

THE CORRELATION OF SERUM BICARBONATE AND METABOLIC ACIDOSIS TO
ALBUMIN IN HEMODIALYSIS PATIENTS

BY

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ABSTRACT

Metabolic acidosis, indicated by low serum bicarbonate levels (CO_2), is common in patients with end stage renal disease (ESRD). The specific aim of this project is to statistically correlate laboratory and descriptive human data with the association of serum CO_2 , metabolic acidosis, and nutritional assessment indices in hemodialysis patients. In a retrospective observational design, 144 hemodialysis patient charts were reviewed. One year of data was collected. To control for differences within individuals, within-subject correlations and analysis of covariance (ANCOVA) was used to analyze variables. Pearson and Spearman correlations were used to analyze correlations across the sample. Serum CO_2 significantly correlated with albumin as an individual variable collected in the same month within-subjects ($r = 0.079$, $p = 0.005$), however not from the prior month ($r = 0.042$, $p = 0.140$). When including additional nutrition and inflammation related biomarkers (creatinine, hemoglobin, nPCR) with albumin and CO_2 in an ANCOVA mixed model, within-subject correlation strengthened and was significant ($r = 0.093$, $p = 0.004$) for the prior month's CO_2 impact on albumin. Albumin and the same month's CO_2 changed to not significant ($r = 0.026$, $p = 0.412$) in the mixed model. Despite small correlations with some variables, this study provides insight into why albumin does not always correlate with CO_2 in hemodialysis patients. Results portray the benefit of correcting metabolic acidosis and the limitation of albumin as the main nutrition indicator and outcome goal in ESRD. Future research should focus on validating better nutritional outcome measures for patients with ESRD.

KEY WORDS: End Stage Renal Disease (ESRD), Hemodialysis, Albumin, Bicarbonate, Malnutrition, Nutrition Indicators in ESRD, Nutritional Assessment

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CHAPTER 1

INTRODUCTION

Low serum bicarbonate levels are common in individuals with chronic kidney disease (CKD) (1). According to the National Kidney Foundation's Kidney Disease Outcome Quality Indicators (K/DOQI), serum bicarbonate levels should be measured monthly and maintained ≥ 22 mEq/L. Levels < 22 mEq/L indicate metabolic acidosis (2). Metabolic acidosis in End Stage Renal Disease (ESRD) is the result of the kidney's inability to synthesize ammonia from protein and excrete hydrogen ions (3). Concern arises when patients with ESRD are not able to maintain acid-base balance due to loss of kidney function. Negative nutrition outcomes including renal osteodystrophy, protein catabolism, decreased normalized protein catabolic rate (nPCR), decreased serum albumin synthesis, and protein energy wasting are observed with metabolic acidosis during maintenance hemodialysis (3, 4). Maintenance hemodialysis refers to the process of cleaning water and waste from blood using an artificial kidney or hemodialyzer. Maintenance hemodialysis can be done at a clinic, referred to as in-center dialysis (5). For the purpose of this thesis, the term dialysis refers to in-center maintenance hemodialysis.

There is no one indicator providing a comprehensive assessment of nutritional status in ESRD (6, 7). Serum albumin is the main nutrition indicator and outcome used in assessment of ESRD and a measure of the visceral protein pool. The outcome goal for albumin according to K/DOQI is set at ≥ 4.0 g/dL. Albumin values < 4.0 g/dL are associated with increased mortality in ESRD on dialysis (6, 8). One disadvantage of using serum albumin is its long half-life of ~ 20 days.

Correcting low serum bicarbonate shows improved serum albumin levels in this patient population (9). It is hypothesized a low serum bicarbonate, indicating metabolic

acidosis, influences albumin and other nutritional assessment indices in hemodialysis patients. Nutrition assessment indices include any of the monthly laboratories, subjective nutrition status designation, or anthropometrics. With serum albumin's long half-life of 20 days, the prior month's serum bicarbonate level (from ~ 20 days ago) would likely impact current serum albumin greater than current serum bicarbonate. The specific aim of this project was to statistically correlate laboratory and descriptive human data from in-center hemodialysis patients at Renal Advantage Incorporated in Westwood, KS.

Purpose:

The purpose of this thesis is to:

- 1) Determine if serum bicarbonate influences albumin and nutrition assessment indices in hemodialysis patients. Nutrition assessment indices include any of the monthly laboratories, subjective nutrition status designation, or anthropometrics.
- 2) Demonstrate the prior month's serum bicarbonate level has a greater impact on current serum albumin versus the current month's serum bicarbonate in hemodialysis patients.

Research questions:

1. Are low bicarbonate levels (CO_2) associated with low albumin and nutritional assessment indices in hemodialysis patients? Nutrition assessment indices include any of the monthly laboratories, subjective nutrition status designation, or anthropometrics.
2. Is the preceding month's serum CO_2 (from ~ 20 days ago) associated with current serum albumin levels more than current serum bicarbonate levels?

CHAPTER 2

LITERATURE REVIEW

Chronic kidney disease stages

The prevalence of ESRD is rising in the United States. The rate of ESRD cases was 1,763 per million in 2010, a four percent increase from 2009. At the end of 2010, there were 594,374 prevalent hemodialysis patients (10). Chronic kidney disease (CKD) is based on the presence of kidney damage and specific a glomerular filtration rate (GFR). Kidney damage is defined as pathological abnormalities or markers of damage with abnormalities in blood, urine, or imaging studies. Chronic kidney disease is defined as a $GFR < 60 \text{ mL/min/1.73 m}^2$ for \geq three months. The stages of CKD range from one to five and are outlined in Table 1.

TABLE 1.
Stages of Chronic Kidney Disease (11)

Stage	Definition
1	Normal GFR of $\geq 90 \text{ mL/min/1.73 m}^2$ but notable kidney damage
2	Mild decrease in GFR of $60\text{-}89 \text{ mL/min/1.73 m}^2$
3	Moderately decreased GFR of $30\text{-}59 \text{ mL/min/1.73 m}^2$
4	Severely decreased GFR with a level of $15\text{-}29 \text{ mL/min/1.73 m}^2$
5	End stage renal disease, indicates kidney failure, a GFR of $<15 \text{ mL/min/1.73 m}^2$, and need for dialysis

Kidney disease has numerous etiologies. Management and evaluation is based on the type of kidney disease. Clinical presentations and causal factors specify the type and origin of CKD. Final diagnosis is based on biopsy or imaging studies. The most frequent cause of kidney disease is diabetes mellitus. Poorly controlled type one and type two diabetes can result in CKD, with type two as the higher frequency. Diabetic

kidney disease often begins first with the onset of diabetes, followed by microalbuminuria, then proteinuria, hypertension, and finally decreasing GFR (11).

Other glomerular diseases, vascular diseases, tubulointerstitial diseases, and cystic diseases, are often grouped as “nondiabetic kidney diseases”. In this category, hypertension is the second most common cause of renal disease, and glomerular diseases the third most common cause of renal failure. The diseases in this group differ based on history, clinical presentation, risk for progression, and response to treatment. Biopsy or invasive imaging studies are needed to differentiate among the diseases (11).

The fourth most common causes of kidney disease are those related to transplants. Causes for failed transplants include organ rejection, toxicity due to anti-rejection medications such as Cyclosporine or Tacrolimus, recurrence of the original disease, which caused their native kidneys to fail, and transplant glomerulopathy. Definitive diagnosis in failed transplants is performed with biopsies (11).

Acid-base balance

End stage renal disease can result in low serum bicarbonate levels, indicating metabolic acidosis (1, 2, 12). For the purpose of this paper, serum bicarbonate refers to CO_2 . Metabolic acidosis is shown to have negative effects on nutrition indices including negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, reduced serum albumin synthesis, loss of lean body mass, and muscle weakness. Correcting metabolic acidosis is associated with improving these negative effects (2, 3,13).

