabetic (CMS – 0 months)	0.40	18
Diabetic (0 – 3 months)	0.29	10
Diabetic (3 – 6 months)	0.11	4
Diabetic (0 – 6 months)	0.40	14
Nondiabetic (CMS – 0 months)	0.37	17
Nondiabetic (0 – 3 months)	0.25	9
Nondiabetic (3 – 6 months)	0.10	3
Nondiabetic (0 – 6 months)	0.35	12
All Hispanic Population (CMS – 0 months)	0.39	17

All Hispanic Population (0 – 3 months)	0.28	10
All Hispanic Population (3 – 6 months)	0.11	3
All Hispanic Population (0 – 6 months)	0.39	13

Note. CMS is Centers for Medicare and Medicaid Services

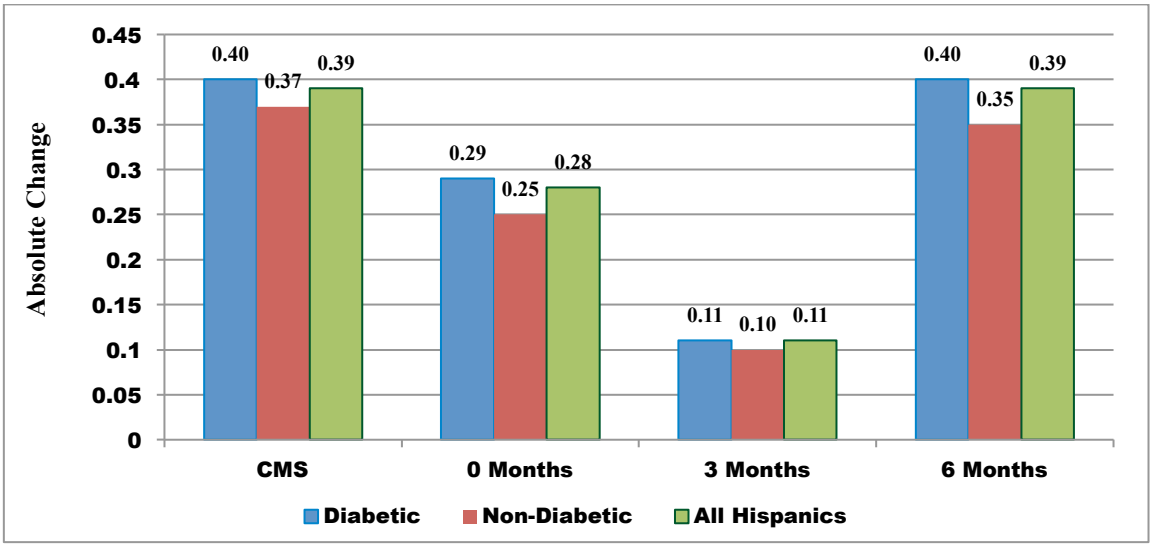


Figure 3. Albumin Absolute Change Among Hispanics With and Without Type II Diabetes. CMS is Centers for Medicare and Medicaid Services

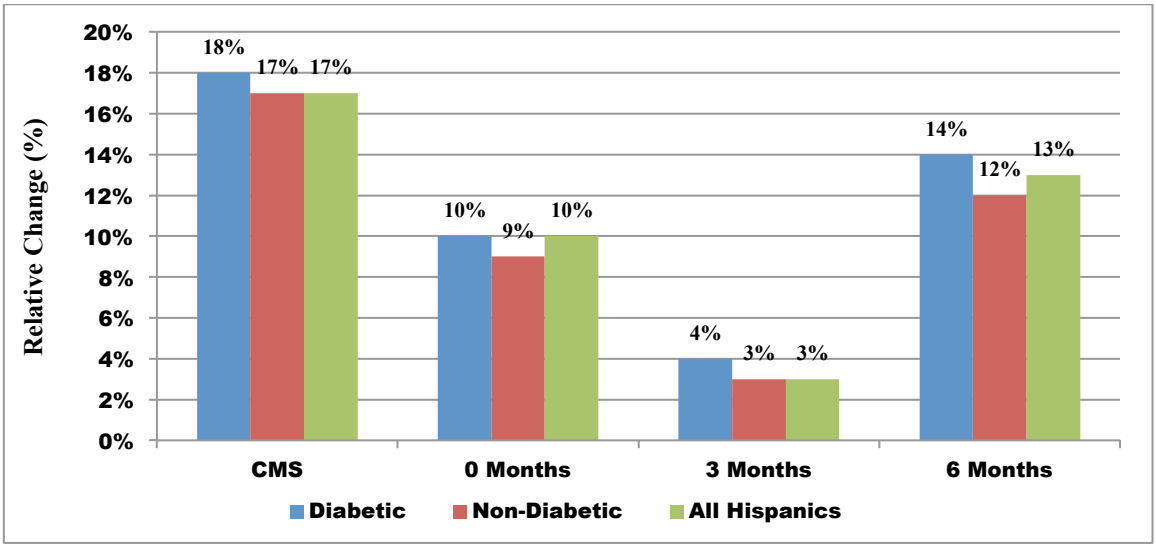


Figure 4. Albumin Relative Change Among Hispanics With and Without Type II Diabetes. CMS is Centers for Medicare and Medicaid Services

Compared to the entire Hispanic cohort, the results show a greater albumin level absolute and relative change at time interval CMS to 0 months in the diabetic group than

any other time interval (0.40mg/dL and 18%). At the 3 to 6 month interval, the least amount of change occurred, (0.11mg/dL and 4%). This was also true for the entire Hispanic sample population, which showed a 0.11mg/dL and 3% absolute and relative change, respectively.

Spearman's Correlation

Spearman's rank-order correlation was conducted to determine if a correlation exists between albumin levels and Type II diabetes over time. This nonparametric test was selected because the data violated the required assumptions for the Pearson's Correlation test and therefore it was not a suitable model. Upon scatterplot analysis, the data points were not normally distributed and the data showed monotonicity between the variables at each time interval, satisfying the requirement for the Spearman Correlation (Data not shown). A monotonic relationship exists when either the variables increase in value together, or as one variable value increases, the other variable value decreases. The results showed a strong, positive correlation between albumin levels at all four intervals and Type II diabetes. In terms of the direction of the correlation, a Type II diabetes diagnosis influenced albumin levels over time. In terms of the magnitude of the correlation, both the CMS baseline and the 0 month intervals showed the highest correlation value ($r = .723$), followed by the 3 and 6 month intervals ($r = .629$). A more moderate correlation was noted between the 0 and 6 month interval ($r = .441$). All intervals were statistically significant as denoted by the asterisks and a $p < .000$ (Table 10).

Table 10

Spearman Correlation for Albumin Levels at Four Intervals

		Diabetic Status	CMS baseline	0 months	3 months	6 months
Diabetic Status	Correlation Coefficient	1	0.082	0.08	0.072	0.063
	Sig. (2-tailed)	.	0.098	0.11	0.149	0.209
	N	405	405	405	405	405
CMS baseline	Correlation Coefficient	0.082	1	.723**	.447**	.297**
	Sig. (2-tailed)	0.098	.	0.000	0.000	0.000
	N	405	405	405	405	405
0 months	Correlation Coefficient	0.08	.723**	1	.629**	.441**
	Sig. (2-tailed)	0.110	0.000	.	0.000	0.000
	N	405	405	405	405	405
3 months	Correlation Coefficient	0.072	.447**	.629**	1	.689**
	Sig. (2-tailed)	0.149	0.000	0.000	.	0.000
	N	405	405	405	405	405
6 months	Correlation Coefficient	0.063	.297**	.441**	.689**	1
	Sig. (2-tailed)	0.209	0.000	0.000	0.000	.
	N	405	405	405	405	405

** Correlation is significant at the 0.01 level (2-tailed); Note. CMS is Centers for Medicare and Medicaid Services

Repeated Measures *t* test for Albumin Levels

Repeated measures analysis can be used to assess and serially measure changes over time in an outcome variable. This test is also used to test for differences in one or more treatments based on repeated assessments in the same subjects. To address Research Question 2, a repeated measures *t* test was conducted to determine if albumin level differences exist over time in hemodialysis patients with and without Type II diabetes. Because albumin levels were examined over four different intervals and because the examination was conducted on a cohort of subjects who's serum albumin were serially measured and compared, this statistical test fits the model to address

Research Question 2. A regression analysis with the variable time integrated into the model, although quicker, would not show specific potential albumin level decreases in patients. Furthermore, a regression model assumes a linear relationship between the outcome variable and the independent variable. Albumin level changes over time differ among patients; in some patients, albumin levels may initially increase and then decrease over time, and in some patients the opposite effect is observed. Furthermore, in some patients albumin levels remain relatively constant from dialysis onset over the course of their treatment therefore albumin levels do not follow a linear trend. The repeated measures *t* test was used to generate information for future larger cohort studies for which a regression model would be ideal, as it would account for more information in variance over all time points. For this study, repeated measure *t* tests provide very specific albumin level data points over time and therefore, although a bit more time consuming, were ideal for this study. These values serve as useful clinical indicators vital for patient care. The results of the repeated measures *t* tests of albumin levels at four different time intervals, CMS – 0 months, 0 – 3 months, 3 – 6 months, and 0 – 6 months are shown in Tables 11-18.

The patients in the diabetic group had a Type II diabetes diagnosis (ICD-9 code 25040 and 25000A) as either cause of renal failure or as an associated comorbidity. For the diabetic group (n = 281) CMS to 0 month interval, the difference in albumin means was -0.41, 95% CI [-0.46, -0.35], suggesting that the albumin levels decreased from the time the patients were hospitalized and diagnosed with renal failure to when they initiated treatment at the dialysis treatment centers. The correlation was significant, ($p < .000$) at

0.730. Table 11 shows a significant 2-tailed paired samples *t* test at ($p < .000$) and an upper and lower 95% confidence interval of the difference that does not include the value of 0, confirming the significance.

Table 11

Repeated Measures t test: CMS – 0 Months (Diabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
CMS baseline 0 months	-0.40544	0.49253	0.02938	-0.46328	-0.34761	-13.799	280	0.000

Note. CMS is Centers for Medicare and Medicaid Services

For the 0 to 3 month interval, the diabetic population ($n = 281$), the difference between both means was significant ($p < .000$) at -0.3, 95% CI [-0.35, -.026], suggesting that peritreatment the albumin levels were improving through the course of their dialysis. The correlation was significant ($p < .000$) at 0.615. The upper and lower bounds of the 95% confidence interval of the difference did not include the value of 0, thus confirming this result (Table 12).

Table 12

Repeated Measures t test: 0 Months – 3 Months (Diabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
0 months 3 months	-0.30381	0.40840	0.02436	-0.35177	-0.25585	-12.470	280	0.000

For the 3 to 6 month interval, the diabetic population ($n = 281$), the difference between both means was significant ($p < .000$) at -0.11, 95% CI [-0.15, -0.07], suggesting

that peritreatment the albumin levels continued to improve, albeit not as markedly as the 0 to 3 month interval, through the course of their dialysis. Comparing the two mean differences (-0.30 and -0.11) at the 0 to 3 month and the 3 to 6 month intervals, respectively, although significant, suggests the albumin level changes were not as pronounced through the course of their treatment and therefore improvement trends decreased slightly during that time interval. The correlation at the 3 to 6 month interval was significant ($p < .000$) at 0.598. Additionally, the upper and lower bounds of the 95% confidence interval of the difference did not include the value of 0, thus confirming this result (Table 13).

Table 13

Repeated Measures t test: 3 Months – 6 Months (Diabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
3 months 6 months	-0.10996	0.34159	0.02038	-0.15008	-0.06985	-5.396	280	0.000

To achieve a more comprehensive albumin profile, the 0 to 6 month interval was also tested. For the diabetic group at this interval ($n = 281$), the difference between both means was significant ($p < .000$) at -0.41, 95% CI [-0.47, -0.35], suggesting that peritreatment the albumin levels showed an improvement trend. This trend reflected the improvement trend of the CMS to 0 interval. The computed mean difference between these two intervals was a mere -.01, 95% CI [-0.47, -0.35], suggesting that at this larger interval albumin trends demonstrated similar improvement patterns as when they were first initiated on dialysis. The overall trend at this larger interval suggests that

improvement patterns throughout the entire 6-month course of their treatment were increasing. The slight acceleration noted between the CMS to 0 and the 0 to 3 month interval may be due to the newly prescribed, vigorous and effectual dialysis treatments, which would begin to effectively remove the excess fluid collected in their body because of their renal failure. At the 0 to 6 month interval, the correlation was significant ($p <$ .000) at .399. Furthermore, as shown in Table 14, the upper and lower bounds of the 95% confidence interval of the difference did not include the value of 0, thus confirming this result.

Table 14

Repeated Measures t test: 3 Months – 6 Months (Diabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
0 months 6 months	-0.41377	0.50197	0.02994	-0.47272	-0.35483	-13.818	280	0.000

The repeated measures statistical treatment was also applied to the nondiabetic group for comparative analysis. First, the CMS to 0 interval was conducted on the nondiabetic subpopulation ($n = 124$). The results showed a significant ($p <$ .000) correlation value of 0.764. The mean difference was -0.36 with a lower and upper bound values that did not include the value of 0, 95% CI [-0.45, -0.26]. The 2-tailed test was significant at $p <$ .000 (Table 15).

Table 15

Repeated Measures t test: CMS – 0 Months (Nondiabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
CMS baseline 0 months	-0.35677	0.53009	0.0476	-0.451	-0.26255	-7.495	123	0.000

Note. CMS is Centers for Medicare and Medicaid Services

The results of the repeated measures *t* test at the 0 to 3 month interval are shown on Table 16. The mean difference was -0.25, which was lower than the CMS to 0 interval. This smaller difference suggests that, although significant at $p < .000$, albumin level changes were not as marked as the previous interval. The correlation value of 0.738 was significant at $p < .000$. The 95% confidence interval of the difference did not include the value of 0, CI [0.32, -0.18], thus confirming the statistical significance.

Table 16

Repeated Measures t test: 0 Months – 3 Months (Nondiabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
0 months 3 months	-0.24839	0.40233	0.03613	-0.3199	-0.17687	-6.875	123	0.000

The mean difference at the 3 to 6 month interval ($n = 124$) dropped to -0.11, 95% CI [-0.16, -0.06]. A similar drop in mean differences was noted in the diabetic group (-0.11). This slightly lower value noted in the diabetic group, suggests that for these data a diabetes diagnosis might be, at least in part, slightly lowering albumin levels compared to the nondiabetic group. The correlation value at this interval was significant ($p < .000$) at 0.853. Correspondingly, the 95% confidence interval of the difference, CI [-0.16, -0.06] did not include the value of 0, thus confirming the results (Table 17).

Table 17

Repeated Measures t test: 3 Months – 6 Months (Nondiabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
3 months 6 months	-0.11129	0.26264	0.02359	-0.15798	-0.0646	-4.719	123	0.000

Lastly, the 0 to 6 month time interval (n = 124) provided an expanded timeline to analyze albumin levels. The data generated from this test in the nondiabetic group served as the comparison group for the diabetic group. The difference in mean values between the diabetic group and the nondiabetic group were -0.41 and -0.36, 95% CI [0.45, -0.27], respectively. The slightly higher value in the diabetic cohort suggests albumin levels differences were slightly more pronounced than those in the nondiabetic cohort. It's reasonable to suggest that this higher value may be due to some degree to having Type II diabetes. The correlation at this larger interval was significant (p < .000) at 0.544. The 95% confidence interval of the difference was CI [-0.45, -0.27] and did not include the value of 0, confirming the significance of the statistical treatment (Table 18).

Table 18

Repeated Measures t test: 0 Months – 6 Months (Nondiabetic Group)

	Paired Differences					*t*	*df*	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
0 months 6 months	-0.35968	0.50973	0.04578	-0.45029	-0.26907	-7.857	123	0.000

Strong, positive correlation values in both groups coupled with *p* values less than .05, suggests that in this population a Type II diabetes diagnosis may modulate albumin levels in hemodialysis patients. The slightly higher mean differences at the larger time interval in the diabetic group suggests that albumin level changes are slightly more pronounced, revealing that albumin level patterns, albeit nuanced, are different between both groups. The albumin level patterns seen at three different intervals are summarized in Figure 5. The separation between the diabetic group (blue) and the nondiabetic group (red) at the CMS and 0 month interval confirms the results of the repeated measures *t* tests. Also in alignment with the repeated measures *t* test, the latter intervals of 3 and 6 months show trend lines demonstrating similar improvement trends. Both trend lines gradually approach each other and plateau at the 6-month time interval, suggesting that improvement trends in the diabetic group were normalizing faster in order to reach normoalbuminemic levels similar to the nondiabetic group.

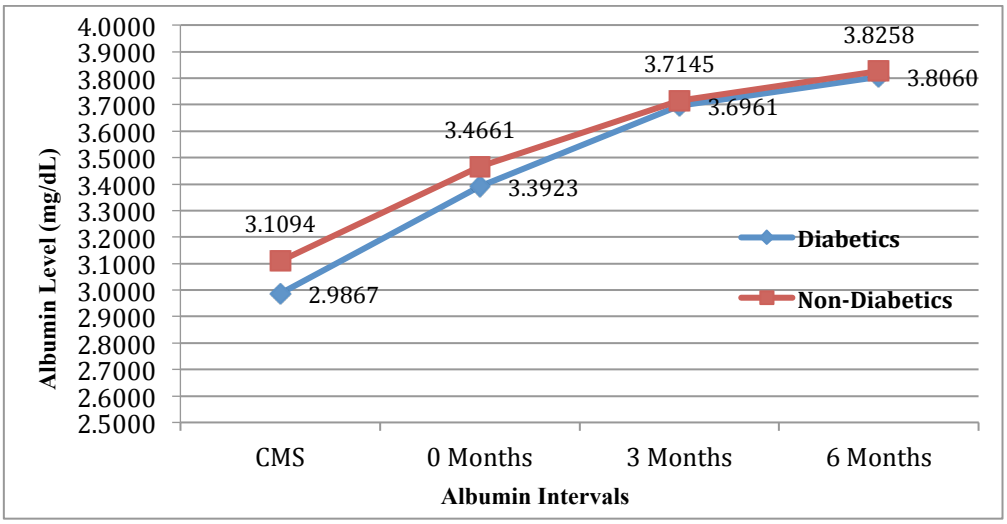


Figure 5. Albumin Level Differences Between Diabetic and Nondiabetics. CMS is Centers for Medicare and Medicaid Services

Stratified Analysis of Albumin Levels

The sample data were stratified to investigate whether any interaction occurred within specific strata that may not be appreciable in the entire cohort. First, the data were "split" on SPSS according to gender and the previous statistical tests were conducted to determine if albumin level differences mirrored or deviated from those of the whole Hispanic cohort. A new post-hoc power analysis was generated using G*Power software to determine power with the new strata. Each post-hoc power analysis amply satisfied statistical power for the study. Generated descriptive statistics showed 215 males and 190 females total in each strata. In the male stratum, there were $n = 147$ and $n = 68$ patient records in the diabetic and nondiabetic group, respectively. Post-hoc power analysis for the male stratum was (Power > 0.99, effect size = 0.5, alpha = 0.05). The female stratum had $n = 134$ and $n = 56$ diabetic and nondiabetic records, respectively. Post-hoc analysis for the female stratum was (Power > 0.99, effect size = 0.5, alpha = 0.05). The stratified ANOVA revealed there was no difference in the mean albumin values between males and females. p values for males were .522, .666, .685, and .475 and .137, 171, .916 and .846 for females, all of which fall above the standard $p < .05$ demarcation, which confirmed this conclusion. Furthermore, the results did not reflect the outcome from the entire Hispanic cohort since both the CMS to 0 months and 0 to 3 month intervals were statistically significant in that test.

A Spearman correlation was run to determine if a significant correlation exists within strata. The results reflected that of the entire cohort. Albumin levels at each time interval showed significant 2-tailed correlation at .01. Whereas the p values in the

original unstratified Spearman Correlation showed a strong correlation value of $p < .000$, within these strata, a slight increment ($p = .002$) in the correlation between the CMS baseline and 6 month interval was observed in the male stratum.

For the repeated measures *t* test, the strata were comprised of $n = 147$ male diabetics and $n = 134$ female diabetics. These strata generated sufficient power for analysis (Power = .99). The significance values at each time interval were essentially identical to the original test in the diabetic group at $p < .000$. All other intervals showed significant values of $p < .000$; the only remarkable interval was the 0 to 6 month interval in the male stratum, which showed a *p* value of .001.

When the test was repeated for the nondiabetic group, the results were similar. The *n* value to qualify for this group decreased within each stratum ($n = 68$ males and $n = 56$ females). The post-hoc power analysis generated a value of 0.78, which is sufficient power with medium effect size of .50 to warrant further analysis. Overall, the tests were identical to the original repeated measures *t* test, except for the 3 to 6 month time interval in the female stratum, which revealed a significant .014 *p* value.

After running a post-hoc power analysis for the stratified multiple logistic regression analysis, there was insufficient power between both groups and associated comorbidities (Power = 0.47). Since G*Power generated insufficient power, further analysis was not conducted.

Next, the data were split by clinic locale to determine if albumin levels differed within clinics. Since each clinic is located in a different region and represents a different demographic of San Antonio, the same statistical tests were conducted to identify

potential albumin level differences in each San Antonio region. For four consecutive weeks, the medical records at seven dialysis clinics were accessed with prior IRB and Frenova Renal Research approval. Data were extracted from each record and amassed on spreadsheets. The seven dialysis clinics are no more than 20-30 minutes away from each other; their proximity facilitated access and minimized driving time between clinics in order to easily verify data that were incomplete, inaccurate, missing, or pending. The four weeks entailed diligently analyzing medical records and amassing the necessary data to conduct the study. The data were collected daily for 6-16 hours a day including weekends until all electronic and paper medical records in each facility were reviewed and necessary data extracted for analysis. The one-way ANOVA test showed that of the seven clinics, only clinic 8861 showed significance at the 3 and 6 month interval ($p < .005$), with insufficient power generated by G*Power (Power = 0.45). This clinic is located in downtown San Antonio, so is a centralized location with a predominately Hispanic and Black population and a mean age of 63.2 years, which is the second lowest among the seven clinics. This was the only remarkable difference from the ANOVA run for the unstratified cohort.

The repeated measures *t* tests for the original cohort revealed strong correlation ($p < .05$) for each interval for both groups. In the stratified analysis repeated measures *t* tests there were some remarkable differences from the original unstratified analysis. First, in the diabetic group the CMS to 0 month interval showed identical significant correlation and significant 2-tailed values except in clinic 6618 which showed a correlation value of .002. This clinic is located on the west side of San Antonio, which is predominately a

Mexican population and Hispanic Americans of Mexican decent. Second, in the 0 to 3 month interval, only clinic number 8855 (n = 46) showed a 2-tailed p value for the paired samples test of .018 that was different from the unstratified cohort. This significant value was generated with sufficient power (Power = .66). Third, both the 3 to 6 month and the 0 to 6 month intervals showed differences in significant values for both correlation and paired samples t tests. Clinics 1664 (stratum = 53), 8855 (stratum = 46), and 8868 (stratum = 42 showed significant 2-tailed p values of .033, .003, and .025, respectively, with sufficient power (1664 power = 0.72, 8855 power = 0.66, and 8868 power = 0.63) for a medium effect size. Clinics 1648, 8856, and 8861 were not significant ($p > .05$) at this time interval (p value = .232, .942 and .186), respectively. Although the sample size for both strata were smaller than the original unstratified cohort, (n = 147 for males and n = 134 for females), the generated power for this analysis was amply achieved by G*Power.

Lastly, at the larger time interval 0 to 6 months, clinics showed significant 2-tailed paired test $p < .000$. Clinics 1648, 1664, 1618, 8855, 8856, 8861, and 8868 showed significant correlation values of .001, .001, .004, .060, .002, .073, and .004, respectively; these values were all significant except clinics 8855 and 8861. The pair samples t test values at a 95% confidence interval, stratified by seven clinics overall showed statistical significance ($p < .000$). Amongst the groups, the smallest stratum (n = 28) did not satisfy statistical power (Power = .45) and therefore further stratified analysis on this clinic was not further investigated.

Next, SPSS was used to filter the nondiabetics and the cases were again split to report on individual clinics. None of the clinics generated sufficient power on G*Power to warrant stratification analysis. Since clinic 8861 had the largest strata from this group (n = 23), it was used as the threshold to determine power. G*Power generated 0.32 as the statistical power, which meant none of the other clinics would generate sufficient power to warrant further stratification analysis.

After running a post-hoc power analysis for the Spearman correlation, only clinic 8856 (strata = 28) did not retain sufficient power for analysis (Power = 0.45). The six remaining clinics qualified with sufficient power to warrant further analysis. Clinics 1648, 8855, 8856, 8861 had significant correlation values of $p < .000$, which was comparable to the original Spearman Correlation test run for the unstratified cohort. Three clinics showed correlation values that were not statistically significant and this result was not seen in the unstratified test; clinic 1664, 6618, and 8868 had p values of .246, .772, and .183 at the CMS to 6 month interval. Clinics 6618 also had correlation values at the CMS to 3-month interval that were not significant (p = .276.). Similarly, clinic 8868 had a correlation value of .234 that was not significant at the 0 to 6 month interval. The six clinics that qualified for stratified analysis showed strong, positive correlations between albumin levels and Type II diabetes at each time interval.

In the nondiabetic group, the minimum stratum size was n = 23. After running a post-hoc power analysis for the Spearman Correlation analysis for the nondiabetic group stratified by clinic locale, there was insufficient power generated by G*Power (Power = .38), so further analysis was not pursued.

Multiple Logistic Regression

Logistic regression was carried out to assess the interrelationships and the relative contributing strengths and probabilities for each of the covariables (predictors) that could potentially modify albumin levels over time in this study population. Research Question 3 aims to investigate if patients with and without a Type II diabetes diagnosis and associated comorbidities such as hypertension, peripheral vascular disease, and infection/inflammation, might modulate albumin levels in hemodialysis patients. As presented in the stratified analyses, gender was a demographic consideration, but was not controlled for in the regression analysis because G*Power generated insufficient power (Power = .74) after introducing it into the model. Additionally, age was not controlled in this analysis for similar reasons. The mean age was nearly identical (*Average M* = 64.7 years) across the board for each clinic, as was educational level and employment for each clinic and therefore were not included in the model. For this analysis, the independent variables were operationalized and uploaded onto SPSS for analysis and retained in all iterations to assess the relative contribution at each time interval. Diabetic patient records with one or more of these covariables were transformed into dichotomous variables, yes or no. The dependent variable albumin was transformed into binary variables of 0 if the values were <4.0mg/dL and 1 for albumin values ≥4.0mg/dL. These cut off values were based upon KDOQI clinical guidelines, which recommend a target albumin level of ≥4.0mg/dL, which is consistent with optimal cardiovascular and renal function. Tables 19 -22 illustrate the final results of this test at each time interval.

Each regression analysis model had 405 total records. For the CMS baseline time interval, $n = 359$ (88.6%) patients had an albumin level value <4.0mg/dL. For the 0, 3, and 6-month intervals, the values were $n = 333$ (82.2%), $n = 289$ (71.4%), and $n = 252$ (62.2%), respectively. The post-hoc analysis for CMS baseline, 0, 3, 6 month intervals was greater than 0.99. The declination of participants with albumin levels <4.0mg/dL over time suggests that improvement trends were observed in this population. There were $n = 366$ patients with hypertension, $n = 43$ with PVD, and $n = 74$ with infection/inflammation according the case processing summary. The parameter estimates table showed p values of .447, .935, and .173 for hypertension, PVD, and infection/inflammation, respectively, for the three comorbidities. The medium effect size of 0.5 was appropriate for this analysis. The p values for each comorbidity suggest that the relative contribution by each predictor variables to patients with Type II diabetes is not significant and hence the inclusion of these covariables did not significantly contribute to influencing albumin levels in this population. The confidence interval for each predictor included 1, 95% CI [.47, 5.5], 95% CI [.36, 2.6], 95% CI [.19, 1.3], thus confirming this result (Table 19).

Table 19

Parameter Estimates – CMS Baseline Interval

CMS Baseline Albumin[a]	B	Std. Error	Wald	*df*	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Intercept	2.627	0.668	15.448	1	0.000			
[HBP = 0]	0.474	0.624	0.578	1	0.447	1.607	0.473	5.457
[HBP = 1]	0[b]	.	.	0	.	.	.	.
[PVD = 0]	-0.041	0.506	0.007	1	0.935	0.959	0.356	2.588
[PVD = 1]	0[b]	.	.	0	.	.	.	.

[Infect = 0]	-0.673	0.494	1.857	1	0.173	0.51	0.194	1.343
[Infect = 1]	0_b	.	.	0	.	.	.	.

a The reference category is: Albumin =>4.0
b This parameter is set to zero because it is redundant
Note. CMS is Centers for Medicare and Medicaid Services; HBP is high blood pressure; PVD is peripheral vascular disease; Infect is infection/inflammation

The 0 month interval showed similar results. For this interval there were $n = 366$ patients with hypertension, $n = 43$ with PVD, and $n = 74$ with infection/inflammation, according to the case processing summary. Although the results showed lower p values for hypertension and PVD than the CMS time interval ($p = .389$, .700, and .278) for each predictor, respectively, overall the results were not significant at this interval. This suggests that there is no significant difference in albumin levels in diabetic patients with one or more of these associated comorbidities in this population. Decrements in albumin levels, therefore, may have been due to other factors. Once again, the lower and upper bounds of the 95% confidence interval included 1, CI [.58, 4.1], CI [.36, 2.0], CI [.33, 1.4], thus confirming this outcome (Table 20).

Table 20

Parameter Estimates – 0 Month Interval

0 Month Albumin$_a$	B	Std. Error	Wald	*df*	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Intercept	1.981	0.539	13.528	1	0.000			
[HBP = 0]	0.43	0.499	0.743	1	0.389	1.537	0.579	4.084
[HBP = 1]	0_b	.	.	0	.	.	.	.
[PVD = 0]	-0.169	0.437	0.148	1	0.700	0.845	0.359	1.991
[PVD = 1]	0_b	.	.	0	.	.	.	.
[Infect = 0]	-0.401	0.369	1.179	1	0.278	0.67	0.325	1.381
[Infect = 1]	0_b	.	.	0	.	.	.	.

a The reference category is: Albumin => 4.0
b This parameter is set to zero because it is redundant
Note. HBP is high blood pressure; PVD is peripheral vascular disease; Infect is infection/inflammation

The improvement in statistical significance is most notable in the 3 month time interval. At this interval, there were $n = 366$ patients with hypertension, $n = 43$ with PVD, and $n = 74$ with infection/inflammation. The generated p values and 95% confidence intervals were $p = .124$, CI [.83, 4.5], $p = .830$, CI [.46, 1.9], and $p = .519$ CI [.47, 1.5]. Though not significant, hypertension showed a lower p value from the 3 month interval, suggesting that when compared to the other two comorbidities included in the model, this predictor contributed the most towards modulating albumin levels. Since albumin trends showed improvement trends with the inclusion of these covariables in the analysis, it is reasonable to conclude that the prescribed dialysis treatments along with other dietary, educational, and lifestyle modifications may be improving albumin levels in this population despite their comorbidities (Table 21).

Table 21

Parameter Estimates – 3 Month Interval

3 Month Albumin[a]	B	Std. Error	Wald	*df*	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Intercept	1.083	0.435	6.186	1	0.013			
[HBP = 0]	0.666	0.433	2.366	1	0.124	1.947	0.833	4.548
[HBP = 1]	0[b]	.	.	0	.	.	.	.
[PVD = 0]	-0.078	0.362	0.046	1	0.830	0.925	0.455	1.880
[PVD = 1]	0[b]	.	.	0	.	.	.	.
[Infect = 0]	-0.19	0.294	0.417	1	0.519	0.827	0.465	1.472
[Infect = 1]	0[b]	.	.	0	.	.	.	.

a The reference category is: 1
b This parameter is set to zero because it is redundant
Note. HBP is high blood pressure; PVD is peripheral vascular disease; Infect is infection/inflammation

Lastly, the 6 month interval regression analysis was also not significant. The p values and 95% confidence intervals were $p = .541$, CI [.62, 2.5], $p = .696$, CI [.45, 1.7],

and $p = .612$, CI [.68, 1.9] for the same predictors, respectively. There were $n = 366$ patients with hypertension, $n = 43$ with PVD, and $n = 74$ with infection/inflammation. These data were also not significant and relative to the previous three intervals, the p values were higher in most of the models in comparison (Table 22), suggesting that the contribution of these covariables in modulating albumin levels was less than the three previous intervals.

Table 22

Parameter Estimates – 6 Month Interval

6 Month Albumin[a]	B	Std. Error	Wald	*df*	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
							Lower Bound	Upper Bound
Intercept	0.488	0.4	1.491	1	0.222			
[HBP = 0]	0.218	0.357	0.374	1	0.541	1.244	0.618	2.502
[HBP = 1]	0[b]	.	.	0	.	.	.	.
[PVD = 0]	-0.132	0.339	0.153	1	0.696	0.876	0.451	1.703
[PVD = 1]	0[b]	.	.	0	.	.	.	.
[Infect = 0]	0.134	0.264	0.257	1	0.612	1.143	0.682	1.916
[Infect = 1]	0[b]	.	.	0	.	.	.	.

a The reference category is: Albumin => 4.0
b This parameter is set to zero because it is redundant
Note. HBP is high blood pressure; PVD is peripheral vascular disease; Infect is infection/inflammation

Summary of Findings

This study was focused on investigating potential albumin level differences between dialysis patients with and without Type II diabetes. This research study has three research questions. The statistical tests conducted and presented in this chapter aimed to address these questions to determine if the null hypotheses were to be rejected. Research Question 1 aimed to determine if there was a difference in albumin levels between dialysis patients with and without Type II diabetes. The quantitative computations of

absolute and relative changes showed a difference in albumin levels between both groups. The results of the ANOVA were significant at all CMS baseline and 0 month time intervals. The 3 and 6 month intervals, however, were not significant. The Spearman Correlation test showed a strong, positive correlation between albumin levels and a Type II diabetes diagnosis at all four time intervals. This finding suggests that hemodialysis patients with Type II diabetes have albumin levels that trend differently than nondiabetic hemodialysis patients.

Research Question 2 aimed to investigate if albumin levels differed amongst both groups over four time intervals during their treatment. The repeated measures *t* tests for both groups showed strong, statistically positive correlations. These findings suggest that there were significant differences in albumin levels within each time interval. When both groups were compared, changes between each group followed dissimilar modulation patterns. When mean differences were compared between both groups, the diabetic group showed disproportionately larger mean differences at the CMS to 0 and 0 to 3 month intervals, while plateauing at the 3 and 6 month time intervals (Figure 5). This suggests that albumin level differences in the diabetic group deviated from those in the nondiabetic group and it may be reasonably plausible that in this population Type II diabetes may be lowering albumin levels when compared to patients without the disease.