Blood acid-base balance is maintained through the lungs, kidneys, and a system of buffers. The lungs regulate the partial pressure of carbon dioxide (PaCO_2 or P_{CO_2}). A normal P_{CO_2} is 35–45 mm Hg. The lungs also assist in the oxygenation of blood. Oxygen

in the arterial blood is present as PaO₂, dissolved oxygen and oxygen bound to hemoglobin. The lungs respond the quickest to acid-base imbalances through exhaling carbon dioxide, the acid component of the carbonic acid/bicarbonate buffer system (14).

The role of the renal system in acid-base balance is to maintain the concentration of bicarbonate (CO₂) in the blood at about 24 mEq/L with a normal range of 22-30 mEq/L for normal kidney function (14). The goal for CO₂ for those receiving hemodialysis is \geq 22 mEq/L (2). The kidneys maintain acid-base balance through reabsorption of filtered bicarbonate by the enzyme carbonic anhydrase in the proximal tubule. The kidneys also maintain acid-base balance through acid production (H⁺) and excretion of ammonium in the urine (14). To further review the role of the kidneys and lungs in maintaining acid-base balance, respiratory alkalosis, respiratory acidosis, metabolic alkalosis, and metabolic acidosis, is outlined in Table 2.

TABLE 2.
Acid-Base Diagnoses (14)

Diagnosis	Description
Respiratory alkalosis	<ul style="list-style-type: none"> Elevated pH > 7.45 Low P_{CO2} < 35 mm Hg
Respiratory acidosis	<ul style="list-style-type: none"> Low pH < 7.35 Elevated P_{CO2} > 45 mm Hg
Metabolic alkalosis	<ul style="list-style-type: none"> Elevated pH > 7.45 Elevated serum CO₂ of > 30 mEq/L
Metabolic acidosis	<ul style="list-style-type: none"> Low pH of < 7.35 Low serum CO₂ level of < 22 mEq/L

The kidney's role in acid-base balance

The kidney is the main organ of excretion of acid load and hydrogen ions (H^+) (2, 3). Sources of acid production include loss of bicarbonate from the lower intestine, breakdown of proteins from diet, and oxidation of carbohydrates and fats in muscle cells (13, 15). The kidney assists in regenerating bicarbonate used for buffering acids and is vital in acid-base balance. Hydrogen ion concentration in the body is 40 nEq/L and equals a pH of 7.398, and normal acid base status. The use of pH may be misleading for the diagnosis of acidemia since pH does not clearly correlate to H^+ concentration changes. A blood pH of 7.30 would equal a H^+ concentration of 50 nEq/L and a diagnosis of acidemia. A pH of 7.10 indicates severe acidemia, but the H^+ concentration equals 80 nEq/L and double the normal H^+ concentration (13). Although the use of blood pH is useful in determining acidosis, standard clinical practice in outpatient dialysis uses CO_2 as an estimate of serum bicarbonate since dialysis clinics often do not have access to blood gas measurement instruments (1). Blood gas instruments use the Henderson-Hasselbalch equation to calculate CO_2 . The Henderson-Hasselbalch equation measures the partial pressure of CO_2 (P_{CO_2}) (representing lung function) and bicarbonate (HCO_3^-) (representing kidney function):

$$[H^+] = 24 \times P_{CO_2} / [HCO_3^-] \quad (13)$$

The laboratory RenaLab used chemistry analyzers. Chemistry analyzers have blood gas instruments that convert HCO_3^- into CO_2 and measure the ("total" $CO_2 = 0.03 \times P_{CO_2}$) in samples. These levels are sometimes 1-2 mEq/L higher than true serum bicarbonate levels (13). Most of the CO_2 is in the form of HCO_3^- in the body. Therefore, the CO_2 blood test is a measure of blood bicarbonate level and the nonrespiratory or metabolic component of acid-base balance (16).

A review by Chui et al. agrees routine measurement of arterial pH is often not

feasible or common in clinical practice. A high-normal arterial pH is generally associated with a CO₂ level of 24–30 mEq/L when using the Henderson-Hasselbalch equation. The authors recommend this range as the therapeutic goal for chronic kidney disease patients with protein-energy wasting (17).

Impact of metabolic acidosis in ESRD

According to the National Kidney Foundation's Kidney Disease Outcome Quality Indicators (K/DOQI), CO₂ levels should be measured monthly and maintained ≥ 22 mEq/L. Levels < 22 mEq/L indicate metabolic acidosis (2). Metabolic acidosis in ESRD is the result of the kidney's inability to synthesize ammonia and excrete hydrogen ions (3). Concern arises due to the inability of the kidney to excrete the hydrogen ions. Negative nutrition outcomes including renal osteodystrophy, protein catabolism, decreased normalized protein catabolic rate (nPCR), decreased albumin synthesis, and protein energy wasting are observed with metabolic acidosis in maintenance hemodialysis (3, 4).

In a retrospective observational study in 2011 by Raphael et al., African Americans with higher and more normal CO₂ levels of 28-30 mEq/L were associated with a lower risk of mortality. Low CO₂ was an independent predictor of chronic kidney disease progression in this study (18). Soleymanian et al. found patients with metabolic acidosis to have a lower albumin even with adequate hemodialysis. An inverse effect of nPCR on albumin was found in acidotic patients. The authors believe metabolic acidosis leads to hypercatabolism and contributes to negative effects on nutritional status (19).

Mortality is linked to metabolic acidosis with higher CO₂ considered better for long-term patient outcomes (18). Wu et al. found the lowest unadjusted mortality to be associated with predialysis CO₂ below 17-23 mEq/L. Bicarbonate values > 23 mEq/L were associated with higher total and cardiovascular death rates. After adjusting for

patient characteristics and malnutrition-inflammation complex syndrome multivariate adjustment, patients with bicarbonate values > 22 mEq/L had lower death risk (20). The international observational Dialysis Outcomes and Practice Patterns Study (DOPPS) found CO_2 concentration to have no association between mortality at baseline or six-months (21).

A review by Gennari suggests attention should focus on patients with very low (< 18 mEq/L), and very high CO_2 levels (> 27 mEq/L). Gennari's review found the lowest mortality risk in patients with levels of 18-23 mEq/L. Ensuring correct alkali delivery during hemodialysis therapy, evaluating potential acid–base disorders, and assessing diet and fluid retention between treatments is recommended for patients with low bicarbonate levels (22).

Role of hemodialysis in correcting metabolic acidosis

Hemodialysis assists in correcting metabolic acidosis and compensates for the kidney in ESRD. Dialysate fluids with added sodium bicarbonate are infused during the hemodialysis treatment. The concentration of bicarbonate dialysate can range from 30-40 mmol/L for in-center hemodialysis (2, 23, 24). The mmol/L of bicarbonate dialysate prescribed is adjusted and based on a patient's CO_2 level. Oral pill supplementation is an option with the recommendation usually of 2-4 g/day or 25 to 50 mEq/day (2). Patients discussed in this study are all in-center hemodialysis patients who receive dialysate fluids with added bicarbonate during their dialysis treatment on average three days per week.

Positive and negative results in correcting metabolic acidosis

Studies indicate correcting acid-base imbalances have a positive effect on

preventing muscle wasting, low albumin, and decreased nutrition status. In acidosis, there is loss of protein from skeletal muscle. The protein loss results from accelerated breakdown of the myofibril proteins actin and myosin. The adenosine triphosphate (ATP)-dependent ubiquitin-proteasome system is increased and possibly responsible for accelerated proteolysis in metabolic acidosis (13, 25). A Cochrane review on the correction of metabolic acidosis found few randomized control trials demonstrate positive effects on nutrition when correcting metabolic acidosis in patients with kidney disease. Some studies in the Cochrane review demonstrated positive results while others did not (3).

Lin et al. attempted to distinguish between metabolic acidosis due to poor nutrition versus metabolic acidosis due to better nutrient intake causing greater hydrogen production. They found patients with metabolic acidosis had a higher protein intake, higher nPCR, and were associated with better nutritional parameters. The authors suggest metabolic acidosis was not found to be a negative risk factor due to reflecting a higher protein intake, which is the precursor of hydrogen production (26).