Lastly, Research Question 3 aimed to determine if three known predictors modulated albumin levels in patients with and without Type II diabetes undergoing hemodialysis treatments. The multiple logistic regression analyses showed the three predictor variables hypertension, peripheral vascular disease, and infection /inflammation

did not significantly modulate albumin levels in this population, contrary to what was hypothesized in Research Question 3. Previous literature confirms that these covariables are known to influence albumin levels in dialysis patients in some manner and to some magnitude. These findings were not confirmed with appreciable significance in this sample population. Further discussion, elaboration, and interpretation of these findings will be presented in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

As the most abundant plasma protein, albumin plays significant physiological roles to maintain physiological homeostasis. As elucidated in Chapter 2, the protein's primary role in the body is colloid osmotic pressure maintenance, which is explicated from and framed by osmosis and osmotic pressure principles that underpin this study. It is by these fundamental principles that fluids are moved into various cellular compartments pulling fluid into the circulatory system through the capillaries, maintaining homeostatic blood pressure. A reduction of albumin in plasma, therefore, can cause a decrease in colloid osmotic pressure and subsequently tissue edema (Ahren & Burke, 2012).

Epidemiological information about renal disease, hypoalbuminemia, albuminuria, and Type II diabetes reveals a significant public health concern. According to Chukwueke and Cordero-MacIntyre (2010), an estimated 17.5 million people in the United States were diagnosed with either Type I or Type II diabetes in 2007. In that year, diabetes was the leading cause of blindness in people between the ages 20 and 74 years and of end-stage renal disease (ESRD) in Hispanic Americans (Chukwueke & Cordero-MacIntyre, 2010). Type II diabetes prevalence is 14% in the Hispanic population (Black, 2002). This group suffers a higher risk of mortality and microvascular complications including renal disease. When kidney disease is strongly associated as a comorbidity, the consequence is often albuminuria in patients with Type II diabetes (Choi et al., 2011; Yokoyama et al., 2011; Zakerkish et al., 2013). Albuminuria is confirmation of the consequences of glomerular destruction, compromised renal filtration (Mendez et al.,

2005), and of the complete departure from fundamental osmotic pressure principles that govern basic membrane function and physiological homeostasis. Albumin levels are lower in Hispanics since the incidence of diabetes is higher in this population. The higher occurrence of renal failure and subsequent improper renal filtration, the lower albumin levels become in Hispanic patients receiving maintenance hemodialysis (Black, 2002; Lorenzo et al., 2009; Yokoyama et al., 2011; Zakerkish et al., 2013). Consequently, the number of Hispanics requiring hemodialysis rose by 70% between 1996 and 2001 (Lash et al., 2005), correlating with observations that this population is the fastest growing demographic in the U.S. (Kanna et al., 2007) and thus the most appropriate population for this study.

The objective of this quantitative, retrospective study was to examine the relationship between and potential differences of serum albumin levels in Hispanic patients initiating hemodialysis treatment due to renal disease associated with a Type II diabetes diagnosis and those without the disease after controlling for gender, hypertension and other comorbidities. A retrospective examination of the medical records of these patients was conducted to determine if albumin levels differ in a population of adult Hispanic, hemodialysis patients with and without a Type II diabetes diagnosis. Furthermore, the research aimed to ascertain if albumin levels followed improvement trends observed from hemodialysis treatment onset and if known predictors influenced normoalbuminemic levels. Patient medical records were analyzed at baseline (CMS), 0 months, 3 months, and 6 months post baseline to ascertain potential differences in

albumin levels between patients with and without Type II diabetes during the course of their dialysis treatments.

This was a historic, records-based cohort study of all $N = 827$ hemodialysis patients, Hispanic diabetic group ($n = 367$) and Hispanic nondiabetic group ($n = 186$), evaluated and treated at Fresenius Medical Center - North America clinics in San Antonio. The cohort included all current patients on the treatment schedules at each dialysis facility and patients that were deceased that had complete medical records stored at these facilities. The overarching research question was: Is there a difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment? The null hypothesis for this study was that there was no difference in serum albumin levels between Hispanics with and without Type II diabetes initiating hemodialysis treatment (Mean differences: CMS baseline interval = 3.1 mg/dL, $p = .032$, 0 month interval = 3.4 mg/dL, $p = .004$, 3-month interval = 3.7 mg/dL, $p = .687$, 6-month interval = 3.8 mg/dL, $p = .646$). The prescribed hemodialysis treatment applied at the CMS baseline interval and the albumin level improvements that indirectly occur are reflected in the 0 month interval. The rigorous hemodialysis treatments are designed to remove fluid overload during the interdialytic period and remove uremic toxins in the bloodstream. The 0 month interval specifically reflects these hemodynamic improvements and hence greater improvements in albumin levels. Compared to the other intervals, the 0 month interval reflects these greater albumin differences from CMS baseline interval, with a statistically significant p value of .004. For Research Question 2 and Research Question 3, the research questions were: Is there a difference in albumin

levels over the course of patient treatments? And, is there a relationship between known predictors, albumin levels, and Type II Diabetes that may modulate albumin levels? Null hypotheses were: there is no difference in albumin levels over time and no significant relationship between the study covariables and the dependent variable.

In this study, albumin levels were compared in both groups. The comparison group without diabetes showed baseline albumin levels from which the diabetic group could be compared. The variables of interest were baseline (CMS) albumin levels, albumin levels at, 0, 3 and 6 months, and a Type II diabetes diagnosis. Bivariate and multivariate analyses were employed to evaluate these differences. In addition to the variables of interest, the other well established covariables known to have significant influence in modulating albumin levels such as hypertension, peripheral vascular disease, and infection/inflammation needed to be included in the analyses and appropriately controlled for analysis.

In contrast to the results of this study, other studies have reported a clear association between the known predictors hypertension, serum albumin, and renal failure. Reasons for this conflicting outcome might be due to the proposed sample size, underreporting of the comorbidity on the CMS forms, differences of water consumption during the interdialytic period, or any combination of these factors. Because the results of this comorbidity contrasted with what is known in the literature, this warrants further explanation. As explicated in Chapter 2, under normal physiological circumstances albumin is excluded from being filtered through the glomeruli because of its relative size and negative charge (Mendez et al., 2005). Essential hypertension changes glomerular

hemodynamics, which leads to progressive glomerular damage (Yokoyama et al., 2011). As renal damage progresses, glomerular perfusion pressure increases in the remaining viable glomeruli in order to drive compensatory hyperfiltration. This glomerular capillary hypertension is translated into increased mechanical stress affecting glomerular cells, including podocytes, mesangial, and endothelial cells (Fogo, 2000). Hypertension consequently destroys the glomeruli in the kidneys, compromising renal filtration and thus allowing albumin to seep into the urinary system for eventual excretion. This abnormal albuminuria affects albumin levels in patients with renal failure. Although not demonstrative in this study, the literature does show an association between hypertension, serum albumin, and renal failure.

The hypoalbuminemia observed in hypertensive hemodialysis patients is similarly observed in patients with peripheral vascular disease (PVD). PVD is a common circulatory problem in which narrowed arteries reduce blood flow to the extremities (American Heart Association, 2015). The added pressure that is incurred on the circulatory system affects the glomeruli in the kidneys, compromising the renal filtration system, thus permitting albumin seepage into the urine. The literature elucidates that PVD is a known predictor that can potentially affect albumin levels. This elucidation, however, was not evidenced in this study.

A compromised immune system due to renal failure and/or associated comorbidities, increases the risk of infections in patients on maintenance hemodialysis. Patient susceptibility to infection increases with renal failure. Access to the vascular system through arteriovenous graft implantation may exacerbate this risk (Nassar &

Ayus, 2001). In the predialysis era, 60% of patients with chronic renal failure that required hospitalization were infected and 39% died from infectious causes (Antimicrobe, 2014). At that time, it was assumed that the debility caused by the uremic state increased the risk of infection, and the reversal of uremia would therefore reduce infection risk. The prescription of maintenance hemodialysis for the reduction of the uremic state did not effectively minimize infection risk; it merely changed the paradigm. Maintenance hemodialysis superimposes new issues onto patients already suffering relentless renal deterioration. Infections pre or peritreatment exacerbate this problem. The results of this study did not confirm this assertion; the study did not find with appreciable confidence that the variable infection/inflammation contributed in modulating albumin levels with statistical significance in Hispanic, hemodialysis patients with and without Type II diabetes.

For population based studies such this one, demographic factors are an important consideration. Covariates such as age, race, gender, economic status, educational level, income level, and employment therefore must be considered in statistical analysis models. This study is no exception. First, gender was an important covariable that was considered during the stratified analyses. Although the entire cohort generated sufficient power (Power = .99), after exclusion criteria was conducted G*Power did not generate sufficient power within each clinic to conduct this analysis with a small effect size. A medium effect size was chosen instead to satisfy statistical power for the stratified analyses. As presented in Chapter 4, the regression analysis was not significant in the potential of known predictors to modulate albumin levels in this cohort. When gender

was introduced into the model, the data were not significant to pursue further analysis. Age was not controlled in this analysis for similar reasons. The mean age was nearly identical (Average M = 64.7 years) across the board for each clinic, as was educational level (elementary or high school) and employment (unemployed, housewife) for each clinic and therefore were not an analysis concern.

Interpretation of Results

The final study population of N = 405 was comprised 53.1% males and 46.9% females. Two hundred and eighty-one of those were diabetic patients and 124 were nondiabetic. This distribution of study subjects is consistent with the percentages of dialysis patients across each of the seven dialysis clinics. No statistical differences were identified during the analysis of these descriptive data for any of the variables based on comparisons between both groups. Strong, positive correlations, however, were seen between albumin levels and Type II diabetes at each time interval. Statistically significant mean differences in albumin levels within each group were seen, (Repeated Measures t test: p = .000 and ANOVA: F = 2.28, p = .032 and F = 1.62, p = .004 for CMS baseline and 0 month intervals, respectively). The study design was a complete data analysis of the treatment records of all patients attending seven dialysis clinics. The average age for subjects in the diabetic group (n = 281) was nearly identical (M = 64.3 years SD = 10.9 and 62.6 years SD = 15.2) to that of the nondiabetic comparison group (n = 124), thus there is no concern that age differences may have influenced the statistical outcomes of this study.

As detailed in Chapter 4, correlations exist between the independent variable Type II diabetes and dependent variable albumin levels. This was confirmed within each group independently through Spearman Correlation and repeated measured *t* test analysis. Between both groups, differences or trends in albumin levels were equally significant. The null hypothesis can be rejected in favor of the alternative. The results were similarly confirmed with the one-way ANOVA, which showed *p* values below $p = .05$ and significant *F* values (2.28 and 1.62) at the CMS baseline and 0 month time intervals, which again suggests albumin levels are different between both groups. Surprisingly, some findings of this study do not align with the published literature. The literature shows that infections acquired during the course of the dialysis treatments would lower albumin levels in these patients. Neither group, however, exhibited this tendency with confirmatory statistical significance upon logistic regression analysis. This finding was inconsistent with Kaysen et al, 1995, Kaysen et al., 2001, Kaysen, et al., 2002, for example, which found significant associations between lower albumin levels with the development of an infection. This inconsistency may be due to a reduced sample size because of patients that were excluded from the final sample that did not meet inclusion criteria due to underreporting of the comorbidity infection or inflammation on CMS-2728 forms. The exclusion criteria used for this study may have therefore influenced the final outcomes of the regression analysis.

Severe infection and inflammation almost invariably leads to hemostatic abnormalities. When a microorganism invasion occurs in the body, there is a biological response to try to promptly destroy and remove it. The typical signs and symptoms of

inflammation show that the body is actively trying to heal itself. The inflammatory response does not necessarily indicate infection, even when an infection causes inflammation. Infection is caused by a bacterial, viral, or fungal infiltration, while inflammation is the body's response to the microorganism's proliferation (Szymanski, 2001).

Infection and inflammation trigger an acute-phase response that can precipitate the development of mild to severe hematological disorders (Szysmanksi, 2001). In many cases, changes in hematological parameters such as reticulocytes may be the initial sign of an occult infectious or inflammatory disorder. In dialysis patients, the decrease in reticulocytes and hence a disruption in erythropoiesis can indicate an infection that may affect the way the liver synthesizes albumin. Reticulocytes are immature erythrocytes, typically comprising approximately 1% of the red cells in the human body (Tsuchiya et al., 2003). Reticulocytes develop and mature in the bone marrow and then are introduced into the systemic circulation where they then further develop into mature erythrocytes. A low reticulocyte count may indicate various conditions, one of which is an infectious disorder. In addition to a high white blood cell count, reticulocyte indices can serve as a second indicator for the presence of an infection.

To verify the final sample size (n = 74) of patients with the comorbidity infection and inflammation (Figure 2), ferritin levels were collected at 0, 3, and 6 month intervals. Ferritin is a protein produced in mammalian metabolism that serves to store iron in body tissues (Wish, 2006). Normal ferritin levels in males and females are 12-300 ng/mL and 12-150 ng/mL, respectively. Serum ferritin levels are directly related to the amount of

iron stored in the body. Iron is necessary for erythropoiesis. Any inflammatory disorder can raise ferritin levels and hence is a reliable hematological indicator of inflammation. Patients with an infection or inflammation comorbidity with an elevated white blood cell count (>10.8 mg/dL) and confirmed with elevated ferritin levels (>800 ng/mL) were assigned to the infection/inflammation subgroup.

Transferrin saturation (TSAT) values were collected for this study to further verify the presence of an infection or inflammatory process. TSAT is the ratio of serum iron and total iron-binding capacity, multiplied by 100. Of the transferrin that is available to bind iron, this value indicates how much serum iron is actually bound. Because serum ferritin is an acute-phase reactant and because the inflammatory state may inhibit the mobilization of iron from reticuloendothelial stores, the scenario of patients with serum ferritin >800 ng/mL, suggesting iron overload, and transferrin saturation ≤20%, suggesting iron deficiency was a reliable indicator of an inflammatory disorder for this study (Koo et al., 2014).

For this study, both ferritin and TSAT were collected to verify the presence of an infection or an inflammatory response. Reticulocyte counts were not available in patient treatment records and were therefore not collected. Verification of and qualification for inclusion for patients with infection/inflammation comorbidity relied on four factors: (a) proper documentation by nursing staff of the comorbidity pre and peritreatment, (b) white blood cell count at CMS baseline, 0, 3, and 6-month intervals, (c) pre and peritreatment ferritin levels, and (d) TSAT ratios documented over 6 months.

This study also showed another unexpected result. Although a specific comorbidity can predispose an individual to a disease initially, this does not mean once the disease is established that the association will be similar with disease progression. For this study, hypertension can affect renal function by disrupting glomerular function, but the effects in modulating albumin levels may be dissimilar as the renal disease progresses. Hypertension influences albumin levels, as it puts an inordinate amount of pressure on the glomeruli, but it is challenging to find a relative effect between diabetic and nondiabetic groups with a relatively short time frame among a cohort of patients with consistently higher baseline blood pressure levels. It was surprising that hypertension did not contribute in modulating albumin levels as was found through logistic regression analysis. Considering that essential hypertension exerts an inordinate amount of pressure on the glomeruli on a chronic basis (Milojkovic, 2014), and considering the overly compelling body of knowledge consistent with this information (Milojkovic et al., 2014, Reddenna et al., 2014), the results from this study did not reflect this. Logistic regression analysis for each time interval was not statistically significant. This study relied on the comorbidity hypertension being physician-diagnosed. Actual hypertension assessments documented on treatment flow sheets were not collected since these data were not accessible on eCube Clinicals or Proton. Furthermore, a hypertensive episode is a cardiovascular event that can only be assessed by a nephrologist. Blood pressure values documented on flow sheets may represent predialysis (or interdialytic) fluid overload and/or therapeutic noncompliance and not necessarily a cardiovascular event indicating hypertension.

With respect to the variable of interest, albumin levels, the results showed that at time intervals 0 to 3 months and 3 – 6 months the mean differences in both groups followed similar improvement trends not observed at the earlier intervals. This was confirmed with the repeated measures *t* test, which was used to quantify albumin level changes over time. These findings suggest two biological processes. First, in this latter interval during treatments, albumin levels may be normalizing to adequate levels and so the progressive deceleration may be due to homeostatic restoration. Second, as albumin levels approach adequacy (≥4.0mg/dL), (Davita, 2015; National Kidney Foundation, 2002; National Kidney Foundation, 2013a; National Kidney Foundation, 2013b), the slower increments and eventual plateauing may simply be due to the values reaching the maximum albumin level of 5.2mg/dL that is consistent with compatibility of life. Graphical comparisons between both groups showing a greater disparity between mean differences at the CMS to 0 and 0 to 3 month interval are shown in Figure 5. The trend lines between both groups confirm that a Type II diabetes diagnosis lowers albumin levels compared to those without the disease. With regards to the repeated measures *t* test, the findings showed a similar trend in all the other time intervals as well. It can be concluded that the independent variable Type II diabetes in this study contributed to lowering albumin levels in this study population based upon comparisons of repeated measures *t* tests conducted in both groups.

The absolute and relative change computations between both groups confirmed differences in albumin levels. The greatest differences in absolute and relative albumin level changes were seen during the CMS to 0 month interval, 0.4 and 18%, respectively.

Furthermore, the smallest change occurred, .11 and 3%, during the 3 to 6 month interval. These results may be due to various factors, including patient noncompliance, dietary changes, additional comorbidities, lifestyle changes, or any combination of these factors acquired peritreatment. Additionally, it is possible that during the 3 to 6 month interval patients grow accustomed to and accepting of their dialysis treatments, dietary modifications, and lifestyle changes, becoming more lax with their dialysis regimen. With this new outlook, patients may develop tendencies that challenge or test these limits or restrictions, possibly contributing to the diminished absolute and relative changes in albumin levels at this interval.

The conceptual foundation for conducting this study as laid out in Chapter 1 and supported by the literature review presented in Chapter 2 is sound and predicated upon good biological plausibility. Given the significance of the role albumin plays in the vascular system in maintaining colloid osmotic pressure, and its implication with osmosis in blood pressure maintenance, it was reasonable to conclude that albumin level differences in patients with Type II diabetes may also consequently show greater hypotensive disparities than do those without the disease, which is consistent with the findings of Nakamoto, et al. (2006).