De Brito-Ashurst et al. found bicarbonate supplementation to slow the rate of progression of renal failure to ESRD and improve nutrition status in chronic kidney disease (CKD) patients (27). Blair and colleagues conducted an observational study and found increasing dialysate bicarbonate improved predialysis CO₂ levels, decreased protein catabolism as measured by nPCR, and enhanced phosphorus control, but found no positive change in albumin (28).

Ruggieria et al. conducted an intervention on eight hemodialysis patients. Patients were treated daily with oral sodium bicarbonate for 10–14 days. Despite improved acid-base balance of the patients, increasing patients to a more alkalotic state was not associated with a positive effect on albumin, muscle protein synthesis, or

nutritional and endocrinal parameters (29). Full benefits of the oral sodium bicarbonate could not have been seen in albumin due to albumin's long half-life of about 20 days. In contrast, a six month study by Verove et al. found significant increases in both albumin and prealbumin levels using oral sodium bicarbonate (30). Movilli et al. in 2009 found no adverse effects in high interdialytic weight gains, plasma sodium, or blood pressure using oral sodium bicarbonate supplementation to correct metabolic acidosis in hemodialysis patients. Correcting metabolic acidosis was effective in reducing protein catabolism as defined by nPCR in hemodialysis patients. Albumin was only improved in patients without inflammation (31). One contributing factor for the varied results between metabolic acidosis and albumin could be the long half-life of albumin.

Serum albumin as a nutrition indicator in ESRD

There is no single protein-energy nutrition indicator for ESRD patients. The International Society of Renal Nutrition and Metabolism recommends the use of the term protein-energy wasting for loss of body protein mass and energy stores in chronic kidney disease and ESRD. To diagnose protein-energy wasting, three characteristics are present. The first includes low serum levels of albumin, prealbumin, or cholesterol. All three biomarkers have been used in the CKD population as nutritional biomarkers. The second characteristic includes reduced body mass as low or reduced body or fat mass or weight loss with reduced intake of protein and energy. Reduced muscle mass with muscle wasting, sarcopenia, or reduced mid-arm muscle circumference is the third recommended characteristic to diagnose protein energy wasting (32). In the United States, albumin continues to primarily be used as the main nutrition indicator and outcome goal for ESRD (8).

Albumin is synthesized in the liver and has a long half-life of ~ 20 days (6, 33, 34).

It functions in maintaining osmotic pressure and transporting a variety of molecules throughout the body (7). Visceral protein pool size can be estimated by the measurement of circulating proteins in the blood, such as serum albumin (6, 34). Levels are influenced by exchanges between intra- and extracellular fluid compartments, lymphatic uptake, alterations in fluid status, protein degradation, body losses (i.e. proteinuria), inflammation, acid-base imbalance, the liver's production of albumin, and acute phase response (4, 6-8, 33, 34). Debate continues regarding use of serum albumin as a nutrition indicator since a low level does not always indicate protein-energy malnutrition (6, 33). Although albumin levels of < 4.0 g/dL are associated in ESRD with higher mortality rates, Friedman and Fadem suggest albumin should be used more as an index of the severity of illness versus nutrition status (7). Steinman suggests eliminating albumin totally as the nutrition indicator for ESRD (6).

CHAPTER 3

MATERIALS AND METHODS

Approval for the study was initially received from The University of Kansas Medical Center Human Subjects Committee. Renal Advantage, Incorporated (RAI) Medical Advisory Committee and RAI's Chief Legal Counsel determined final approval. A limited data set was created with the assistance of RAI by removing protected health information as required by the Health Insurance Portability and Accountability Act (HIPAA). Kirk Finchem, RAI Vice President of Clinical Operations, assisted in creating the limited data set. All data was kept in a password protected and locked computer in a secure location at all times.

Study design

This study was a retrospective observational study using a convenience sample of 144 patients being treated with hemodialysis at RAI in Westwood, Kansas. Greater than one year's data was collected to account for demonstrating the prior month's serum bicarbonate level has an impact on nutrition indicators. Laboratory and medical histories were collected from electronic medical records from December 2010 through January 2012. The electronic medical records were kept and backed up at RAI headquarters in Nashville, Tennessee. Patients were predominately on Medicaid and Medicare and of a lower socioeconomic status.

Inclusion and exclusion criteria

Subjects were included in data analysis regardless of comorbidities. Subjects were excluded for: 1) being on hemodialysis at RAI as defined as less than three months; 2) receiving artificial intravenous nutrition containing amino acids, such as total

parenteral nutrition (TPN) or intradialytic parenteral nutrition (IDPN).

Serum chemistry methods

Certified Hemodialysis Technicians or Registered Nurses collected arterial blood samples at the beginning of each week on a Monday or a Tuesday based on a patient's dialysis schedule. The blood tests listed below were collected monthly at the dialysis center according to the doctor's orders (35). Blood samples were collected through the patients' dialysis accesses (e.g. AV fistula, graft, or catheter). If a sample was hemolyzed, the clinic was notified and the samples were recollected. RenaLab, RAI's laboratory located in Richland, Mississippi, analyzed the blood samples. RenaLab is no longer in business as of summer 2012 due Renal Advantage Inc. being purchased by another dialysis company. Details regarding laboratory assays and instruments are limited to what was available in the policies and procedures outlined below.

Blood samples were air shipped overnight to RenaLab, Inc. for processing. Cold packs were first placed in the bottom of a RenaLab Transport Box on top of an absorbent blue pad. Samples were placed in holes of a foam insert in the shipping box. They were then packed in sealed plastic bags to prevent any broken or punctured tubes leaking into the box. Cold packs were placed on top to maintain preservation. A Styrofoam lid was placed on top of the contents. An itemized list of contents was placed between the Styrofoam lid and the outer box. The box was sealed with packing tape, labeled with a packing slip, and sent to RenaLab. Samples resulted in the patient electronic medical record after two days from shipment to RenaLab due to travel time (36).

Patients' body temperatures were recorded to assist in tracking potential illness or infection. Post dialysis weight (kg) was used to estimate dry weight after each

hemodialysis treatment. The dry weights recorded in the limited data set were from the same days as monthly lab days. Height (cm) was updated at least annually (37, 38). The dry weights and heights were used to calculate BMI as kg/m^2 on the same day as monthly lab day.

Subjective nutrition assessment data was collected from the comprehensive patient assessments with the classifications of “well nourished”, “mild malnutrition”, “moderate malnutrition”, and “severe malnutrition” (Appendix A). The nutrition status classification is based on criteria adopted from the Center for Disease Control’s ICD-9 codes (39) and the Academy of Nutrition and Dietetics (AND) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommendations for malnutrition (40). Appendix B outlines the Nutrition Status Criteria table used in this study.

A total of four blood tubes were collected with monthly labs including one serum separator tube (SST), two lavender topped tubes, and one green topped tube. Patient monthly labs included the following:

1) Serum albumin: Serum albumin is an acute-phase protein with a goal of ≥ 4.0 g/dL in ESRD (8). The normal non-ESRD range for albumin is 3.5-5.2 g/dL (41). Albumin was analyzed by RenaLab using the bromocresol green assay (BCG). The BCG assay is a colorimetric method for the measurement of the serum albumin concentration and is shown to be the preferred method for hemodialysis patients (41). Bromocresol green dye binds with albumin at a specific pH. For example, a pH of 4.2 has a specific colored complex measured spectrophotometrically at 628 nm. It is directly proportional to the albumin concentration in the sample (42).

Arterial blood was collected in a serum separator tube (SST) tube and

allowed to clot for about 15 minutes (41). Each SST tube contained clot activator and gel for serum separation (43). The sample was centrifuged for 20 minutes at 3000 rotations per minute (rpm) (8, 41).

2) Serum bicarbonate: Serum bicarbonate (CO_2) levels are influenced by kidney and respiratory function. The goal for ESRD is ≥ 22 mEq/L CO_2 (2). The kidney is the primary organ responsible for maintaining normal bicarbonate levels. The procedure uses a blood gas instrument and the Henderson-Hasselbalch equation where the partial pressure of CO_2 (P_{CO_2}) represents lung function and bicarbonate (HCO_3^-) represents kidney function:

$$[\text{H}^+] = 24 \times P_{\text{CO}_2} / [\text{HCO}_3^-] \quad (13).$$

Because CO_2 content primarily reflects the concentration of bicarbonate, it is primarily a measure of the nonrespiratory or metabolic component of acid-base balance (16). Arterial blood was collected in an SST and allowed to clot for about 15 minutes (41). Each SST tube contained clot activator and gel for serum separation (43). The sample was then centrifuged for 20 minutes at 3000 rpm (41).

3) Serum calcium: Serum calcium is used to determine parathyroid function and calcium homeostasis. Hyperparathyroidism is the most common cause of elevated serum calcium values, which leads to bone disease in ESRD. Hypoalbuminemia is the most common cause of decreased calcium values since calcium is bound to serum albumin (41). Adjusted calcium was calculated when albumin levels are < 4.0 g/dL using the equation:

$[0.8 \times (4.0 - \text{Measured Serum Albumin g/dL}) + \text{Serum Calcium mg/dL}]$ (41, 44).

The desired goal for adjusted calcium range is $> 8.4 - < 10.2$ mg/dL in ESRD. Measurement is performed using a colorimetric assay. Arterial blood was collected in an SST and allowed to clot for about 15 minutes (41). Each SST tube contained clot activator and gel for serum separation (43). The sample was then centrifuged for 20 minutes at 3000 rpm (41).

4) Serum creatinine: Serum creatinine is a product in the breakdown of muscle creatine phosphate from energy exertion. It is produced at a constant rate based on muscle mass and is excreted from the body by the kidneys (41). Patients with little or no renal function receiving dialysis will have predialysis serum creatinine levels proportional to dietary protein intake and skeletal muscle mass:

Predialysis Serum Creatinine = $[(\text{Intake of Foods Rich in Creatine and Creatinine} + \text{Endogenous Creatinine Production}) - (\text{Urine Output} + \text{Removal During Hemodialysis} + \text{Degradation of Creatinine})]$ (45)

Normal kidney function creatinine range is 0.7-1.3 mg/dL for males and 0.5-0.9 mg/dL for females (41). Creatinine levels above these ranges indicate impairment of kidney function, but a level < 10 mg/dL can be a sign of protein energy malnutrition, inadequate intake, and muscle wasting (45). Measurement was performed using a kinetic colorimetric Jaffe assay (41, 46). Creatinine reacts with alkaline picrate forming a red color in the Jaffe assay. The intensity of the color is measured spectrophotometrically. Sodium lauryl sulphate is added to prevent protein influence. Acidifying the sample with 30% acetic acid prevents influence from non-specific chromogens in the samples. A second absorbance

reading is taken. To determine creatinine results, the second absorbance values are subtracted from the first set of values. Corrected absorbance values are then plotted on a calibration graph. The measurable range with this graph is from 0.2 to 8.0 mg/dL. Plotting the corrected absorbance of the test provides the values of creatinine (47).

Arterial blood was collected in an SST and allowed to clot for about 15 minutes (41). Each SST tube contained clot activator and gel for serum separation (43). The sample was then centrifuged for 20 minutes at 3000 rpm (41).

5) Hemoglobin: Hemoglobin is a protein used to determine the oxygen-carrying capacity of blood, to assess ESRD related anemia, and to assess patient response to erythropoietin therapy. The kidney produces the hormone erythropoietin, which signals red blood cell production. Patients with ESRD do not produce a sufficient amount of erythropoietin to make red blood cells, resulting in erythropoietin-deficient anemia (48). The goal range for hemoglobin is 9-11 g/dL per RAI protocol (49). Measurement was performed using a colorimetric assay. Arterial blood was collected in the first lavender-topped tube and immediately mixed by gentle inversion to allow the anticoagulant to combine with the blood and prevent clotting (41). Each lavender top tube contained the spray dried additive potassium (K_2) ethylene diamine tetraacetic acid (K_2 EDTA) to assist in clotting (50).

6) Intact parathyroid hormone: Intact parathyroid hormone (PTH) is produced by the parathyroid gland. Disorders of the parathyroid glands can lead to

hypercalcemia or hypocalcemia due to a change in PTH secretion (51). Patients with CKD frequently develop secondary hyperplasia of the parathyroid glands causing high blood levels of PTH. The abnormality develops due to hypocalcemia common in the course of kidney disease. A deficiency of 1,25-dihydroxycholecalciferol [$1,25(\text{OH})_2\text{D}_3$] (active vitamin D) also affects the function of the parathyroid glands. A decrease in vitamin D receptors and calcium-sensing receptors in the parathyroid gland occurs resulting in resistance to the action of vitamin D and calcium (52).

Measurement of PTH was performed using an electrochemiluminescent immunoassay. Intact parathyroid hormone was collected monthly after Zemplar® vitamin D analogue medication adjustments or if PTH levels were considered unstable. An unstable PTH was defined as < 150 or > 300 pg/dL per RAI protocol (49). If PTH was stable after two months, it was tested quarterly. Arterial blood was collected in the second lavender-topped tube and immediately mixed by gentle inversion to allow the anticoagulant to combine with the blood and prevent clotting (51). Each lavender top tube contained the spray dried additive potassium (K_2) ethylene diamine tetraacetic acid (K_2EDTA) to assist in clotting (50).

7) Serum phosphorus: There is an inverse relationship between serum phosphorus and serum calcium levels. Excess serum phosphorus levels cause the kidneys to excrete serum calcium. Excess serum calcium levels cause the kidneys to excrete serum phosphorus. The ESRD goal range for serum phosphorus is 3.5-5.5 mg/dL per RAI protocol (49). Measurement was performed using a colorimetric assay. Arterial blood was collected in an SST and allowed to

clot for about 15 minutes (51). Each SST tube contained clot activator and gel for serum separation (43). The sample was then centrifuged for 20 minutes at 3000 rpm (51).

8) Serum potassium: Serum potassium is the primary electrolyte of intracellular fluid. The goal range for potassium is 3.5-5.5 mEq/L per RAI protocol (49). Measurement was performed using an ion selective electrode for potassium. Arterial blood was collected in an SST and allowed to clot for about 15 minutes (51). Each SST tube contained clot activator and gel for serum separation (43). The sample was then centrifuged for 20 minutes at 3000 rpm (51).

9) Kt/V, pre-blood urea nitrogen, and post-blood urea nitrogen: Hemodialysis adequacy, defined by Kt/V, is taken at least monthly using pre-treatment blood urea nitrogen (pre-BUN) and post-treatment BUN (mg/dL) (post-BUN). The letter *K* represents clearance of urea, *t* represents hemodialysis time, and *V* represents volume of distribution of urea (53). Blood urea nitrogen is used to evaluate kidney function. Urea is formed in the liver in the urea cycle and represents the final products of protein and amino acid metabolism. Urea is carried to the kidneys to be excreted in the urine (41). A normal BUN is 7-20 mg/dL (54). Protein catabolism and impairment of kidney function results in a high BUN above 20 mg/dL (41). The Daugirdas II logarithmic kinetics Kt/V method is the tool used for measuring and assessing the effectiveness of hemodialysis (41, 55):

$$Kt/V = -\ln(\text{Post BUN}/\text{Pre BUN} - 0.008 \cdot t) + (4 - 3.5 \cdot \text{Post-BUN}/\text{Pre-BUN}) \cdot \text{Ultrafiltrate Volume/Weight (56)}$$

Pre-BUN samples were collected arterially in an SST and allowed to clot for

about 15 minutes. The sample was then centrifuged for 20 minutes at 3000 rpm. Post-BUN samples were collected arterially in a green-topped tube. Green topped tubes are mixed by gentle inversion to allow the anticoagulant to combine with blood and prevent clotting. Green topped tubes required no centrifuging (41). Each green topped tube contained spray dried lithium heparin to prevent clotting (57). If Kt/V levels were less than the goal of 1.4, hemodialysis prescriptions were adjusted to achieve the goal of ≥ 1.4 .