The findings in this sample population show a correlation between albumin levels at four different time intervals and Type II diabetes. Both the ANOVA and the Spearman correlation tests showed statistically significant results that confirm this assertion, with the one exception at the latter intervals of the one-way ANOVA, which were not statistically significant for reasons previously explicated. Because of these results, the

null hypothesis, which states that there are no differences in albumin levels between hemodialysis patients with and without Type II diabetes, can be rejected in favor of the alternative. Logistic regression analysis, however, did not demonstrate with satisfactory significance that the three predictors included in the analysis contributed to modulating albumin levels in this sample. Therefore, the null hypothesis, which states that there is no relationship between serum albumin, Type II diabetes, and known predictors that may modulate albumin levels, cannot be rejected; any observed differences in albumin levels may have occurred by chance. However, the differences in albumin levels at each interval within and between groups were statistically significant. Therefore, in this case the null hypothesis there are no differences between albumin levels over time can be rejected in favor of the alternative.

Strength of Study

Quantitative research designs have key strengths that maximize the study's credibility, validity, and accuracy. A distinguishing feature of this design is the collection of numerical data that, in turn, can be subjected to statistical analysis. This groundbreaking study is no exception; study strengths include: (a) generating precise, numerical data; (b) the ability to study large populations; (c) generalizable research findings; (d) a relatively quick data collection phase; and (e) a swift data analysis phase. First, quantitative designs provide precise, numerical data. For this study, ANOVA, repeated measures *t* tests, and multiple regression analysis provided empirical, statistically based data that addressed each research question with achieved power. Second, quantitative study designs provide the opportunity to study large populations.

Over 800 records were reviewed in this study from seven different hemodialysis clinics. This large cohort of patients ensured statistical power as well as generalizability. Third, the study findings are generalizable since medical records were selected randomly. For this study, a complete data review was conducted of all current patients on the treatment schedules and deceased patients with complete medical records on file. This minimized potential biases, thus increasing the study's generalizability. And, lastly, both data collection and data analysis phases are less time consuming with quantitative designs. Because this is a historic, retrospective design, very large cohorts were accessible at once with appropriate permission. Since the data were previously collected, the time frame for secondary data collection and analysis phases were reduced. Additionally, since each dialysis facility has streamlined the way they collect, compile, store, and access medical records, data extraction from each medical record was relatively simple and straightforward.

The Hispanic population is the fastest growing demographic. This rapid growth corresponds to higher incidences of Type II diabetes and renal failure, as this group is genetically predisposed to Type II diabetes. This study focuses on the Hispanic population in San Antonio, Texas and provides information on a rapidly emerging population. The researcher is able to construct a situation that eliminates confounding influence of many variables, allowing for more credibly established cause-and-effect relationships. The study is therefore useful and attractive from a research perspective. More importantly, hemodialysis patients exist worldwide and so the outcomes of this quantitative research study are useful and applicable to patients across the globe. Because

of the many strengths of this study, its usefulness, applicability, and educative features are unparalleled, rendering significant contributions to academia, research, and medicine.

Limitations of the Study

There are limitations in this type of study design, which may have influenced the study outcome. Principal among these is the fact that this was a records-based study. Records-based studies are dependent upon the quality and thoroughness of the records (Checkoway et al., 2004). This cohort was amassed over a time period of multiple years, during which time there were multiple dialysis clinicians who documented their findings in these records and the quality of the efforts to solicit all the patient information may not have been uniformly comprehensive. As clinical policies and protocols change through the years, this may also have been influenced by the nature of the clinical circumstances at the time of presentation for treatment. A listwise deletion of patients that did not meet strict inclusion criteria was conducted to minimize data cleaning and to avoid overestimation during the analyses. Although very rare, it is possible that truncated medical records or patients with essential missing data values were not properly documented on patient records, which would favor the null hypothesis in this study. This is an inherent problem in conducting records-based studies (Checkoway et al., 2004).

Fluid overload (edema), during the interdialytic period is a critical factor in maintenance hemodialysis and therefore a study limitation consideration. Interdialytic weight gain is considered a measurement of compliance because it may be dictated, at least in part, by patient behavior. The volume of fluid weight gained is dependent on the amount of fluid that is consumed, how often a dialysis patient receives the dialysis

treatment, and whether kidney function is merely insufficient and therefore capable of removing some fluid through normal urine excretion. Some dialysis patients are unable to urinate (renal failure), while others retain some renal function and hence have some residual urine output (renal insufficiency). Individual goals for weight gain during the interdialytic period must be determined by the nephrologists, and may vary based on small or large body frames and other considerations.

The goal for an average sized hemodialysis patient is to keep fluid weight gain during this period at or below 1 kilogram (2.2 pounds) each day. This equates to 2 kg (4.4 pounds) fluid weight gain when there are 2 days between treatments and 3 kg (6.6 pounds) fluid weight gain when there are 3 days between treatments. Therefore, during this period it is expected that patients with renal failure may accumulate anywhere between 2-5 kilos of fluid. The more fluid they accumulate, be it because noncompliance, magnitude of renal failure, or inherent physiological osmotic fluid movement variances, could produce a diluted serum albumin concentration. Edematous manifestations of diluted albumin concentrations at various concentrations due to excessive fluid build-up may have posed an inherent study limitation and skewed outcomes towards the null.

There is a considerable body of evidence indicating that serum albumin is a prognostic indicator of malnutrition (Sridhar & Josyula, 2013). In this condition a disparity between the amount of food and other nutrients that the body requires for proper growth and health and the amount that it absorbs deviates from physiological homeostasis. This imbalance is most frequently associated with undernutrition (Friedman & Fadem, 2010). Considering the mean age of the population (M = 62.4 years), and other

anthropometric indices, it can be reasonably deduced that any observed albumin level differences may be due to malnutrition rather than the proposed independent variable, Type II diabetes, investigated in this study. It is also uncertain if a combination of these factors, malnutrition plus Type II diabetes, may have contributed to differences in albumin levels in this sample population.

Other important considerations that may have limited this study include patient phobias and demographics, as were presented in Chapter 1. Patients that for lack of insurance or that simply refused dialysis treatment either because of disease denial or because of physician, needle, or blood phobias may not be included in the sample population. The sample population may have captured only those that were sick that were actually attending the dialysis clinics and excluding those that were sick and not receiving necessary treatments. The clinics from which the data were collected may represent a demographic limitation in that the community in which the clinic is located may have a higher or lower Hispanic representation than do other similar clinics in other regions of the city. Additional limitations include cohort size, especially over multiple strata as was shown in the stratified analyses, uninsured patients that are unable to pay for out-of-pocket dialysis services, and immigration status concerns.

Limitations can be overcome in related, subsequent research studies. Modifications in methodology or design can help minimize inherent study limitations. For instance, future studies conducted using other ethnic populations, and encompassing a broader population of patients in home-health and in-patient hospital setting hemodialysis venues may help expand the generalizability and reduce study limitations.

Selecting clinics with similar demographics may provide data uniformity. The limitations discussed in this section collectively confer shortcomings, conditions, or influences that cannot be controlled and that may place methodological and study conclusion restrictions.

Implications for Social Change

The positive social change from this research endeavor is extensive, distinctive, and beneficial at the individual, community, and global levels. Numerous studies have investigated large cohorts of diabetic hemodialysis patients (Choi et al, 2011; Goldwasser et al., 1999; Noori et al., 2011). Some have examined specific ethnic populations receiving maintenance hemodialysis treatments (Liu et al., 2008; Locatelli et al., 2011; Yokoyama et al., 2011; Zakerish et al., 2013). Several have examined or compared survival analysis, dialysis modalities, glycemic/$A1_C$ control, race/ethnicity and age, renal disease risk, and prevalence of Type II diabetes mellitus in various populations (Hsu et al. 2011; Leavy et al., 2000; Lorenzo, et al., 2009; Marimoto et al., 2010). These studies, although informative, instructive, and pedagogic to the discipline, may not provide the magnitude of social change that this endeavor achieves. From the exhaustive literature review presented in Chapter 2, studies have not investigated a direct association between serum albumin, a Type II diabetes diagnosis, and related predictors in Hispanic patients to date. Additionally, the literature does not show if and to what magnitude a Type II diabetes diagnosis influences albumin levels or whether albumin level patterns exist from treatment onset through the course of their hemodialysis treatments. This research effort

was the first to do so, with a comprehensible and profound aim towards positive social change.

This research study provides a platform to promote positive social change. The efforts and subsequent results from this study contribute to the evolving public health discipline. This study was conducted to identify disease-specific albumin trends that could influence the course of diseases such as diabetes and renal disease so that ethnic-specific and disease-specific care can be developed for patients on maintenance hemodialysis. At the individual level, Hispanic patients with Type II diabetes can benefit from individualized albumin supplementation provided by the dieticians at each clinic. Since each patient is unique in terms of the dietary preferences and the amount of food consumed, individualized dietary recipes can be created to better suit the needs of each patient. As a cohort, hemodialysis patients with Type II diabetes may benefit from this research by its potential to inform and empower dialysis clinical care professionals to devote concerted efforts towards raising albumin levels in these patients. Thusly, these efforts may improve the quality of life of patients afflicted with Type II diabetes and renal disease. The positive social change, therefore, extends to a vast community of health care providers that devote their time and efforts to educate and facilitate hemodialysis patients initiating treatments transition to a new life. Lastly, on a global scale, the study's research findings contribute to the paucity of literature in this field and helps address diabetes health and renal disease to potentially improve diabetic and renal health outcomes to the broader population. The social change implications from this study are clear, definitive, broad, and long-term.

There is a strong conceptual premise, clinical basis, and biological plausibility to suggest that albumin levels are different in patients with and without Type II diabetes and that albumin level restoration trends are different post treatment onset. The conventional standards of care among dialysis clinicians were to provide standardized albumin level care/supplementation for all patients as a homogenous group. However, there was no empirical evidence to fully support this standardized albumin care. Currently, there is no diversity in serum albumin management for patients with a Type II diabetes diagnosis, despite the theoretical concerns. A unique aspect of this particular endeavor was that whatever the outcome, assuming adequate study power, useful and immediately relevant information would ensue that would elucidate a nuanced albumin level protocol for Hispanic patients with a Type II diabetes diagnosis on maintenance hemodialysis. Should no association be defined, dialysis clinicians should continue to use the same standardized albumin level care protocols without concern that they may be in some way deleterious to the health and well being of the patients. If, on the other hand, an association was identified, dialysis clinicians could be advised to modify and tailor their albumin level care guidelines that would reinforce the nuances associated with patients in this specific population to dialysis clinicians, support better albumin level outcomes in patients with Type II diabetes, and promote better overall clinical health outcomes for hemodialysis patients. In all instances, dialysis clinical experts, diabetologists, as well as clinical providers would be informed by data from an evidence-based study rather than serendipity or gestalt, magnifying the positive social change potential of this investigation.

Recommendations for Action

This study represents a first step towards filling the information gap that presently exists. Given the compelling nature of the theoretical bases, which underpin this study, it was important to pursue the research questions that were asked. The results of this particular effort, some of which were not statistically confirmatory, suggest that there may be some merit to pursuing the questions further.

The lack of statistical significance specifically at two time intervals in the one-way ANOVA should not be interpreted to mean that albumin levels in the diabetic group should not be addressed differently than those without a Type II diabetes diagnosis; it only means that it was not entirely demonstrable in this specific study. Similarly, the lack of statistical significance in the logistic regression analysis should not be dismissed as not showing important associations between albumin and known predictors and their potential to modulate albumin levels. This, too, only represents one sample population that may not have demonstrated the expected results that align with the existing body of knowledge. As was presented in Chapter 2, it is important to consider serum albumin concentrations to regulate blood pressure in patients on maintenance hemodialysis. Additionally, a Type II diabetes diagnosis, which may mediate and/or exacerbate albumin levels can therefore influence not only blood pressure homeostasis and hemodynamics, but hemodialysis outcomes and overall health. This study, although not statistically significant for all research questions posed, provided some substantiation to this assertion.

The results of this study may be of significant interest to Nephrologists, certified nephrology nurses, hemodialysis technicians, diabetologists, renal scientists, and physiology experts in academia in hopes that it will spawn additional inquiry into not only albumin level differences among Hispanic patients, but other populations as well; such endeavor would expand the study's generalizability. Additionally, albumin supplementation strategies can be designed to be ethnic-specific for populations that are deeply rooted in long-standing Latin customs and traditions like the one selected for this research. Certainly, hemodialysis facilities in other regions of the world should be advised as to the findings of this investigation with the caveat that these are preliminary conclusions, which will require additional studies aimed at investigating the potential associations of albumin levels, Type II diabetes, and associated covariables to verify the outcome. These results should be presented at annual scientific meetings of the American Nursing Nephrology Association with follow up on publication in peer-reviewed journals. Lastly, this information should be disseminated to Nephrologists and diabetologists through trade journals as *American Diabetes Association, Journal of Nephrology, American Society of Nephrology, Nephrology Nursing Journal* and the like.

Recommendations for Further Study

This was the first study to investigate whether differences in albumin levels exist in patients with and without a Type II diabetes diagnosis. This investigation has demonstrated that an appreciable association exists between albumin levels and a Type II diabetes diagnosis. Disparate albumin level differences, however, were not statistically significant between both groups at the earlier stages of their treatment. The study also

found that albumin level differences at each time interval showed statistically significant changes; albeit slight, this was demonstrably notable in the diabetic group when compared to the nondiabetic group. When the known comorbidities were introduced into the model, the relationships and relative contribution by each variable were not significant in this population.

The inherent limitations associated with records-based studies may have underestimated this association in this study. It is important, therefore, that future research be undertaken to help clarify this concern. The ideal approach would be to conduct an experimental study in which all other covariables could be controlled for through the study design so as to isolate the independent variable alone. This would be best accomplished using a blinded clinical trial format with a carefully defined study population.

A critical recommendation would include collecting data on the volume of fluid accumulated during the interdialytic period. Streamlining data collection to patients that are compliant and that consistently show similar fluid accumulation patterns during the interdialytic period over time would be an ideal strategy to isolate the dependent variable and reduce this study limitation.

Conclusions

This was a groundbreaking study designed to investigate the potential association between albumin levels, Type II diabetes, and associated covariables. Furthermore, trends seen from treatment onset through the course of patient dialysis treatments were also investigated. The results showed that differences exist in albumin levels from treatment

onset through the course of their treatment. Type II diabetes confirmatively showed differences in albumin levels compared to the nondiabetic comparison group. Given the sample size and power of this study, it is reasonable to conclude that in this study albumin level differences are seen at four different time intervals within each group. Furthermore, between both groups (diabetic and nondiabetic), albumin levels also showed appreciable differences. From this study, it can also be concluded that Type II diabetes was influential in modulating albumin levels in a statistically significant way. And, when known predictors such as a history of hypertension, peripheral vascular disease, and the development of an infection or inflammatory response were considered during analysis, albumin levels followed similar improvement trends and were therefore not significantly influenced in this sample population.

There were univariate, bivariate and multivariate statistical treatments used to address the three research questions in this study. First, an ANOVA was conducted to compare means between two groups, diabetic and nondiabetic hemodialysis patients. The albumin levels in the diabetic group were lower at time intervals CMS baseline and 0 months and therefore revealed disparate trends towards normoalbuminemic restoration over time. The Spearman Correlation showed significant associations between Type II diabetes and albumin levels at all time intervals. The repeated measures *t* tests results were significant at all intervals, suggesting that albumin levels were different between both groups. Lastly, the results of the multiple regression analysis were not statistically significant for the three known predictors, hypertension, peripheral vascular disease, and infection/inflammation in this sample population.

This investigation helps narrow the literature gap about human serum albumin in hemodialysis patients with and without Type II diabetes. The study elucidates key information that is both attractive and useful to the academic, scientific and medical communities. Because of the many physiological functions albumin provides for the body, it can be used therapeutically for a myriad of diseases and conditions. Amongst these are hypovolemia to help restore blood volume in trauma, for burn and surgery patients to treat and expedite the restoration of fluid loss, and even as a dietary supplementation to treat malnourished patients (Mendez et al., 2005). From this study, the expectation is that albumin-specific and ethnic-specific guidelines, clinical policies, and treatment protocols be created for albumin management in patients. This study provides a foundation for future albumin studies. The results from this study provide the impetus to design subsequent albumin investigations with methodological modifications that would elucidate further information about albumin levels in hemodialysis patients with and without Type II diabetes. These modifications might include extending the study time frame, investigating a different ethnic population, and/or examining other dialysis clinics in different cities in Texas.

References

Ahren, B., & Burke, B. (2012). Using albumin to improve the therapeutic properties of diabetes treatments. *Diabetes, Obesity and Metabolism*, *14*(2), 121-129.

Alpern, R. J., Caplan, M. J., & Moe, O. W. (2013). *Seldin and Giebisch's the kidney: Physiology and pathophysiology* (5th Ed.) (pp. 45-319). Saint Louis, MO: Academic Press.

American Heart Association. (2015). Peripheral artery disease. Retrieved from http://www.heart.org/HEARTORG/Conditions/More/PeripheralArteryDisease/Peripheral-Artery-Disease-PAD_UCM_002082_SubHomePage.jsp

American Journal of Kidney Diseases. (2007). KDOQI kidney disease outcomes quality initiative. Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Retrieved from http://www.kidney.org/professionals/kdoqi/pdf/Diabetes_AJKD_FebSuppl_07.pdf

Antimicrobe. (2014). Infections in patients undergoing chronic dialysis. Retrieved from http://www.antimicrobe.org/e41.asp

Antlanger, M., Hecking, M., Haidinger, M., Werzowa, J., Kovarik, J. J., Paul, G… Saemann, M. D. (2013). Fluid overload in hemodialysis patients: a cross-sectional study to determine its association with cardiac biomarkers and nutritional status. *BMC Nephrology*, *14*(266), 1-10.