10) Normalized protein catabolic rate: Normalized protein catabolic rate (nPCR) is calculated with each Kt/V as an estimate of protein intake by g/kg/day. The ideal nPCR range is ≥ 1.2 , indicating an intake of about 1.2 g/kg/day of protein (53). There are limitations to nPCR as an estimate of protein intake. First, nPCR approximates protein intake only when the patient is in nitrogen equilibrium (steady-state). In a catabolic patient, nPCR will appear higher than protein intake from degradation and metabolism of protein pools to form urea. Second, a single measurement may not reflect usual protein intake. When protein intake is high, nPCR underestimates protein intake where nitrogen balance is positive. Normalized protein catabolic rate may overestimate protein when the protein intake is less than 1 g/kg/day, possibly due to protein catabolism (58).

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences 20 (SPSS 20). Outliers in the limited data set for all variables were removed. An outlier was defined as a not feasibly possible value or lies outside the possible range of values for any given variable. The program SPSS automatically removed variables through pairwise deletion

for cases with missing values. Laboratory and anthropometric data analyzed included serum albumin, serum CO₂, serum phosphorus, hemoglobin, adjusted serum calcium, serum potassium, PTH, Kt/V, pre- BUN, post-BUN, serum creatinine, nPCR, temperature during hemodialysis, weight, height, and BMI. Patient characteristics collected included gender, age, cause of renal failure, BMI class, months on hemodialysis, and subjective nutrition status. The variable of race/ethnic group was originally requested, however was excluded from analysis.

To control for differences among individuals, within-subject correlations were used to analyze individual variables and the mixed model ANCOVA variables. For example, to determine if a decrease in albumin within an individual was associated with a decrease in CO₂, the differences between subjects were removed and only changes within the individual was calculated (59). The following calculation was used to find within-subjects correlation:

$$\sqrt{(\text{Sum of Squares for Variable of Interest})/(\text{Sum of Squares for Variable of Interest} + \text{Sum of Squares Residual})} \text{ (59)}$$

P-values of ≤ 0.05 were considered to be statistically significant for all within-subjects correlations.

Pearson correlations were calculated to ensure reliability of the within-subjects correlation for continuous variables across subjects. Spearman correlations were calculated to ensure reliability of the within-subjects correlation for categorical variables across subjects. Pearson and Spearman calculations also assisted in determining the directionality (positive or negative) of the correlation as the within-subject correlation losses the negative directionality when calculating with a square root. *P*-values of ≤ 0.05 and ≤ 0.01 were considered to be statistically significant depending on variable.

Chapter 4

RESULTS

Sample characteristics and descriptives

The sample included 144 in-center hemodialysis patients, 87 males and 57 females. Patient characteristics are presented in Table 3. The mean age was 56.75 ± 15.21 years with a majority of patients between the ages of 40 and 69 years (68.7%).

Cause of renal failure was subcategorized according to the Department of Health and Human Services and Center for Medicare and Medicaid Services Form-CMS-U3: List of Primary Causes of ESRD (60). The primary causes of ESRD categories are listed in Table 3. The top two causes of ESRD were 28.5% caused by diabetes and 35.4% caused by hypertension/large vessel disease.

The mean BMI was 28.11 ± 6.65 kg/m². The majority of patients had a desirable weight (39.6%). Subcategories were based on the BMI criteria of the National Heart Lung and Blood Institute and National Institutes of Health (61) (Table 3).

Patients were excluded if they were new to hemodialysis as defined by less than three months of receiving treatment. The mean months on hemodialysis were 51.78 ± 45.80 months with a minimum of three months and a max of more than 23 years (287.10 months) (Table 4).

Monthly laboratory values included albumin, bicarbonate, phosphorus, hemoglobin, adjusted calcium, potassium, PTH, Kt/V adequacy calculation derived from pre-BUN and post-BUN, creatinine, nPCR, and patient temperature during hemodialysis. Patient laboratory descriptives are shown in Table 4.

TABLE 3.
Patient Characteristics (n = 144)^{1, 2}

	Number	Percent (100%) ³
Gender		
Male	87	60
Female	57	40
Age (Years)		
20-29	8	5.6
30-39	9	6.3
40-49	30	20.8
50-59	39	27.1
60-69	30	20.8
70-79	17	11.8
80-89	10	6.9
90-100	1	0.7
Cause of Renal Failure ⁴		
Diabetes	41	28.5
HTN/Large Vessel Disease	51	35.4
Glomerulonephritis	14	9.7
Secondary Glomerulonephritis/Vasculitis	4	2.8
Interstitial Nephritis/Pyelonephritis	1	0.7
Cystic/Hereditary/Congenital Diseases	2	1.4
Neoplasms/Tumors	5	3.5
AIDS Nephropathy	2	1.4
Hepatorenal Syndrome	1	0.7
Complications of Transplant	3	2.1
Not specified/Other Diagnosis	20	13.9
BMI ⁵		
Underweight	6	4.2
Desirable Weight	57	39.6
Overweight	44	30.6
Obese Class I	20	13.9
Obese Class II	8	5.6
Obese Class III	8	5.6

¹ Does not always add to total sample size due to missing values

² Race/ethnic group not included due to more than 50% missing data from the database

³ Percents do not always add up to 100 due to rounding

⁴ Subcategories based on Form CMS-2728-U3: List of Primary Causes of ESRD

⁵ Subcategories based on National Heart Lung and Blood Institute and National Institutes of Health BMI criteria

TABLE 4.
Patient Laboratory Descriptives (n = 144)¹

Biomarker	Mean	Minimum	Maximum	Standard Deviation
Age (years)	56.75	21.10	90.50	15.21
BMI (kg/m²)	28.11	15.60	53.50	6.65
Months on Hemodialysis	51.78	3.00	287.10	45.80
Albumin (g/dL)	3.75	1.90	5.00	0.40
Bicarbonate (mEq/L)	23.95	12.00	35.00	3.24
Phosphorus (mg/dL)	5.48	1.50	13.00	1.68
Hemoglobin (g/L)	10.86	5.50	15.60	1.36
Adjusted Calcium (mg/dL)	9.05	5.80	13.20	0.81
Potassium (mEq/L)	4.63	2.50	8.10	0.73
Intact PTH (pg/dL)	489.09	2.00	2272.00	396.10
Kt/V	1.69	0.44	4.53	0.36
Pre-BUN (mg/dL)	60.40	14.00	139.00	19.87
Post-BUN (mg/dL)	17.55	2.00	80.00	9.71
Creatinine (mg/dL)	9.71	2.13	22.29	3.46
nPCR	0.89	0.17	2.29	0.32
Temperature During Hemodialysis (°F)	97.17	93.90	101.40	1.01

¹ Each variable does not always include total sample size due to missing values.

Nutrition Assessment

Dietary intake was not collected for this project due to time constraints. Nutrition status was determined at least annually on stable patients by a Registered Dietitian. Medically unstable patients were assessed more often until deemed stable. The Comprehensive Patient Nutrition Assessment included appetite, typical meal pattern, anthropometrics, and laboratory results (Appendix A) (62). Each Comprehensive Patient Nutrition Assessment provided a designation of whether a patient was “well-nourished”, or had a “mild”, “moderate”, or “severe malnutrition” status. Criteria for nutrition status were based on findings from the Comprehensive Patient Nutrition Assessment and Nutrition Status Criteria outlined in Appendix B. Table 5 shows the nutrition status of those patients who had nutrition assessments during the study time. The chi-squared test is used to test hypotheses relating to group differences in proportions (63). When evaluating the difference between the nutrition status designations, the groups were not statistically the same as designated by a Chi-squared of 50.44 ($p = 1.11325E-11$).

TABLE 5.
Patient Nutrition Status from Comprehensive Patient Assessment (n = 104) ¹

Nutrition Status ²	Number	Percent
Well Nourished	63	61
Mild Malnutrition	37	35
Moderate Malnutrition	4	4
Severe Malnutrition	0	0

¹ Does not add up to total population due to patients who were not up for their annual review or those who had expired, transplanted, or transferred before their annual review

² Based on Appendix A and Appendix B criteria

Correlation of patient variables

Pearson correlations designate the relationship or magnitude between two continuous variables measured on an interval scale. For example, the variable albumin is a continuous variable that was measured using Pearson correlation. Spearman correlations indicate the relationship or magnitude between two variables measured on an ordinal or categorical scale. The variable nutrition status is a categorical variable and was measured using Spearman correlation (63). Pearson and Spearman correlations determine relationships between subjects in the sample.