Aschengrau, A., & Seage, III, G. (2008). Overview of epidemiologic designs. In Aschengrau, A., & Seage, G. *Essentials of Epidemiology in Public Health* (2nd ed., pp. 139-167). Sudbury, MA: Jones and Bartlett Company.

Balakrishnan, V. S., & Rao, M. (2007). Genetics and reverse epidemiology among patients on chronic hemodialysis. *Seminars in Dialysis*, *20*(6), 570-576.

Banerjee, A., Chitnis, U. B., Jadhav, S. L., Bhawalkar, J. S., & Chaudhury, S. (2009). Hypothesis testing, type I and type II errors. *Industrial Psychiatry Journal*, *18*(2), 127-131.

Bazzano, L. A., Serdula, M., & Liu, S. (2005). Prevention of type 2 diabetes by diet and lifestyle modification. *Journal of the American College of Nutrition*, *24*(5), 310-319.

Biesheuvel, C., Vergouwe, Y., Oudega, R., Hoes, A., Grobbee, D., & Moon, K. (2008). Advantages of nested case-control design in diagnostic research. *BMC Medical Research Methodology*, *8*(48), 1-7.

Black, S. A. (2002). Diabetes, diversity, and disparity: What do we do with the evidence? *American Journal of Public Health*, *92*(4), 543-548.

Borg, F. (2003). What is Osmosis? Explanation and understanding of a physical phenomenon. Retrieved from http://arxiv.org/pdf/physics/0305011.pdf

Bouchard, J, Soroko, S. B., Chertow, G. M., Himmelfarb, J., Ikizler, T. A., Paganini, E. P., & Mehta, R. L. (2009). Fluid accumulation, survival and recovery of kidney of kidney function in critically ill patients with acute kidney injury. *Kidney International*, *76*, 422-427.

Brin, H., & Christensen, E. (2006). Renal albumin absorption in physiology and pathology. *Kidney International*, *69*, 440-449.

Campbell, I. W. (2000). Epidemiology and clinical presentation of type 2 diabetes. *Value in Health*, *3*, Suppl. 1, S3-S6.

Castillo, A., Giachello, A., Bates, R., Concha, J., Ramirez, V., Sanchez, C…Arrom, J. (2010) Community-based diabetes education for Latinos: The diabetes empowerment education program. *Diabetes Educator*, *36*(4), 586-594.

Centers for Disease Control and Prevention. (2005). National diabetes fact sheet. Retrieved from www.cdc.gov/diabetes/pubs/factsheet05.htm

Chaufan, C., Davis, M., & Constantino, S. (2011). The twin epidemics of poverty and diabetes: Diabetes disparities in a low-income Latino and immigrant neighborhood. *Journal of Community Health*, *36*, 1032-1043.

Checkoway, H., Pearce, N., & Kriebel, D. (2004). Overview of study designs. In: Checkoway, H., Pearce, N., & Kriebel, D. *Research methods in occupational epidemiology* (2nd ed., pp. 59-81). New York, NY: Oxford University Press.

Choi, A. I., Karter, A. J., Liu, J. Y., Young, B. A., Go, A. S., & Schillinger, D. (2011). Ethnic differences in the development of albuminuria: The DISTANCE study. *The American Journal of Managed Care*, *17*(11), 737-745.

Chukwueke, I., & Cordero-MacIntyre, Z. (2010). Overview of type 2 diabetes in Hispanic Americans. *International Journal of Body Composition Research*, *8*, (Suppl. S77-81), 77-81.

Cigarran, S., Barril, G., Cirugeda, A., Bernis, C., Aguilera, A., Sanz, P…Selgas, R. (2007). Hypoalbuminemia is also a marker of fluid excess determined by bioelectrical impedance parameters in dialysis patients. *Therapeutic Apheresis and Dialysis*, *11*(2), 114-120.

Creswell, J. (2009). *Research design.* Los Angeles, CA: Sage, 129-145.

Dalrymple, S. L., Johansen, K. L., Chertow, G. M., Grimes, B., Anand, S., McCulloch, C. E., & Kaysen, G. A. (2013). Longitudinal measures of serum albumin and prealbumin concentrations in incident dialysis patients: The comprehensive dialysis study. *Journal of Renal Nutrition*, *23*(2), 91-97.

Davita. (2013). Calcium and chronic renal disease. Retrieved from http://www.davita.com/kidney-disease/diet-and-nutrition/diet-basics/calcium-and-chronic-kidney-disease/e/5300

Davita. (2014). Overview about the kidneys. Retrieved from http://www.davita.com/kidney-disease/overview/the-basics/overview-about-kidneys/e/4666

Davita. (2015). What is albumin? Retrieved from http://www.davita.com/kidney-disease/diet-and-nutrition/diet-basics/what-is-albumin?/e/5317

Don, B. R. & Kaysen, G. (2004). Serum albumin: Relationship to inflammation and nutrition. *Seminars in Dialysis*, *17*(6), 432-437.

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175-191.

Fennelly, K. (2005). The 'Healthy Migrant' Effect. Healthy Generations, *5*(3), 2-11. Retrieved from http://www.epi.umn.edu/mch/resources/hg/hg_immi.pdf

Fogo, A. B. (2000). Glomerular hypertension, abnormal glomerular growth, and progression of renal diseases, *Kidney International*, *57*, Suppl. 75, S-15–S-21.

Folsom, A. R., Ma, J., Eckfeldt, J. H., Nieto, F. J., Metcalf, P. A., Barnes, R. W. (1995). Low serum albumin. Association with diabetes mellitus and other cardiovascular risk factors but not with prevalent cardiovascular disease or carotid artery intima-media thickness. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Annals of Epidemiology*, *5*(3), 186-191.

Fortmann, A., Gallo, L., Walker, C., Philis-Tsimikas, A. (2010) Support for disease management, depression, self-care, and clinical indicators among Hispanics with type 2 diabetes in San Diego County, United States of America. *Revista Panamericana de Salud Publica*, *28*(3), 230-234.

Franzini, L., Ribble, J. C., & Keddie, A. M. (2001). Understanding the Hispanic paradox. *Ethnicity and Disease*, *11*(3), 496-518.

Fresenius Medical Care. (n. d.). Dialysis compact: The invention, development and success of the artificial kidney. Retrieved from http://www.fresenius.com/documents/Dialysis_Compact_HD_e.pdf

Fresenius Medical Care. (2013). Fresenius Medical Care notice of privacy practices. Retrieved from http://www.fmcna.com/idc/idcplg?IdcService=GET_FILE&allowInterrupt=1&Re

visionSelectionMethod=LatestReleased&Rendition=Web&dDocName=DOC_10
0035421

Fresenius Medical Care. (2013). What is dialysis? from http://www.ultracare-dialysis.com/Treatment/WhatIsDialysis.aspx

Fukuoka, K., Nakao, K., Morimoto, H., Nakao, A., Takatori, Y., Arimoto, K…Makino, H. (2007). Glycated albumin levels predict long-term survival in diabetic patients undergoing haemodialysis. *Nephrology*, *13*, 278-283.

Girman, C. J., Kou, T. D., Brodovicz, K., Alexander, C. M., O'Neill, E. A., Engel, S…Katz, L. (2011). Risk of acute renal failure in patients with type 2 diabetes mellitus. *Diabetic Medicine*, 614-621, doi:10.1111/j.1464-5491.2011.03498.x

Goldwasser, P., Kalda, A. I., & Barth, R. H. (1999). Rise in serum albumin and creatinine in the first half year on hemodialysis. *Kidney International*, *56*, 2260-2268.

Guo, Yi., Logan, H. L., Glueck, D. H., & Muller, K. E. (2013). Selecting a sample size for studies with repeated measures. *BMC Medical Research Methodology*, *13*:100, 2-8. doi: 10.1186/1471-2288-13-100.

Haddy, F. J., Vanhoutte, P. M., & Feletou, M. (2006). Role of potassium in regulating blood flow and blood pressure. *American Journal of Physiology, Regulatory, Integrative, and Comparative Physiology*, *290*(3), 546-552.

Haller, C. (2006). Hypoalbuminemia in renal failure: Pathogenesis and therapeutic considerations. *Kidney & Blood Pressure Research*, *28*, 307-310.

Hatcher, E., & Whittemore, R. (2007). Hispanic adults' beliefs about type 2 diabetes: clinical implications. *Journal of the American Academy of Nurse Practitioners, 19*, 536-545.

Hecking, M., Antlanger, M., Winnicki, W., Reiter, T., Werzowa, J., Haidinger, M…(2012). Blood volume-monitored regulation of ultrafiltration in fluid-overloaded hemodialysis patients: Study protocol for a randomized control trial. *Trials*, *13*(79), 1-12.

Hsu, C., Chang, H., Huang, M., Hwang, S., Yang, Y., Tai, T…Kuo, K. N. (2011). Association between insulin resistance and development of microalbuminuria in type 2 diabetes. *Diabetes Care*, *34*, 982-987.

In Control. (2007). Dialysis patients' need for protein. Retrieved from http://lifeoptions.org/catalog/pdfs/news/icv4n1.pdf

Ing, T. S., Rahman, M. A., & Kjellstrand. (2012). Dialysis history, development, and promise. Hackensack, NJ: World Scientific Publishing Co. Pte. Ltd.

Iseki, K., Kawazoe, N., & Fukiyama, K., (1993). Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney International*, *44*, 115-119.

Ismael, S., Savalle, M., Trivin, C., Gillaizeau, F., D'Auzac, C., & Faisy C. (2014). The consequences of fluid shifts on body composition in critically ill patients. *Critical Care*, *18*:R49, doi:10.1186/cc13794.

Janacek, K. & Sigler, K. (1996). Osmotic Pressure: Thermodynamic basis and units of measurement. *Folia Microbiology*, *41*(2), 2-9.

Jolly, S. E., Burrows, N. R., Chen, S., Li, S, Jurkovits, C. T., Norris, K. C., & Shlipak, M. G. (2011). Racial and ethnic differences in mortality among individuals with chronic kidney disease: results from the kidney early evaluation program (KEEP). *Clinical Journal of the American Society of Nephrology*, *6*, 1858-1865.

Kanna, B., Fersobe, S., Soni, A., & Michelen, W. (2007). Leading health risks, diseases and causes of mortality among Hispanics in the United States of America (USA). *Internet Journal of Health*, *8*(1). Retrieved from http://ispub.com/IJH/8/1/13070

Kaysen, G. A., Dubin, J. A., Muller, H., Mitch, W. E., Rosales, L. M., & Levin, N. W. (2002). Relationships among inflammation nutrition and physiological mechanisms establishing albumin levels in hemodialysis patients. *Kidney International*, *61*, 2240-2249.

Kaysen, G. A., Rathore, V., Shearer, G. C., & Depner, T. (1995). Mechanisms of hypoalbuminemia in hemodialysis patients. *Kidney International*, *48*, 510-516.

Kidney Dialysis Information Centre. (n. d.). Willem Johan Kolff, the inventor of dialysis. Retrieved from http://www.kidneydialysis.org.uk/inventor-of-dialysis.htm

Kim, S., Sung, J., Sook, E., Park, H. C., Lee, H., Chin, H. J…Joo, K. W. (2012). Hemodynamic and biochemical benefits of the objective measurement of fluid status in hemodialysis patients. *The Tohoku Journal of Experimental Medicine*, *228*, 125-133.

Koo, H. M., Kim, C. H., Doh, F. M., Lee, M. J., Kim, E. J., Han, J. H…Kang, S. W. (2014). The relationship of initial transferrin saturation to cardiovascular parameters and outcomes in patients initiating dialysis. *PLoS one, 9*(2), e87231.

Lachish, U. (1999). Osmosis reverse osmosis and osmotic pressure what they are. Retrieved from http://urila.tripod.com

Lachish, U. (2007). van't Hoff's evidence. Retrieved from http://urila.tripod.com/evidence.htm

Lash, J. P., Vijil, J. C., Gerber, B., & Go, A. S. (2005). Kidney disease in the U.S Hispanic population. *Kidney: A current survey of world literature*, *14*, 1-5.

Leavey, S. F., Strawderman, R. L., Young, E. W., Saran, R., Roys, E., Agodoa, L. Y.C…Port, F. K. (2000). Cross-sectional and longitudinal predictors of serum albumin in hemodialysis patients. *Kidney International*, *58*, 2119-2128.

Lindberg, M., Prutz, K., Lindberg, P., & Wikstrom, B. (2009). Interdialytic weight gain and ultrafiltration rate in hemodialysis: Lessons about fluid adherence from a national registry of clinical practice. *Hemodialysis International*, *13*(181), 181-188.

Liu, H., Peng, Y., Liu, F., Xiao, H., Chen, X., Huang, A., & Liu, Y. (2008). Renal function and serum albumin at the start of dialysis in 514 Chinese ESRD in-patients. *Renal Failure*, *30*, 685-690.

Locatelli, F., Cavalli, A., Manzoni, C., & Pontoriero, G. (2011). The membrane permeability outcome study. *Conributions to Nephrology*, *175*, 81-92.

Longnecker, M. & Daniels, J. (2001). Environmental contaminants as etiologic factors for diabetes. *Environmental Health Perspectives*, *109* suppl. 6, 871-876.

Lopez, C. M. (2008). Cultural diversity and the renal diet: The Hispanic. *Issues in Renal Nutrition*, *35*(1), 69-72.

Lorenzo, V., Saracho, R., Zamora, J., Rufino, M., & Torres, A. (2009). Similar renal decline in diabetic and non-diabetic patients with comparable levels of albuminuria. *Nephrology Dialysis Transplantation*, *25*, 835-841.

Lukowsky, L. R., Kheifets, L., Arah, O. A., Nissenson, A. R., & Kalantar-Zadeh, K. (2012). Patterns and predictors of early mortality in incident hemodialysis patients: New insights. *American Journal of Nephrology*, *35*, 548-558.

Mahbub, T., Chowdhury, N. U., Jahan, F., Arefeen, S., Rahman, M., & Sarker, M. S. (2013). Diabetes in the leading cause of ESRD in haemodialysis patients. *Journal of Medicine*, *13*, 62-64.

Mahler, R. & Adler, M. (1999). Type II diabetes mellitus: Update on diagnosis, pathophysiology, and treatment. *The Journal of Clinical Endocrinology & Metabolism*, *84*(4), 1165-1171.

Malliara, M. (2007). The management of hypertension in hemodialysis and CAPD patients. *Hippokratia*, *11*(4), 171-174.

Marieb, E., & Hoehn, K., (2007). Cells: The living units. In Human Anatomy and Physiology (7th Ed.) (pp. 64-75). San Francisco, CA: Pearson Benjamin Cummings.

Mariomoto, S., Nishioka, H., Morita, T., Jo, F., Someya, K., Nakahigashi, M…Maki, K. (2010). Characteristics of 20-year survivors undergoing maintenance hemodialysis. *Therapeutic Apheresis and Dialysis*, *14*(6), 547-551.

Mason, E. A. (1991). From pig bladders and cracked jars to polysulfones: A historical perspective on membrane transport. *Journal of Membrane Science*, *60*, 125-145.

McBean, A. M., Li, S., Gilbertson, D. T., & Collins, A. J. (2004). Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: Whites, blacks, Hispanics, and Asians. *Diabetes Care*, *27*(10), 2317-2324.

Mendez, C. M., McClain, C. J., & Marsano, L. S. (2005). Albumin therapy in clinical practice, *Nutrition in Clinical Practice*, *20*(3), 314-320.

Mihaescu, R., Serban, C., Dragan, S., Timar, R., Mozos, J., Craina, M., & Schiller, A. (2012). Diabetes and renal disease. Retrieved from http://cdn.intechopen.com/pdfs-wm/31991.pdf

Milojkovic, B., Dinkjic, B., Radenkovic, S., Kocic, G., Milojkovic B. (2014). Essential arterial hypertension and risk factors associated with hypertensive nephropathy. *Acta Medica Medianae*, *53*(4), 15-20.

Morales, L. S., Lara, M., Kingston, R. S., Valdez, R. O., Escarce, J. (2002). Socioeconomic, cultural, and behavioral factors affecting Hispanic health outcomes. *Journal of Health Care for the Poor and Underserved*, *13*(4), 477-503.

Murthy, B. V.R., Molony, D. A., & Stack, A. G. (2005). Survival advantage of Hispanic Patients initiating dialysis in the United States is modified by race. *Journal of the American Society of Nephrology*, *16*, 782-790.

Nassar, G. & Ayus, J. C. (2001). Infectious complications of the hemodialysis access. *Kidney International*, *60*, 1-13.

National Kidney Foundation. (2000). Guidelines and commentaries. Retrieved from http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm

National Kidney Foundation. (2013). Guidelines and commentaries. Retrieved from http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm

National Kidney Foundation. (2000). K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Retrieved from http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p6_comp_g9.htm

National Kidney Foundation. (2002). NKF KDOQI Guidelines. Retrieved from http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm

Nezelof, C. (2003). Henri Detrochet: An unheralded discoverer of the cell. *Annals of Diagnostic Pathology*, *7*(4), 264-272.

Noble, J. and LaCasa, J. (1991). The Hispanic way: Aspects of behavior, attitudes, and customs of the Spanish-speaking world. Chicago, Il. Passport Books.

O'Hare, A. M., Hsu, C. Bacchetti, P. & Johansen, K. L. (2002). Peripheral vascular disease risk factors among patients undergoing hemodialysis. *Journal of the American Society of Nephrology*, *13*, 497-503.

Peacock, T. P., Shihabi, Z. K., Bleyer, A. J., Dolbare, E. L., Byers, J. R., Knovich, M. A…Freedman, B. I. (2008). Comparison of glycated albumin and hemoglobin A_{1c} levels in diabetic subjects of hemodialysis. *Kidney International*, *73*, 1062-1068.

Pickstone, J. (1977). Absorption and osmosis: French physiology and physics in the early nineteenth century. *The Physiologist*, *20*(3), 30-37.

Pickstone, J. V. (1994). Discovering the movement of life: Osmosis and microstructure in 1826. *International Journal of Microcirculation, clinical and experimental*, *14*(1-2), 77-82.

Plantinga, L. C., Fink, N. E., Coresh, J., Sozio, S. M., Prarekh, R. S., Melamed, M…Jaar, B. G. (2009). Peripheral vascular disease-related procedures in dialysis patients: Predictors and prognosis. *Clinical Journal of the American Society of Nephrology*, *4*, 1637-1645.

Reddenna, L., Basha, S. A., & Reddy, K. S. (2014). Dialysis treatment: A comprehensive description. *International Journal of Pharmaceutical Research & Allied Sciences*, *3*(1), 1-13.

Ricks, J., Molnar, M. Z., Kovesday, C. P., Kopple, J. D., Norris, K. C., Mehrotra, R…Kalantar-Zadeh, K. (2011). Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. *American Journal of Kidney Diseases*, *58*(4), 574-582.

Ricks, J., Molnar, M., Kovesdy, C., Shah, A., Nissenson, A. R., Williams, M., & Kalantar-Zadeh, K. (2012). Glycemic control and cardiovascular morality in hemodialysis patients with diabetes: A 6-year cohort study. *61*, 708-715.

Ritchie, L. D., Calloway, D. H., Murphy, S. P., Receveur, O., Lamp, C. L. & Ikeda, J. P. (1995). Poor diet reflected in height, weight of low-income Hispanics. *California Agriculture*, *49*(2), 33-35.

Robinson, B., Tong, L., Zhang, J., Wolfe, R. A., Goodkin, D. A., Greenwood, R. N…Port, F. K. (2012). Blood pressure levels and mortality risk among hemodialysis patients in the dialysis outcomes and practice patterns study. *Kidney International*, *82*, 570-580.

Rosal, M. C., White, M. J., Restrepo, A., Olendzki, B., Scavron, J., Sinagra, E...Reed, G. (2009). Design and methods for a randomized clinical trial of a diabetes self-management intervention for low-income Latinos: Latinos en control. *BMC Medical Research Methodology. 9*(81), doi 10.1186/1471-2288-9-81.

Rozga, J., Piatek, T., Malkowski, P., (2013). Human albumin: Old, new, and emerging applications. *Annals of Transplantation*, *18*, 205-217.

Sakai, K. (2000). Dialysis membranes for blood purification. *Frontiers of Medical Biological Engineering*, *10*(2), 117-129.

Sattar, A., Argyropoulos, C., Weissfeld, L., Younas, N., Fried, L., Kellum, J. A., & Unruh, M. (2012). All-case and cause-specific mortality associated with diabetes in prevalent hemodialysis patients. *BMC Nephrology*, *13*(130), 1-9.

Schneiderman, N. (2004). Psychosocial, behavioral, and biological aspects of chronic diseases. *American Psychological Society*. *13*(6), 247-251.

Snyder, C. K., Lapidu, J. A., Cawthon, P. M., Dam, T. L. Sakai, L. Y., & Marshall, P. M. (2012). Serum albumin in relation to change in muscle mass, muscle strength, and muscle power in older men. *The Journal of the American Geriatrics Society*, *60*(9), 1663-1672.

Song, J. W., & Chung, K. C. (2010). Observational Studies: Cohort and case-control studies. *Plastic and Reconstructive Surgery*, *126*(6), 2234-2242.

Stat Trek. (2014). Simple random sampling. Retrieved from http://stattrek.com/sampling/simple-random-sampling.aspx

Stoian, M., Stoica, V., & Radulian, G. (2012). Albuminuria-marker of progressive renal disease. *Journal of Medicine and Life*, *5*(4), 420-422.

Szymanski, N. (2001). Infection and inflammation in dialysis patients: impact on laboratory parameters and anemia. Case study of the anemic patient. *Nephrology Nursing Journal*, *28*(3), 337-340.

Texas Diabetes Institute. (2014). Diabetes Statistics. Retrieved from http://www.universityhealthsystem.com/texas-diabetes-institute/diabetes-statistics

Thiese, M. S. (2014). Observational and interventional study design types; an overview. *Biochemia Medica*, *24*(2), 199-210.

Tienda M, Mitchell F. (2006). Hispanics and the Future of America. Washington (DC): National Academies Press.

Tsuchiya, K., Okano, H., Teramura, M., Iwamoto, Y., Yamashita, N., Suda, A… Ando, M. (2003). Content of reticulocyte hemoglobin is a reliable tool for determining iron deficiency in dialysis patients. *Clinical Nephrology*, *59*(2), 115-123.

Tuomilehto, J., Lindstrom, J., Eriksson, J., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P…Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England Journal of Medicine*. *344*(18), 1343-50.

United States Census Bureau. (2014). State and County quick facts, San Antonio, Texas. Retrieved from http://quickfacts.census.gov/qfd/states/48/4865000.html

Vigano, S. M., Di Filippo, S., Manzoni, C., & Locatelli, F. (2008). Dialysate composition. *Contributions to Nephrology*, *161*, 7-11, doi: 10.1159/000129748.

Villani, P., Dunlop, R., & Damitz, B. (2007). Investigating the process of diffusion using an analytical puzzle. *The American Biology Teacher*, *69*(7), 411-415.

Wen, L., Parchman, M., & Shepherd, M. (2004). Family support and diet barriers among older Hispanic adults with type 2 diabetes. *Family Medicine*, *36*(6), 423-30.

Wilson, J. W. (1947). Detrochet and the cell theory. *Isis*, *37*(1/2), 14-21.

Wish, J. B. (2006). Assessing iron status: Beyond serum ferritin and transferrin saturation. *Clinical Journal of the American Society of Nephrology*, *1* Suppl. S4-S8.

Wisniak, J. (2013). Thomas Graham. II. Contributions to diffusion of gasses and liquids, colloids, dialysis, and osmosis. *Educacion Quimica*, *24* Suppl. 2, 506-515.

Yan, G., Norris, K. C., Yu, A. J., Ma, J. Z., Greene, T., Yu, W., & Cheung, A. K. (2013). The relationship of age, race, and ethnicity with survival in dialysis patients. *Clinical Journal of the American Society of Nephrology*, *8*, 953-961.

Yokoyama, H., Kanno, S., Tkahashi, S., Yamada, D., Honjo, J., Saito, K…Haneda, M. (2011). Risks for glomerular filtration rate decline in association with progression of albuminuria in type 2 diabetes. *Nephology Dialysis Transplantation*, *26*, 2924-2930.

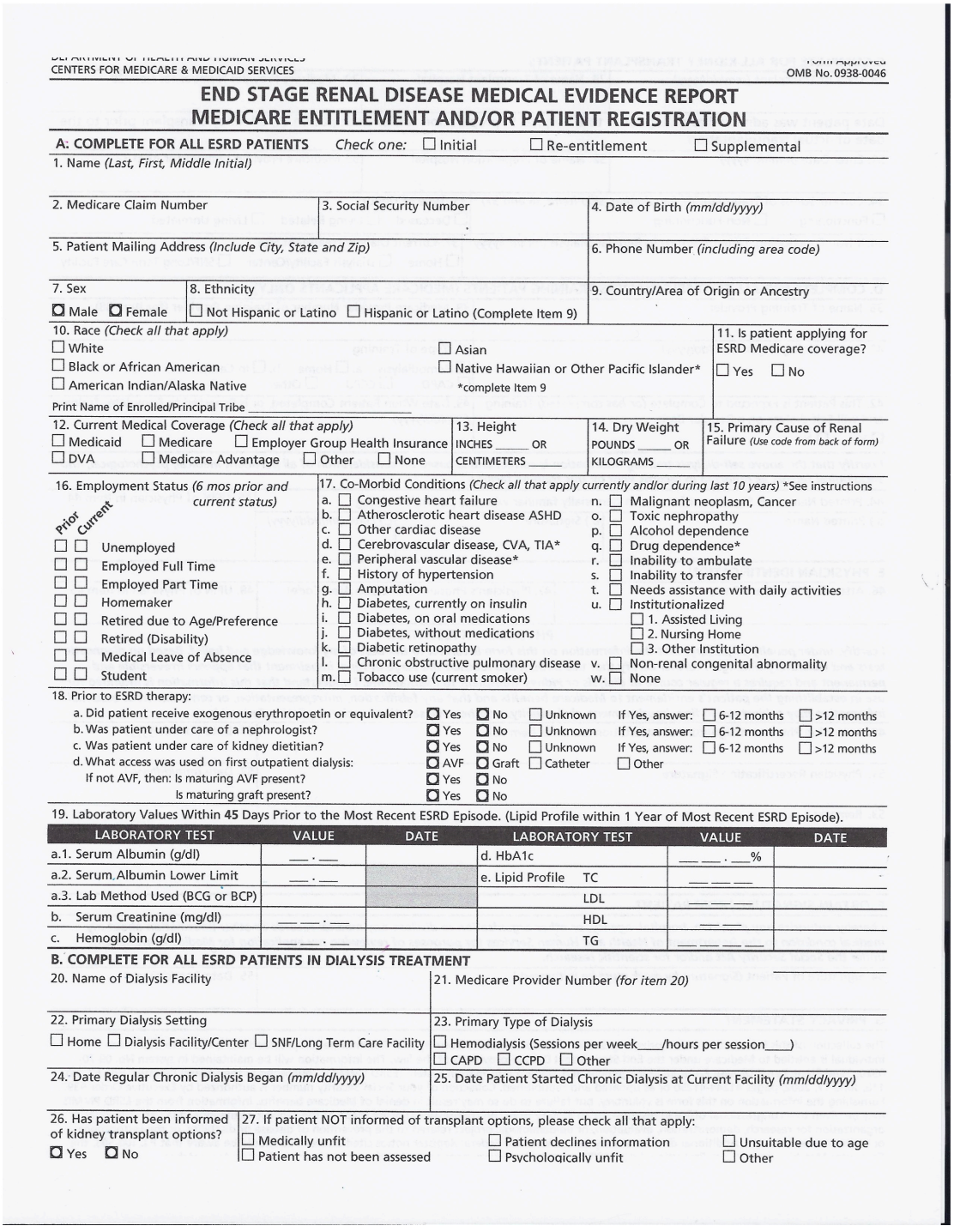
Yurugi, T., Morimoto, S., Okamoto, T., Amari, Y., Kasuno, Y., Fukui, M…Iwasaka, T. (2012). Accumulation of visceral fat in maintenance hemodialysis patients. *Clinical and Experimental Nephrology*, *16*, 156-163.

Zakerkish, M., Shahbazian, H. B., Shahbazian, H., Latifi, S. M., Aleali, A. M. (2013). Albuminuria and its correlates in type 2 diabetic patients. *Iranian Journal of Kidney Diseases*, *7*(4), 268-276.

Zaldivar, A., & Smolowitz, J. (1994). Perceptions of the importance placed on religion and folk medicine by non-Mexican American Hispanic adults with diabetes. *Diabetes Educator, 20*, 303–306.

Zambanini, A., McIntosh, C. S., Mitchell, J., & Catalan, J., (1999). Psychological issues in diabetes. *The Lancet*, *354*, 74.

Appendix A: Centers for Medicare and Medicaid Services CMS-2728 Form



DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

Form Approved
OMB No. 0938-0046

END STAGE RENAL DISEASE MEDICAL EVIDENCE REPORT
MEDICARE ENTITLEMENT AND/OR PATIENT REGISTRATION

A. COMPLETE FOR ALL ESRD PATIENTS *Check one:* ☐ Initial ☐ Re-entitlement ☐ Supplemental

1. Name *(Last, First, Middle Initial)*

2. Medicare Claim Number | 3. Social Security Number | 4. Date of Birth *(mm/dd/yyyy)*

5. Patient Mailing Address *(Include City, State and Zip)* | 6. Phone Number *(including area code)*

7. Sex ☐ Male ☐ Female | 8. Ethnicity ☐ Not Hispanic or Latino ☐ Hispanic or Latino (Complete Item 9) | 9. Country/Area of Origin or Ancestry

10. Race *(Check all that apply)*
☐ White ☐ Asian
☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander* *complete Item 9
☐ American Indian/Alaska Native
Print Name of Enrolled/Principal Tribe _____

11. Is patient applying for ESRD Medicare coverage? ☐ Yes ☐ No

12. Current Medical Coverage *(Check all that apply)*
☐ Medicaid ☐ Medicare ☐ Employer Group Health Insurance ☐ DVA ☐ Medicare Advantage ☐ Other ☐ None

13. Height INCHES _____ OR CENTIMETERS _____

14. Dry Weight POUNDS _____ OR KILOGRAMS _____

15. Primary Cause of Renal Failure *(Use code from back of form)*

16. Employment Status *(6 mos prior and current status)*

Prior	Current	
☐	☐	Unemployed
☐	☐	Employed Full Time
☐	☐	Employed Part Time
☐	☐	Homemaker
☐	☐	Retired due to Age/Preference
☐	☐	Retired (Disability)
☐	☐	Medical Leave of Absence
☐	☐	Student

17. Co-Morbid Conditions *(Check all that apply currently and/or during last 10 years)* *See instructions

a. ☐ Congestive heart failure
b. ☐ Atherosclerotic heart disease ASHD
c. ☐ Other cardiac disease
d. ☐ Cerebrovascular disease, CVA, TIA*
e. ☐ Peripheral vascular disease*
f. ☐ History of hypertension
g. ☐ Amputation
h. ☐ Diabetes, currently on insulin
i. ☐ Diabetes, on oral medications
j. ☐ Diabetes, without medications
k. ☐ Diabetic retinopathy
l. ☐ Chronic obstructive pulmonary disease
m. ☐ Tobacco use (current smoker)
n. ☐ Malignant neoplasm, Cancer
o. ☐ Toxic nephropathy
p. ☐ Alcohol dependence
q. ☐ Drug dependence*
r. ☐ Inability to ambulate
s. ☐ Inability to transfer
t. ☐ Needs assistance with daily activities
u. ☐ Institutionalized
☐ 1. Assisted Living
☐ 2. Nursing Home
☐ 3. Other Institution
v. ☐ Non-renal congenital abnormality
w. ☐ None

18. Prior to ESRD therapy:

a. Did patient receive exogenous erythropoetin or equivalent?	☐ Yes	☐ No	☐ Unknown	If Yes, answer: ☐ 6-12 months	☐ >12 months
b. Was patient under care of a nephrologist?	☐ Yes	☐ No	☐ Unknown	If Yes, answer: ☐ 6-12 months	☐ >12 months
c. Was patient under care of kidney dietitian?	☐ Yes	☐ No	☐ Unknown	If Yes, answer: ☐ 6-12 months	☐ >12 months
d. What access was used on first outpatient dialysis:	☐ AVF	☐ Graft	☐ Catheter	☐ Other	
If not AVF, then: Is maturing AVF present?	☐ Yes	☐ No			
Is maturing graft present?	☐ Yes	☐ No			

19. Laboratory Values Within **45** Days Prior to the Most Recent ESRD Episode. (Lipid Profile within 1 Year of Most Recent ESRD Episode).

LABORATORY TEST	VALUE	DATE	LABORATORY TEST	VALUE	DATE
a.1. Serum Albumin (g/dl)	___ . ___		d. HbA1c	___ ___ . ___%	
a.2. Serum Albumin Lower Limit	___ . ___		e. Lipid Profile TC	___ ___ ___	
a.3. Lab Method Used (BCG or BCP)			LDL	___ ___ ___	
b. Serum Creatinine (mg/dl)	___ ___ . ___		HDL	___ ___	
c. Hemoglobin (g/dl)	___ ___ . ___		TG	___ ___ ___ ___	

B. COMPLETE FOR ALL ESRD PATIENTS IN DIALYSIS TREATMENT

20. Name of Dialysis Facility | 21. Medicare Provider Number *(for item 20)*

22. Primary Dialysis Setting ☐ Home ☐ Dialysis Facility/Center ☐ SNF/Long Term Care Facility

23. Primary Type of Dialysis ☐ Hemodialysis (Sessions per week____/hours per session____) ☐ CAPD ☐ CCPD ☐ Other

24. Date Regular Chronic Dialysis Began *(mm/dd/yyyy)*

25. Date Patient Started Chronic Dialysis at Current Facility *(mm/dd/yyyy)*

26. Has patient been informed of kidney transplant options? ☐ Yes ☐ No

27. If patient NOT informed of transplant options, please check all that apply:
☐ Medically unfit ☐ Patient declines information ☐ Unsuitable due to age
☐ Patient has not been assessed ☐ Psychologically unfit ☐ Other

C. COMPLETE FOR ALL KIDNEY TRANSPLANT PATIENTS

28. Date of Transplant *(mm/dd/yyyy)*	29. Name of Transplant Hospital	30. Medicare Provider Number for Item 29

Date patient was admitted as an inpatient to a hospital in preparation for, or anticipation of, a kidney transplant prior to the date of actual transplantation.