The correlation between albumin and each of the patient variables are shown in Table 6. Notable within-subject positive correlations significant ($p \leq 0.05$) with albumin were biomarkers known to trend with nutrition and inflammation in this patient population including hemoglobin, pre-BUN, creatinine, and nPCR. Pearson or Spearman correlations significant with albumin were the nutrition status and biomarkers known to trend with nutrition and inflammation including hemoglobin and creatinine. Nutrition status had a strong Spearman correlation with albumin in the same month and even strengthened with the prior month's nutrition status. This portrays the concept that due to albumin's long half-life, a stronger correlation will be seen in the current albumin with the health and nutrition status of the patient about 20 days ago. All variables were significant at $p \leq 0.01$ except for temperature, which was significant at $p \leq 0.05$.

The correlation between bicarbonate and each of the patient variables are shown in Table 7. Notable within-subject correlations significant with bicarbonate ($p \leq 0.05$) were mineral-bone related biomarkers including phosphorus and adjusted calcium. Bicarbonate correlated with nutrition biomarkers including hemoglobin, pre-BUN, post-BUN, creatinine, and nPCR. The Pearson or Spearman correlations assisted in assigning directionality to the within-subjects correlation. For example, phosphorus and the nutrition biomarkers BUN and nPCR negatively correlated with bicarbonate. A higher CO_2 therefore indicated a lower phosphorus, BUN, and nPCR. All variables were significant at $p \leq 0.01$ except for BMI, which was significant at $p \leq 0.05$. The correlation between the prior month's bicarbonate and the individual patient variables are shown in Table 8. Within-subject correlations, Pearson, and Spearman correlations did not improve with the prior month's bicarbonate and the individual patient variables in Table 8.

TABLE 6.
Correlation of Patient Variables with Albumin (n = 144) ¹

Patient Variable	Within-Subjects Correlation	P	Pearson or Spearman Correlation ³	P
Age (years)	0.009	0.000 ²	-0.076	0.004 ⁴
BMI (kg/m^2)	0.028	0.314	-0.029	0.272
Months on Hemodialysis	0.009	0.756	-0.066	0.013 ⁴
Nutrition Status	0.098	0.618	-0.566	0.000 ⁴
Nutrition Status Prior Month	0.240	0.212	-0.631	0.000 ⁴
Bicarbonate Same Month (mEq/L)	0.079	0.005 ²	0.024	0.376
Bicarbonate Prior Month (mEq/L)	0.042	0.140	0.083	0.002 ⁴
Phosphorus (mg/L)	0.099	0.000 ²	0.176	0.000 ⁴
Hemoglobin (g/L)	0.287	0.000 ²	0.247	0.000 ⁴
Adjusted Calcium (mg/dL)	0.004	0.886	0.005	0.867
Potassium (mEq/L)	0.108	0.000 ²	0.131	0.000 ⁴
Intact PTH (pg/dL)	0.109	0.001 ²	0.134	0.000 ⁴
Kt/V	0.099	0.001 ²	0.207	0.000 ⁴
Pre-BUN (mg/dL)	0.125	0.000 ²	0.088	0.001 ⁴
Post-BUN (mg/dL)	0.099	0.001 ²	0.051	0.078
Creatinine (mg/dL)	0.097	0.001 ²	0.224	0.000 ⁴
nPCR	0.121	0.000 ²	0.119	0.000 ⁴
Temperature During Treatment (°F)	0.493	0.086	-0.063	0.020 ²

¹ Each variable does not always include total sample size due to missing values

² Correlation is significant at the 0.05 level

³ Pearson values correlate continuous variables and Spearman values correlate categorical variables

⁴ Correlation is significant at the 0.01 level

TABLE 7.
Correlation of Bicarbonate with Patient Variables (n = 144) ¹

Patient Variable	Within-Subjects Correlation	P	Pearson or Spearman Correlation ³	P
Age (years)	0.064	0.022 ²	0.004	0.890
BMI (kg/m ²)	0.018	0.520	0.053	0.046 ²
Months on Hemodialysis	0.064	0.023 ²	0.117	0.000 ⁴
Nutrition Status	0.293	0.138	-0.042	0.643
Phosphorus (mg/L)	0.260	0.000 ²	-0.268	0.000 ⁴
Hemoglobin (g/L)	0.112	0.000 ²	-0.038	0.160
Adjusted Calcium (mg/dL)	0.212	0.000 ²	0.194	0.000 ⁴
Potassium (mEq/L)	0.310	0.000 ²	-0.230	0.000 ⁴
Intact PTH (pg/dL)	0.087	0.009 ²	-0.117	0.000 ⁴
Kt/V	0.022	0.465	0.040	0.162
Pre-BUN (mg/dL)	0.400	0.000 ²	-0.327	0.000 ⁴
Post-BUN (mg/dL)	0.215	0.000 ²	-0.169	0.000 ⁴
Creatinine (mg/dL)	0.266	0.000 ²	-0.037	0.166
nPCR	0.140	0.000 ²	-0.175	0.000 ⁴
Temperature During Treatment (°F)	0.013	0.641	0.017	0.533

¹ Each variable does not always include total sample size due to missing values.

² Correlation is significant at the 0.05 level

³ Pearson values correlate continuous variables and Spearman values correlate categorical variables

⁴ Correlation is significant at the 0.01 level

TABLE 8.
Correlation of Prior Month Bicarbonate with Patient Variables (n = 144) ¹

Patient Variable	Within-Subjects Correlation	P	Pearson or Spearman Correlation ³	P
Age (years)	0.052	0.063	0.007	0.799
BMI (kg/m ²)	0.037	0.194	0.075	0.005 ⁴
Months on Hemodialysis	0.052	0.066	0.115	0.000 ⁴
Nutrition Status	0.021	0.922	0.059	0.508
Phosphorus (mg/L)	0.057	0.045 ²	-0.160	0.000 ⁴
Hemoglobin (g/L)	0.007	0.800	0.044	0.103
Adjusted Calcium (mg/dL)	0.026	0.364	0.081	0.003 ⁴
Potassium (mEq/L)	0.050	0.080	-0.066	0.014 ²
Intact PTH (pg/dL)	0.063	0.063	-0.092	0.004 ⁴
Kt/V	0.010	0.744	0.023	0.417
Pre-BUN (mg/dL)	0.025	0.375	-0.129	0.000 ⁴
Post-BUN (mg/dL)	0.106	0.000 ²	-0.104	0.000 ⁴
Creatinine (mg/dL)	0.012	0.633	0.052	0.056
nPCR	0.145	0.000 ²	-0.158	0.000 ⁴
Temperature During Treatment (°F)	0.046	0.113	-0.010	0.704

¹ Each variable does not always include total sample size due to missing values.

² Correlation is significant at the 0.05 level

³ Pearson values correlate continuous variables and Spearman values correlate categorical variables

⁴ Correlation is significant at 0.01 level

Mixed model ANCOVA

Analysis of covariance is a statistical procedure used to test mean differences among groups on a dependent variable, while controlling for or including one or more covariates (variables) (63). Table 9 shows a mixed model of including additional nutrition indicators with the albumin and bicarbonate analysis. Albumin significantly correlated with bicarbonate within-subjects in the same month when calculated alone in Table 6. Albumin was not significant with bicarbonate within-subjects from the prior month when calculated alone in Table 6. When including additional specific nutrition and inflammation related indicators, the within-subject correlation strengthened and was significant for the prior month's bicarbonate impact on albumin. Albumin and the same month's bicarbonate became not significant and had a lower correlation when adding covariates compared to Table 6.

TABLE 9.
Mixed Model ANCOVA (n = 144) ¹

Patient Variable	Albumin and CO₂ from the Same Month ²	P ³	Albumin from Current Month and CO₂ from Prior Month ²	P ³
Hemoglobin (g/L)	0.284	0.000	0.292	0.000
Creatinine (mg/dL)	0.142	0.000	0.151	0.000
nPCR	0.068	0.031	0.085	0.008
Bicarbonate (mEq/L)	0.026	0.412	0.093	0.004

¹ Each variable does not always include total sample size due to missing values.

² Within-subjects correlations

³ Correlation is significant at the ≤ 0.05 level

Chapter 5

DISCUSSION

Serum CO₂ is the primary hemodialysis outpatient biomarker used to determine acid-base status of this patient population. Low serum bicarbonate is shown to negatively impact nutrition status and biomarkers such as albumin. Albumin is known to have a long half-life of ~20 days and not always indicate the current nutrition status of a patient. As an individual indicator, albumin did not correlate significantly with the prior month's bicarbonate within-subjects ($r = 0.042$, $p = 0.140$), but did in the same month ($r = 0.079$, $p = 0.005$). When including additional nutrition indicators as outlined in the ANCOVA model, albumin did significantly correlate with bicarbonate from the prior month ($r = 0.093$, $p = 0.004$). Because there is no one biomarker indicating overall nutrition status in hemodialysis patients, it is important for clinicians to consider multiple biomarkers versus only albumin as the main nutrition indicator in ESRD.

This study's results support the potential reason some studies find significance for metabolic acidosis on nutrition biomarkers such as albumin while other research does not. Results appear to be the first to take both current and prior month's serum CO₂ and correlate them to nutrition biomarkers in hemodialysis patients. A patient's prior month's CO₂ was used to see if it correlated better with the biomarker albumin which is known to have a long half-life. A further advantage of this study was the use of both within-subjects and Pearson or Spearman correlations. Studies often appear to only use Pearson correlation to look at the relationship of CO₂ and biomarkers between subjects (9, 19, 28) and not at trends within the individual.

Intervention studies have attempted to answer the question whether increasing serum CO₂ improves protein synthesis and albumin. Ruggieri et al. found raising blood pH of dialysis patients was not associated with a positive effect on albumin and muscle

protein synthesis, or nutritional and endocrinal parameters (29). Bossola et al. found no significant effect of bicarbonate treatment on albumin, dry weight, total cholesterol, or C-reactive protein (64). Movilli et al. in 1998 demonstrated the correction of metabolic acidosis improved serum albumin concentrations in hemodialysis patients from 3.49 ± 2.1 g/dL to 3.79 ± 2.9 g/dL ($p < 0.01$) (65). Movilli and colleagues in 2009 found correcting metabolic acidosis in hemodialysis patients increased albumin only in patients without inflammation (C-reactive protein < 10 mg/L) from 3.7 ± 0.3 g/dL to 4.0 ± 0.3 g/dL ($p < 0.01$). In inflamed patients, the correction of low CO₂ did not improve albumin (3.5 ± 0.17 g/dL vs. 3.4 ± 0.13 g/dL; $p = \text{NS}$) (31). This current study suggests when looking within individual patient trends (within-subjects correlation), a higher albumin significantly correlated with a higher CO₂ collected in the same month ($r = 0.079$, $p = 0.005$). Albumin did not significantly correlate as hypothesized with CO₂ collected from the prior month within-subjects. However, the correlation was significant between subjects (Pearson correlation) for albumin and prior month's CO₂.

Normalized protein catabolic rate is used as a biomarker for trending estimated protein intake as defined by grams of protein consumed per kilogram body weight (53). This study showed a significant trend in a lower nPCR with a higher CO₂. Blair et al. found similar results in nPCR after increasing bicarbonate dialysate from 35 to 39 mmol/L for six months. The nPCR decreased significantly compared to baseline (0.99 ± 0.26 vs. 0.93 ± 0.23 , $p = 0.001$) (28). Results from Movilli et al. in 2009 were consistent with this study, but they supplemented ESRD patients with oral sodium bicarbonate. The nPCR decreased significantly (1.13 ± 0.14 g/kg/day to 1.05 ± 0.14 g/kg/day, $p < 0.0001$) (31). Lin et al. evaluated acidotic hemodialysis patients and the effect on nutritional status of increasing the bicarbonate dialysate from 35 to 38 mmol/L for one month and then to 38–40 mmol/L for five months. The nPCR was lower with those patients who had

a higher CO₂ ($p < 0.001$). Lin et al. states, it appears a higher rate of endogenous protein production, and therefore nPCR, from protein oxidation contributes to the lower predialysis CO₂ (26).

Subjective Global Assessment (SGA) scores were not calculated for patients at RAI to determine nutrition status. Scores for SGA are based on a medical history and physical examination using a four-item, seven-point scale by Baker and colleagues. A higher score indicates better nutrition (66). Nutrition status for RAI patients are based on findings from the Comprehensive Patient Nutrition Assessment and malnutrition diagnosis criteria outlined in Appendix B. Albumin and nutrition status designation negatively trended between subjects' results and had an even stronger correlation with the prior month's nutrition status. A strong negative correlation was found because "well-nourished" = 1, "mild" = 2, "moderate" = 3, and "severe malnutrition" = 4 on the patient nutrition assessment, indicating a higher albumin did trend with a better nutrition status of "1". Nutrition status did not correlate with the same month's CO₂ or the prior month's CO₂ in this study. Szeto et al. in 2003 found overall improved SGA score when correcting CO₂ in the treatment group compared the placebo group at 24 weeks (5.07 points \pm 0.94 vs. 4.40 points \pm 1.00, $p = 0.015$). This study's results are more consistent with Bossola et al. Bossolo and colleagues which showed no improved SGA after 12 months (4.53 points \pm 0.37 at baseline and 4.58 points \pm 0.54 ($p = 0.1$)).

Analysis of covariance includes additional variables in the correlation, which could have an impact on the dependent variable. Additional nutrition related covariates such as hemoglobin, creatinine, nPCR, were analyzed with albumin and CO₂ in a mixed model ANCOVA. Other variables were attempted in the mixed model including impact of age, gender, Pre-BUN, and nutrition status, however they were not significant (not shown). ANCOVA correlations were higher and all significant for the prior month's CO₂

and albumin compared to the same month's CO₂ and albumin. ANCOVA correlations were also all higher and significant compared to when albumin was analyzed alone with CO₂. Including multiple nutrition or inflammatory variables versus only albumin improved the correlations with single variables in Table 6. Kovesdy et al. conducted a similar analysis combining three biomarkers albumin, percent lymphocytes, and white blood cells and their correlation on all-cause mortality in CKD patients. Lower serum albumin and percent lymphocytes and a higher WBC count, alone or in combination, were independently associated with increased all-cause mortality (67).

The within-subjects correlations provided positive correlations and significance. The Pearson correlations assisted in detecting the lost negative correlation in the within-subjects correlation. Phosphorus, potassium, and pre-BUN were negatively correlated with CO₂. Results indicate a higher CO₂ trends with lower or more normal phosphorus, potassium, and pre-BUN, which are consistent with findings by Wu et al. (20). The variables did not trend as high when analyzed with the prior month's CO₂. Phosphorus, potassium, and pre-BUN had lower correlations with the prior month's CO₂ and not all variables were significant. The correlation of bone related labs, such as phosphorus, with bicarbonate is consistent with the literature as metabolic acidosis worsens bone disease (15, 68). Due to the buffer function of bone, calcium and phosphate release from bone into blood stream (68). Potassium was inversely associated with bicarbonate. A higher CO₂ was associated with lower potassium in this study. A higher CO₂ was associated with a lower pre-BUN in this study. Pre-BUN was lowered by Ruggieri and colleagues after correcting metabolic acidosis (29). Correction of acidosis can reduce muscle protein degradation and reduce urea generation rates (23). Williams et al. found a slight initial lowered BUN after one month of administering a high 40 mmol/L bicarbonate bath. However they did not find continued lowered urea after 12 months (23).