31. Enter Date *(mm/dd/yyyy)*	32. Name of Preparation Hospital	33. Medicare Provider number for Item 32

34. Current Status of Transplant *(if functioning, skip items 36 and 37)*	35. Type of Donor:
☐ Functioning ☐ Non-Functioning	☐ Deceased ☐ Living Related ☐ Living Unrelated
36. If Non-Functioning, Date of Return to Regular Dialysis *(mm/dd/yyyy)*	37. Current Dialysis Treatment Site ☐ Home ☐ Dialysis Facility/Center ☐ SNF/Long Term Care Facility

D. COMPLETE FOR ALL ESRD SELF-DIALYSIS TRAINING PATIENTS (MEDICARE APPLICANTS ONLY)

38. Name of Training Provider	39. Medicare Provider Number of Training Provider (for Item 38)
40. Date Training Began *(mm/dd/yyyy)*	41. Type of Training ☐ Hemodialysis a. ☐ Home b. ☐ In Center ☐ CAPD ☐ CCPD ☐ Other
42. This Patient is Expected to Complete *(or has completed)* Training and will Self-dialyze on a Regular Basis. ☐ Yes ☐ No	43. Date When Patient Completed, or is Expected to Complete, Training *(mm/dd/yyyy)*

I certify that the above self-dialysis training information is correct and is based on consideration of all pertinent medical, psychological, and sociological factors as reflected in records kept by this training facility.

44. Printed Name and Signature of Physician personally familiar with the patient's training			45. UPIN of Physician in Item 44
a.) Printed Name	b.) Signature	c.) Date *(mm/dd/yyyy)*	

E. PHYSICIAN IDENTIFICATION

46. Attending Physician *(Print)*	47. Physician's Phone No. *(include Area Code)*	48. UPIN of Physician in Item 46

PHYSICIAN ATTESTATION

I certify, under penalty of perjury, that the information on this form is correct to the best of my knowledge and belief. Based on diagnostic tests and laboratory findings, I further certify that this patient has reached the stage of renal impairment that appears irreversible and permanent and requires a regular course of dialysis or kidney transplant to maintain life. I understand that this information is intended for use in establishing the patient's entitlement to Medicare benefits and that any falsification, misrepresentation, or concealment of essential information may subject me to fine, imprisonment, civil penalty, or other civil sanctions under applicable Federal laws.

49. Attending Physician's Signature of Attestation *(Same as Item 46)*	50. Date *(mm/dd/yyyy)*
51. Physician Recertification Signature	52. Date *(mm/dd/yyyy)*

53. Remarks

F. OBTAIN SIGNATURE FROM PATIENT

I hereby authorize any physician, hospital, agency, or other organization to disclose any medical records or other information about my medical condition to the Department of Health and Human Services for purposes of reviewing my application for Medicare entitlement under the Social Security Act and/or for scientific research.

54. Signature of Patient *(Signature by mark must be witnessed.)*	55. Date *(mm/dd/yyyy)*

G. PRIVACY STATEMENT

The collection of this information is authorized by Section 226A of the Social Security Act. The information provided will be used to determine if an individual is entitled to Medicare under the End Stage Renal Disease provisions of the law. The information will be maintained in system No. 09-70-0520, "End Stage Renal Disease Program Management and Medical Information System (ESRD PMMIS)", published in the Federal Register, Vol. 67, No. 116, June 17, 2002, pages 41244-41250 or as updated and republished. Collection of your Social Security number is authorized by Executive Order 9397. Furnishing the information on this form is voluntary, but failure to do so may result in denial of Medicare benefits. Information from the ESRD PMMIS may be given to a congressional office in response to an inquiry from the congressional office made at the request of the individual; an individual or organization for research, demonstration, evaluation, or epidemiologic project related to the prevention of disease or disability, or the restoration or maintenance of health. Additional disclosures may be found in the *Federal Register* notice cited above. You should be aware that P.L.100-503, the Computer Matching and Privacy Protection Act of 1988, permits the government to verify information by way of computer matches.

LIST OF PRIMARY CAUSES OF END STAGE RENAL DISEASE

Item 15. Primary Cause of Renal Failure should be completed by the attending physician from the list below. Enter the ICD-9-CM code to indicate the primary cause of end stage renal disease. If there are several probable causes of renal failure, choose one as primary. **Code effective as of September 2003.**

ICD-9	NARRATIVE
DIABETES	
25040	Diabetes with renal manifestations Type 2
25041	Diabetes with renal manifestations Type 1
GLOMERULONEPHRITIS	
5829	Glomerulonephritis (GN) (histologically not examined)
5821	Focal glomerulosclerosis, focal sclerosing GN
5831	Membranous nephropathy
58321	Membranoproliferative GN type 1, diffuse MPGN
58322	Dense deposit disease, MPGN type 2
58381	IgA nephropathy, Berger's disease (proven by immunofluorescence)
58382	IgM nephropathy (proven by immunofluorescence)
5834	With lesion of rapidly progressive GN
5800	Post infectious GN, SBE
5820	Other proliferative GN
SECONDARY GN/VASCULITIS	
7100	Lupus erythematosus, (SLE nephritis)
2870	Henoch-Schonlein syndrome
7101	Scleroderma
28311	Hemolytic uremic syndrome
4460	Polyarteritis
4464	Wegener's granulomatosis
58392	Nephropathy due to heroin abuse and related drugs
44620	Other Vasculitis and its derivatives
44621	Goodpasture's syndrome
58391	Secondary GN, other
INTERSTITIAL NEPHRITIS/PYELONEPHRITIS	
9659	Analgesic abuse
5830	Radiation nephritis
9849	Lead nephropathy
5909	Nephropathy caused by other agents
27410	Gouty nephropathy
5920	Nephrolithiasis
5996	Acquired obstructive uropathy
5900	Chronic pyelonephritis, reflux nephropathy
58389	Chronic interstitial nephritis
58089	Acute interstitial nephritis
5929	Urolithiasis
27549	Other disorders of calcium metabolism
HYPERTENSION/LARGE VESSEL DISEASE	
40391	Unspecified with renal failure
4401	Renal artery stenosis
59381	Renal artery occlusion
59383	Cholesterol emboli, renal emboli

ICD-9	NARRATIVE
CYSTIC/HEREDITARY/CONGENITAL DISEASES	
75313	Polycystic kidneys, adult type (dominant)
75314	Polycystic, infantile (recessive)
75316	Medullary cystic disease, including nephronophthisis
7595	Tuberous sclerosis
7598	Hereditary nephritis, Alport's syndrome
2700	Cystinosis
2718	Primary oxalosis
2727	Fabry's disease
7533	Congenital nephrotic syndrome
5839	Drash syndrome, mesangial sclerosis
75321	Congenital obstruction of ureterpelvic junction
75322	Congenital obstruction of uretrovesical junction
75329	Other Congenital obstructive uropathy
7530	Renal hypoplasia, dysplasia, oligonephronia
75671	Prune belly syndrome
75989	Other (congenital malformation syndromes)
NEOPLASMS/TUMORS	
1890	Renal tumor (malignant)
1899	Urinary tract tumor (malignant)
2230	Renal tumor (benign)
2239	Urinary tract tumor (benign)
23951	Renal tumor (unspecified)
23952	Urinary tract tumor (unspecified)
20280	Lymphoma of kidneys
20300	Multiple myeloma
20308	Other immuno proliferative neoplasms (including light chain nephropathy)
2773	Amyloidosis
99680	Complications of transplanted organ unspecified
99681	Complications of transplanted kidney
99682	Complications of transplanted liver
99683	Complications of transplanted heart
99684	Complications of transplanted lung
99685	Complications of transplanted bone marrow
99686	Complications of transplanted pancreas
99687	Complications of transplanted intestine
99689	Complications of other specified transplanted organ
MISCELLANEOUS CONDITIONS	
28260	Sickle cell disease/anemia
28269	Sickle cell trait and other sickle cell (HbS/Hb other)
64620	Post partum renal failure
042	AIDS nephropathy
8660	Traumatic or surgical loss of kidney(s)
5724	Hepatorenal syndrome
5836	Tubular necrosis (no recovery)
59389	Other renal disorders
7999	Etiology uncertain

INSTRUCTIONS FOR COMPLETION OF END STAGE RENAL DISEASE MEDICAL EVIDENCE REPORT MEDICARE ENTITLEMENT AND/OR PATIENT REGISTRATION

For whom should this form be completed:

This form **SHOULD NOT** be completed for those patients who are in acute renal failure. Acute renal failure is a condition in which kidney function can be expected to recover after a short period of dialysis, i.e., several weeks or months.

This form **MUST BE** completed within 45 days for **ALL** patients beginning any of the following:

Check the appropriate block that identifies the reason for submission of this form.

Initial

For all patients who initially receive a kidney transplant instead of a course of dialysis.

For patients for whom a regular course of dialysis has been prescribed by a physician because they have reached that stage of renal impairment that a kidney transplant or regular course of dialysis is necessary to maintain life. The first date of a regular course of dialysis is the date this prescription is implemented whether as an inpatient of a hospital, an outpatient in a dialysis center or facility, or a home patient. The form should be completed for all patients in this category even if the patient dies within this time period.

Re-entitlement

For beneficiaries who have already been entitled to ESRD Medicare benefits and those benefits were terminated because their coverage stopped 3 years post transplant but now are again applying for Medicare ESRD benefits because they returned to dialysis or received another kidney transplant.

For beneficiaries who stopped dialysis for more than 12 months, have had their Medicare ESRD benefits terminated and now returned to dialysis or received a kidney transplant. These patients will be reapplying for Medicare ESRD benefits.

Supplemental

Patient has received a transplant or trained for self-care dialysis within the first 3 months of the first date of dialysis and initial form was submitted.

All items except as follows: To be completed by the attending physician, head nurse, or social worker involved in this patient's treatment of renal disease.

Items 15, 17-18, 26-27, 49-50: To be completed by the attending physician.
Item 44: To be signed by the attending physician or the physician familiar with the patient's self-care dialysis training.
Items 54 and 55: To be signed and dated by the patient.

1. Enter the patient's legal name (Last, first, middle initial). Name should appear exactly the same as it appears on patient's social security or Medicare card.
2. If the patient is covered by Medicare, enter his/her Medicare claim number as it appears on his/her Medicare card.
3. Enter the patient's own social security number. This number can be verified from his/her social security card.
4. Enter patient's date of birth (2-digit Month, Day, and 4-digit Year). Example 07/25/1950.
5. Enter the patient's mailing address (number and street or post office box number, city, state, and ZIP code.)
6. Enter the patient's home area code and telephone number.
7. Check the appropriate block to identify sex.
8. Check the appropriate block to identify ethnicity. Definitions of the ethnicity categories for Federal statistics are as follows:

   Not Hispanic or Latino—A person of culture or origin not described below, regardless of race.

   Hispanic or Latino—A person of Cuban, Puerto Rican, or Mexican culture or origin regardless of race. Please complete Item 9 and provide the country, area of origin, or ancestry to which the patient claims to belong.
9. Country/Area of origin or ancestry—Complete if information is available or if directed to do so in question 8.
10. Check the appropriate block(s) to identify race. Definitions of the racial categories for Federal statistics are as follows:

    White—A person having origins in any of the original white peoples of Europe, the Middle East or North Africa.

    Black or African American—A person having origins in any of the black racial groups of Africa. This includes native-born Black Americans, Africans, Haitians and residents of non-Spanish speaking Caribbean Islands of African descent.

    American Indian/Alaska Native—A person having origins in any of the original peoples of North America and South America (including Central America) and who maintains tribal affiliation or community attachment. Print the name of the enrolled or principal tribe to which the patient claims to be a member.

    Asian—A person having origins in any of the original peoples of the Far East, Southeast Asia or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

    Native Hawaiian or Other Pacific Islander—A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. Please complete Item 9 and provide the country, area of origin, or ancestry to which the patient claims to belong.

DISTRIBUTION OF COPIES:

- Forward the first part (blue) of this form to the Social Security office servicing the claim.
- Forward the second part (green) of this form to the ESRD Network Organizations.
- Retain the last part (white) in the patient's medical records file.

11. Check the appropriate yes or no block to indicate if patient is applying for ESRD Medicare. **Note: Even though a person may already be entitled to general Medicare coverage, he/she should reapply for ESRD Medicare coverage.**

12. Check **all** the blocks that apply to this patient's current medical insurance status.

    Medicaid—Patient is currently receiving State Medicaid benefits.

    Medicare—Patient is currently entitled to Federal Medicare benefits.

    Employer Group Health Insurance—Patient receives medical benefits through an employee health plan that covers employees, former employees, or the families of employees or former employees.

    DVA—Patient is receiving medical care from a Department of Veterans Affairs facility.

    Medicare Advantage—Patient is receiving medical benefits under a Medicare Advantage organization.

    Other Medical Insurance—Patient is receiving medical benefits under a health insurance plan that is not Medicare, Medicaid, Department of Veterans Affairs, HMO/M+C organization, nor an employer group health insurance plan. Examples of other medical insurance are Railroad Retirement and CHAMPUS beneficiaries.

    None—Patient has no medical insurance plan.

13. Enter the patient's most recent recorded height in inches **OR** centimeters at time form is being completed. If entering height in centimeters, round to the nearest centimeter. Estimate or use last known height for those unable to be measured. (Example of inches - 62. DO NOT PUT 5'2") NOTE: For amputee patients, enter height prior to amputation.

14. Enter the patient's most recent recorded dry weight in pounds **OR** kilograms at time form is being completed. If entering weight in kilograms, round to the nearest kilogram.

NOTE: For amputee patients, enter actual dry weight.

15. **To be completed by the attending physician**. Enter the ICD-9-CM from back of form to indicate the primary cause of end stage renal disease. These are the only acceptable causes of end stage renal disease.

16. Check the first box to indicate employment status 6 months prior to renal failure and the second box to indicate current employment status. **Check only one box for each time period**. If patient is under 6 years of age, leave blank.

17. **To be completed by the attending physician**. Check all co-morbid conditions that apply.

    ***Cerebrovascular Disease** includes history of stroke/ cerebrovascular accident (CVA) and transient ischemic attack (TIA).

    ***Peripheral Vascular Disease** includes absent foot pulses, prior typical claudication, amputations for vascular disease, gangrene and aortic aneurysm.

    ***Drug dependence** means dependent on illicit drugs.

18. Prior to ESRD therapy, check the appropriate box to indicate whether the patient received Exogenous erythropoetin (EPO) or equivalent, was under the care of a nephrologist and/or was under the care of a kidney dietitian. Provide vascular access information as to the type of access used (Arterio-Venous Fistula (AVF), graft, catheter (including port device) or other type of access) when the patient first received outpatient dialysis. If an AVF access was not used, was a maturing AVF or graft present?

NOTE: For those patients re-entering the Medicare program after benefits were terminated, Items 19a thru 19c should contain initial laboratory values within 45 days prior to the most recent ESRD episode. Lipid profiles and HbA1c should be within 1 year of the most recent ESRD episode. Some tests may not be required for patients under 21 years of age.

19a1. Enter the serum albumin value (g/dl) and date test was taken. This value and date must be within 45 days prior to first dialysis treatment or kidney transplant.

19a2. Enter the lower limit of the normal range for serum albumin from the laboratory which performed the serum albumin test entered in 19a1.

19a3. Enter the serum albumin lab method used (BCG or BCP).

19b. Enter the serum creatinine value (mg/dl) and date test was taken. **THIS FIELD MUST BE COMPLETED.** Value must be within 45 days prior to first dialysis treatment or kidney transplant.

19c. Enter the hemoglobin value (g/dl) and date test was taken. This value and date must be within 45 days prior to the first dialysis treatment or kidney transplant.

19d. Enter the HbA1c value and the date the test was taken. The date must be within 1 year prior to the first dialysis treatment or kidney transplant.

19e. Enter the Lipid Profile values and date test was taken. These values: TC–Total Cholesterol; LDL–LDL Cholesterol; HDL–HDL Cholesterol; TG–Triglycerides, and date must be within 1 year prior to the first dialysis treatment or kidney transplant.

20. Enter the name of the dialysis facility where patient is currently receiving care and who is completing this form for patient.

21. Enter the 6-digit Medicare identification code of the dialysis facility in item 20.

22. If the person is receiving a regular course of dialysis treatment, check the appropriate **anticipated long-term treatment setting** at the time this form is being completed.

23. If the patient is, or was, on regular dialysis, **check the anticipated long-term primary type of dialysis**: Hemodialysis, (enter the number of sessions prescribed per week and the hours that were prescribed for each session), CAPD (Continuous Ambulatory Peritoneal Dialysis) and CCPD (Continuous Cycling Peritoneal Dialysis), or Other. **Check only one block**. NOTE: Other has been placed on this form to be used only to report IPD (Intermittent Peritoneal Dialysis) and any new method of dialysis that may be developed prior to the renewal of this form by Office of Management and Budget.

24. Enter the date (month, day, year) that a "regular course of chronic dialysis" began. The beginning of the course of dialysis is counted from the beginning of regularly scheduled dialysis necessary for the treatment of end stage renal disease (ESRD) regardless of the dialysis setting. The date of the first dialysis treatment after the physician has determined that this patient has ESRD and has written a prescription for a "regular course of dialysis" is the "Date Regular Chronic Dialysis Began" regardless of whether this prescription was implemented in a hospital/ inpatient, outpatient, or home setting and regardless of any acute treatments received prior to the implementation of the prescription.

NOTE: For these purposes, end stage renal disease means irreversible damage to a person's kidneys so severely affecting his/her ability to remove or adjust blood wastes that in order to maintain life he or she must have either a course of dialysis or a kidney transplant to maintain life.

If re-entering the Medicare program, enter beginning date of the current ESRD episode. Note in Remarks, Item 53, that patient is restarting dialysis.

25. Enter date patient started chronic dialysis at current facility of dialysis services. In cases where patient transferred to current dialysis facility, this date will be after the date in Item 24.

26. Enter whether the patient has been informed of their options for receiving a kidney transplant.

27. If the patient has not been informed of their options (answered "no" to Item 26), then enter all reasons why a kidney transplant was not an option for this patient at

28. Enter the date(s) of the patient's kidney transplant(s). If reentering the Medicare program, enter current transplant date.
29. Enter the name of the hospital where the patient received a kidney transplant on the date in Item 28.
30. Enter the 6-digit Medicare identification code of the hospital in Item 29 where the patient received a kidney transplant on the date entered in Item 28.
31. Enter date patient was admitted as an inpatient to a hospital in preparation for, or anticipation of, a kidney transplant prior to the date of the actual transplantation. This includes hospitalization for transplant workup in order to place the patient on a transplant waiting list.
32. Enter the name of the hospital where patient was admitted as an inpatient in preparation for, or anticipation of, a kidney transplant prior to the date of the actual transplantation.
33. Enter the 6-digit Medicare identification number for hospital in Item 32.
34. Check the appropriate functioning or non-functioning block.
35. Enter the type of kidney transplant organ donor, Deceased, Living Related or Living Unrelated, that was provided to the patient.
36. If transplant is nonfunctioning, enter date patient returned to a regular course of dialysis. If patient did not stop dialysis post transplant, enter transplant date.
37. If applicable, check where patient is receiving dialysis treatment following transplant rejection. A nursing home or skilled nursing facility is considered as home setting.

Self-dialysis Training Patients (Medicare Applicants Only)

Normally, Medicare entitlement begins with the third month after the month a patient begins a regular course of dialysis treatment. This 3-month qualifying period may be waived if a patient begins a self-dialysis training program in a **Medicare approved training facility** and is expected to self-dialyze after the completion of the training program. Please complete items 38-43 if the patient has entered into a self-dialysis training program. Items 38-43 must be completed if the patient is applying for a Medicare waiver of the 3-month qualifying period for dialysis benefits based on participation in a self-care dialysis training program.

38. Enter the name of the provider furnishing self-care dialysis training.
39. Enter the 6-digit Medicare identification number for the training provider in Item 38.
40. Enter the date self-dialysis training began.
41. Check the appropriate block which describes the type of self-care dialysis training the patient began. If the patient trained for hemodialysis, enter whether the training was to perform dialysis in the home setting or in the facility (in center). If the patient trained for IPD (Intermittent Peritoneal Dialysis), report as Other.
42. Check the appropriate block as to whether or not the physician certifies that the patient is expected to complete the training successfully and self-dialyze on a regular basis.
43. Enter date patient completed or is expected to complete self-dialysis training.
44. Enter printed name and signature of the attending physician or the physician familiar with the patient's self-care dialysis training.
45. Enter the Unique Physician Identification Number (UPIN) of physician in Item 44. (See Item 48 for explanation of UPIN.)
46. Enter the name of the physician who is supervising the patient's renal treatment at the time this form is completed.
47. Enter the area code and telephone number of the physician who is supervising the patient's renal treatment at the time this form is completed.
48. Enter the physician's UPIN assigned by CMS.

    A system of physician identifiers is mandated by Section 9202 of the Consolidated Omnibus Budget Reconciliation Act of 1985. It requires a unique identifier for each physician who provides services for which Medicare payment is made. An identifier is assigned to each physician regardless of his or her practice configuration. The UPIN is established in a national Registry of Medicare Physician Identification and Eligibility Records (MPIER). Transamerica Occidental Life Insurance Company is the Registry Carrier that establishes and maintains the national registry of physicians receiving Part B Medicare payment. Its address is: UPIN Registry, Transamerica Occidental Life, P.O. Box 2575, Los Angeles, CA 90051-0575.
49. To be signed by the physician supervising the patient's kidney treatment. Signature of physician identified in Item 46. A stamped signature is unacceptable.
50. Enter date physician signed this form.
51. To be signed by the physician who is currently following the patient. If the patient had decided initially not to file an application for Medicare, the physician will be re-certifying that the patient is end stage renal, based on the same medical evidence, by signing the copy of the CMS-2728 that was originally submitted and returned to the provider. If you do not have a copy of the original CMS-2728 on file, complete a new form.
52. The date physician re-certified and signed the form.
53. This remarks section may be used for any necessary comments by either the physician, patient, ESRD Network or social security field office.
54. The patient's signature authorizing the release of information to the Department of Health and Human Services must be secured here. **If the patient is unable to sign the form, it should be signed by a relative, a person assuming responsibility for the patient or by a survivor.**
55. The date patient signed form.

Appendix B: Clinical Research Approval Application

Fresenius Medical Care

Fresenius Medical Services

Compliance Policy C-FMS-009.2

Clinical Research Project Approval Application

Please attach the following documents **(please note, failure to complete/provide the following could lead to delays in approval)**
❒ Study protocol including a short one page protocol summary (abstracts not accepted)
❒ Approval statement from Institutional Review Board (if applicable)
❒ Signed copy of 1572 (if applicable)
❒ Study specific Patient Informed Consent template, including disclosure of financial reimbursement to physician, staff and facility.
❒ Overhead Fee or Application Fee (for investigator initiated or non-profit entities only)
❒ Study materials, if any, used for patient recruitment
❒ IRB Approved Informed Consent Form (ICF) ❒ Waiver of consent ❒ Consent is HIPAA compliant (no HIPAA authorization needed) ❒ Consent is not HIPAA compliant (see Page 8 of this application)
❒ Study specific FMC HIPAA Privacy Authorization template, if consent is not HIPAA compliant (see page 8 of this application)
❒ Lab Agreement (if applicable)
❒ Investigator Statement and Study Coordinator Statement (Page 3 and 4 of Application)
❒ Letter of indemnification from the pharmaceutical company, if study sponsored by pharmaceutical company
❒ Other:

Fresenius Medical Care

Compliance Policy C-FMS-009.2
Clinical Research Project Approval Application

Principal Investigator Statement

Please check one answer for each statement:	YES	NO	N/A
1. Investigator will ensure that the conduct of the study complies with all applicable local, state and federal laws and regulations.			
2. Investigator will ensure that all study participants are fully informed of the study and sign an IRB approved consent form.			
3. Investigator will promptly inform Sponsor and Institutional Review Board of any Serious Adverse Events.			
4. Investigator assures FMCNA that no facility staff will be used in the conduct of the trial.			
5. Investigator assures FMCNA that no study labs will be billed to the patient's insurance provider.			
6. Investigator assures FMCNA that no dialysis facility supplies (including syringes etc.) will be used for research purposes.			
7. Investigator will not change patient's dialysis schedule or delay patient's dialysis treatment for the study.			
8. Investigator will make sure that they and their research staff have undergone appropriate training in research.* (Please see page 3 for *)			
9. If Investigator decides to publish study results, Investigator will provide FMCNA with the manuscript two (2) months prior to submission.			
10. Investigator will reimburse FMCNA for any lost revenue which occurs as a result of patient participation.			
11. Investigator will ensure that approval for study participation has been obtained from study patient's attending physician.			
12. Investigator will provide study specific research training to patient care staff, will complete training attendance log (page 6) and **fax log to Clinical Studies Group**.			
13. Are the labs, medications or services needed by the study different or more frequent from the items and services ordered by the physician as part of the current standard of care? **If yes, will study sponsor provide these? Attach detail.**			
14. As a result of the study or changes in patient care due to the study, will the facility experience loss of profits for items or services that are either purchased or provided by FMS outside of a study, that are submitted to patients' payors for reimbursement? **If yes, the study sponsor will provide FMCNA with reimbursement for facility lost profits.**			
15. Does the study require use of facility staff for study related administrative or clinical services above and beyond, or outside, the normal day to day responsibilities of patient care and documentation during scheduled work hours? **If yes, there must be a written agreement to compensate the facility for this work.**			
16. Other than staff-related costs addressed above, will the facility incur any direct costs related to its participation in the study? **If yes, the study sponsor will provide FMCNA with reimbursement for facility lost profits.**			
17. For all research studies that are investigator initiated and are sponsored by a Pharmaceutical company, the Investigator will provide a letter of indemnification from the Pharmaceutical company indemnifying FMS.			

Principal Investigator Signature: **Date:**

Fresenius Medical Care North America
Clinical Studies Group: 920 Winter Street Waltham, MA 02451 (781) 699-9000

Fresenius Medical Care

Compliance Policy C-FMS-009.2
Clinical Research Project Approval Application

Study Coordinator Statement

Please check one answer for each statement:

	YES	NO	N/A
1. Study Coordinator will work cooperatively with clinic manager in scheduling monitored study subject visits at mutually convenient times.			
2. Study Coordinator will provide a 3 ring study binder labeled with the protocol title, and protocol number. This binder will contain the study protocol, a blank copy of the informed consent document, contact information of the PI and SC, contact information for the Fresenius Clinical Studies Group, and a list of participating patients.			
3. Study coordinator will be responsible for updating the research binder throughout duration of the study.			
4. Study Coordinator will notify clinic manager every time a new patient is consented to participate and make sure clinic manager flags patients in Proton, AMI and eCube systems.			
5. Study Coordinator needs to be sure that all tubes for study bloods are well labeled and readily available for use by patient care staff.			
6. Study Coordinator will communicate with clinic manager when patient bloods will be drawn and coordinate collection of sample.			
7. Study Coordinator will give the governing body meeting document (page 6 of application) to clinic manager and retrieve it after the governing body meeting. Study Coordinator will then return (fax) the governing body meeting document to the Clinical Studies Group.			
8. Study Coordinator will place copies of signed informed consents in patient's dialysis medical records.			

Study Coordinator Signature: **Date:**

***A suggested link to a website for free training in the protection of human participants in research is as follows:** https://www.citiprogram.org/

***NIH training website:** http://crt.nihtraining.com/login.php

***FMC4ME training:** https://fmc4me.fmcna.com/intranet/TrainingEducation/index.htm

Fresenius Medical Care

Compliance Policy C-FMS-009.2

Governing Body Research Review Memorandum

The study coordinator must provide this governing body research review memorandum document to the clinic manager of the facility. Once the governing body has met and reviewed the study protocol, the governing body meeting minute's needs to be put into the facility binder. The Study Coordinator should then send the ***completed*** governing body research review memorandum document to the Fresenius Clinical Studies Group.

DATE:_____ FACILITY NAME/NUMBER: _____

PROTOCOL NAME AND NUMBER (if applicable):
_____

INVESTIGATOR:_____

The undersigned confirm that the above referenced research has been reviewed by the governing body and that the attached summary of the study is made a part of the Governing body's minutes.

_____
Name:
Title: Regional Vice President

_____
Name:
Title: Facility Medical Director

_____
Name:
Title: Clinic Manager

Please fax a copy of this form to the Clinical Studies Group, 781-699-4281. The original should be placed in the Governing Body binder.

Clinical Studies Group: 920 Winter Street Waltham, MA 02451 (781) 699-9000

Fresenius Medical Care

Compliance Policy C-FMS-009.2

Attendance Log Template

The study coordinator must provide an in-service to each facility staff member who may be called in any way to participate in study procedures. The in-service shall include a review of the study summary and procedures for documenting study related items and services. The study coordinator will document the in-service to the Clinical Manager for the facility file. In most cases study related items and services provided are not entered into the current EMR system. If approval has been given to enter study related items and services into the current EMR system instructions to use the "appropriate" code in supply by field must be given.

PROTOCOL NAME AND NUMBER (if applicable):

_____

TO WHOM IT MAY CONCERN:

The following staff members were trained by me on the above mentioned protocol regarding the following:

-Good Clinical Practice guidelines as dictated in clinical research.
-Sound scientific practices and procedures as dictated in the protocol.
-Standardized methodologies and training to collect data or samples dictated in the protocol.
-Familiarity with protocol operations, responsibilities, and overall understanding of procedures to be followed adhering to the protocol as written.

PRINCIPAL INVESTIGATOR SIGNATURE:_____

PRINT NAME:_____ DATE:_____

Staff Members Trained:

Name: Title:	Name: Title:
Name: Title:	Name: Title:
Name: Title:	Name: Title:
Name: Title:	Name: Title:
Name: Title:	Name: Title:

Please fax a copy of this form to the Clinical Studies Group, 781-699-4281. The original should be placed in the Governing Body binder and a copy placed in the Research binder.

Fresenius Medical Care

AUTHORIZATION FOR RELEASE OF PROTECTED HEALTH INFORMATION

PLEASE CHECK THE APPROPRIATE BOX(ES)

Patient or Legal Representative request for:

- ☐ Physical (On-Site) Access to view medical records (PHI), and/or
- ☐ Authorization for the release of medical records (PHI) to third party, and/or
- ☐ Authorization for the release of medical records (PHI) to self.

I. PATIENT INFORMATION
a. Name:
b. Request date:
c. Location where the patient receives treatment:
d. Patient Medical Record Number (MRN):

II. INFORMATION TO BE USED OR DISCLOSED

I hereby authorize Fresenius Medical Care North America ("FMCNA"), and its employees and agents, to use or disclose my protected health information ("information") as specified below.

I understand that this Authorization is valid only for the use(s) and disclosure(s) specifically described in this document.

a. Information to be used or disclosed, check all that apply:

Patient demographic and other general information:

Check		**Type of information**
Y	**N**	
		Name
		Address
		Date of birth or age
		Social Security number
		Medical record number or other identifier
		Financial information

Medical Record Information:

Check	**Record**	**Date(s) of Service(s)**

Fresenius Medical Care

III. PATIENT AUTHORIZATION
(To be completed by the patient or the patient's legal representative.)

I have reviewed the information completed above and understand it. I understand that if I have questions about this form or the information that is completed above that I may ask the manager of the FMCNA location where I receive treatment to answer my questions, I may call 1-800-662-1237 Ext. 9099 and ask that an FMCNA representative contact me, or I may e-mail Privacy@fmc-na.com. **I understand that I should never sign this form if it is blank or if the sections above are not filled out.**

I understand that I may revoke this authorization by submitting a written revocation to:
Privacy Officer
Fresenius Medical Care North America
920 Winter Street
Waltham, Massachusetts 02451-1457

Any revocation shall not be effective with respect to any use or disclosure made by FMCNA in reliance on this authorization prior to the date of FMCNA's receipt of my revocation.

I understand that FMCNA cannot require me to sign this authorization in order to receive treatment unless the provision of health care by FMCNA is only for the purpose of creating information for disclosure to a third party (for example, an employee physical exam) or for research-related treatment, in which case FMCNA will not provide the service unless I sign this authorization.
I understand that the information used or disclosed by FMCNA pursuant to this authorization may be subject to redisclosure by the recipient in which case it might no longer be protected under the HIPAA Privacy Rule.
I understand that in some cases, the person or entity receiving the information covered by this Authorization may be prohibited from disclosing substance abuse information under the Federal Substance Abuse Confidentiality Requirements. I authorize FMCNA to copy this Authorization and to send the recipient the redisclosure notice required under the Federal Substance Abuse Confidentiality Requirements, if my records contain information protected by those laws.

Fresenius Medical Care

Y	N		
		Medical Treatment Record (specify the information being requested, i.e. Treatment Flow Sheets, Progress Notes, Laboratory Results, care Plans, etc.)	
		Confidential information and records regarding AIDS or HIV infection	
		Mental health care	
		The entire medical Treatment Record	

b. The information will be used by or disclosed to the following person(s), entity or class of persons or entities:

c. The address of the person or entity receiving the information is:
(No P.O. Boxes)

☐ Check here if address not known

☐ Check here if in connection with a study. Name of study, if available _____

d. The information will be used for the following purpose(s):

☐ Check here if the disclosure is at the request of the patient and no further purpose is provided.

☐ Check here if the disclosure is to satisfy data collection for a research project, in which the patient has signed an informed consent.

e. This Authorization will expire:
Provide an expiration date or event. This must be a specific date, a specific time period (i.e., "One year from the date of signature"), or an event directly relevant to the individual or the purpose of the use or disclosure (i.e., "When the patient is no longer treated at the facility.").
If no date or event provided, authorization will expire one (1) year from the date of signature.

Fresenius Medical Care

To be completed by FMCNA staff:

FMCNA will charge the following fee for the service requested above:

☐ There will be no fee for the requested service.

☐ The following fees apply to the requested service:

Copying Fee	$
Shipping Fee	$

Name of FMCNA Staff Member (Please Print)	
Signature of FMCNA Staff Member	
Date	

To be completed by the patient if fees apply:

I agree to pay the fees indicated above.

a. Patient Name and Name of patient's legal representative (if applicable) (Please Print)
b. Signature of patient or the patient's legal representative:
c. Date of signature:

Fresenius Medical Care

IV. FOR INTERNAL USE ONLY
(To be completed by the FMCNA location manager or designee)

a. Method for verification of the identification of the person or entity requesting the patient's information:

Check	Method
	Name and address provided by the patient
	Recipient was in the physical presence of the patient
	Medical Record Number (MRN) listed in Section I. Patient Information
	Personally know the identity of the individual or entity
	Received the request from entity on appropriate letterhead
	Reviewed government issued identification
	Obtained appropriate legal document approved by the Law Department
	Reviewed the patient signed, study specific, informed consent form
	Other. Please describe:

b. Date of verification:

c. Print name and title of FMCNA location manager or designee:

d. Signature of FMCNA location manager or designee:

This original must be placed in the patient's medical record. A copy must be provided to the patient or the patient's legal representative and to the recipient.

Appendix C: Governing Body Research Review Memorandum

FRESENIUS MEDICAL CARE

Research Review Memorandum

DATE:_____ FACILITY NAME/NUMBER: _____

PROTOCOL NUMBER AND
NAME:_____
_____

INVESTIGATOR:_____

The undersigned confirm that the above referenced research has been reviewed by the Governing Body and that the attached summary of the study is made a part of the Governing Body's meeting minutes.

ATTACHMENT: STUDY SUMMARY

_____
Name:
Title: Regional Vice President

_____
Name:
Title: Facility Medical Director

_____
Name:
Title: Clinic Manager

Please fax a copy of this form to the Clinical Studies Group, 781-699-4281. The original should be placed in the Governing Body binder.