Limitations

Using serum CO₂ to determine metabolic acidosis has the potential for inaccuracy if sample tubes are underfilled. Underfilled samples influence the dissipation of CO₂ and may result in falsely low measurements (13). Renal Advantage Inc. employees who collect blood samples are educated on the correct method for collection and handling upon hire. The blood samples were not analyzed at a close location to the dialysis unit and were processed in Richmond, Mississippi by RenaLab. The mean total CO₂ content of shipped blood samples can be up to ~5 mEq/L lower than samples processed immediately. Changes in atmospheric pressure in pressurized airliner cabins or in the cargo hold lead to the escape of CO₂ from the tube. If the sample is stored at room temperature or refrigerated for 24 hours, without air transport, the change in total CO₂ is only ~1 mEq/L (2, 13).

Certain labs are only collected on a monthly basis, such as CO₂ and albumin. One monthly result does not fully determine health trends throughout the rest of the month on patients. A nutrition assessment was conducted for most patients one time per year, which does not reflect the nutrition status of the patient throughout the rest of the year. Race/ethnic group was excluded due a significant amount of missing demographics. This was due to the newness of the electronic medical record system for the time the limited data set was collected.

This study was limited by its observational design and establishes associations. The sample was from a single clinic and therefore may not generalize to the entire ESRD population. It would be beneficial for future researchers to both provide intervention of correcting metabolic acidosis and assess the impact the prior month's bicarbonate on nutrition biomarkers and nutrition status.

Implications

In the current study, the prior month's CO₂ as a single variable did not significantly correlate with albumin. When including additional continuous variable nutrition biomarkers with the prior month's CO₂, the selected biomarkers significantly correlated with albumin within-subjects ($r = 0.093$, $p = 0.004$). The results suggest the possibility of using a combination of biomarkers (covariates) to indicate changes in nutrition, which can be used in future interventions. Albumin is useful in trending nutrition, however should be used in combination as illustrated with other biomarkers to assess overall nutrition status in ESRD.

Conclusion

Low serum bicarbonate, indicating metabolic acidosis, influences nutritional assessment indices in hemodialysis patients. Prior month's serum bicarbonate (~ 20 days ago) impacts current albumin slightly more than current serum bicarbonate in a mixed-model ANCOVA within-subjects. Conducting this project provided further insight into the importance of preventing metabolic acidosis to improve nutrition biomarkers as well as portraying one more limitation of albumin as the main nutrition indicator in hemodialysis.

Chapter 6

SUMMARY

The purpose of this thesis was to: (1) determine whether serum CO₂ influences nutrition assessment indices in hemodialysis patients; and (2) demonstrate the prior month's CO₂ level has a greater impact on current serum albumin versus the current month's serum bicarbonate in hemodialysis patients. The sample consisted of adult in-center hemodialysis patients at RAI in Westwood, KS.

A limited data set with 144 patients was created by RAI. Laboratory and medical histories were collected for about one year. Data was collected from electronic medical records from December 2010 through January 2012.

Within-subject correlations and analysis of covariance (ANCOVA) were used to analyze individual variables and a mixed-model to determine correlations within individuals. Pearson and Spearman correlations were calculated to ensure reliability of the within-subjects correlations for variables across subjects. Pearson and Spearman correlations assisted in determining the directionality (positive or negative) of the correlation as within-subject correlations lose negative directionality when calculating with a square root.

A correlation was found between the single variables albumin and CO₂ collected in the same month ($p = 0.005$) however not the prior month's CO₂ when looking at the individual (within-subjects) ($p = 0.140$). A significant Pearson correlation was found with albumin and the prior month's CO₂ when looking at the group as a whole ($p = 0.002$). The correlations for albumin and the prior month's CO₂ improved within-subjects when including additional nutritional and inflammation biomarkers in a mixed model ANCOVA. This suggests including additional covariates provide a better indication of overall nutrition status in hemodialysis patients versus only albumin when evaluating the impact

of metabolic acidosis. A mixed model ANCOVA demonstrates the prior month's serum CO₂ level has a greater impact on current serum albumin versus the current month's serum CO₂ in hemodialysis patients ($p = 0.004$ vs. $p = 0.41$).

Therefore, the prior month's CO₂ significantly correlated to albumin within-subjects when including covariates. Results suggest the importance of considering additional biomarkers to indicate overall nutrition status in hemodialysis patients. Further intervention-based studies are needed to confirm these results.

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APPENDICES

APPENDIX A

Renal Advantage Incorporated Comprehensive Patient Assessment:

Dietitian/Nutritional Assessment

Patient Name: _____

ID#: _____

RAI Care Center: _____

Comprehensive Patient Assessment

Reason for Assessment

Reason for Assessment

☐ Initial ☐ 90 day ☐ Annual (stable patients) ☐ Monthly (unstable patients)

If monthly, choose reason for unstable status. Choose all that apply.

- ☐ Hospitalization – frequent or extended stay
☐ Marked deterioration in health status
☐ Change in psychosocial needs
☐ Poor nutritional status and unmanaged anemia and inadequate dialysis

☐ Other:

Date:

Initials:

Dietitian/ Nutritional Assessment *Complete this section at the initial assessment.*

Subjective Data:

Appetite: ☐ improving ☐ decreasing ☐ no change
☐ good ☐ fair ☐ poor ☐ early satiety

Typical meal pattern:

morning:

noon:

evening:

Food allergies (see section on Allergies/Reactions)

Pica? ☐ Yes ☐ No Type : ☐ clay ☐ dirt ☐ starch ☐ ice ☐ chalk
☐ Paint ☐ Other:

Nutritional supplements

- ☐ Enteral nutritional supplements
☐ herbal supplements
☐ vitamins and/or minerals
☐ Other (explain):

Previous diets:

Nutrition Education: ☐ Yes ☐ No

Activity Level ☐ Inactive ☐ Moderately Active ☐ Active

Subjective Nutrition Reassessment: *Update subjective assessment (above) if patient reports appetite is poor or decreasing*

☐ No change from previous assessment ☐ Appetite is Poor ☐ Appetite is decreasing

Cultural Factors Related to Diet: *Complete at initial assessment*

Religious food preferences:

Cultural foods:

Party responsible for purchasing and preparing food: ☐ patient ☐ spouse ☐ other:

Reading ability:

Primary language for food prep: ☐ English ☐ Spanish ☐ Other:

Lives alone? ☐ Yes ☐ No

Has meals alone? ☐ Yes ☐ No

Frequency for dining out: number of meals eaten out/week:

Types of food usually ordered:

Does patient receive food assistance? ☐ Yes ☐ No

If yes, source:

Reassessment of Cultural Factors Related to Diet: *Complete above assessment if any change is noted in the parameters listed for any reassessment.*

☐ No change from previous assessment

Anthropometrics: *Complete for each assessment*

Height: <Dialysis Orders.Height> Estimated dry weight:: <Dialysis Orders.Target Weight>

BMI: Usual body weight: %UBW: IBW: %IBW:

Adjusted body weight:

☐ for obesity

☐ for amputees

Frame size: ☐ Small ☐ Medium ☐ Large

Recent weight change? ☐ Yes ☐ No

☐ Weight loss greater than 10% in 6 months

Comments:

Weight change history last 6 months:

% Change	Gain to < 5% loss	5-10% loss	> 10% loss

Nutrition-related medications:

☐ Vitamin supplement

- ☐ GI medications
- ☐ Stool softeners
- ☐ Non-Rx vitamin/minerals
- ☐ Nutritional supplements
- ☐ Other:

Objective Data: *Complete for each assessment*

Albumin: <Lab Results.Lab Result>

Potassium: <Lab Results.Lab Result>

Date	Protein (g/kg)	Calories	Sodium (mg)	Potassium (mg)	Fluid In(ml)	Phosphorus(mg)	Supplements	Comments

Diet Rx:

Evaluation of nutritional intake: calories ☐ adequate ☐ inadequate:

Protein ☐ adequate ☐ inadequate

Evaluation of nutritional status:

☐ Well-nourished ☐ Malnourished ☐ Mild ☐ Moderate ☐ Severe

Mineral Bone Disease: *Complete for each assessment*

Lab	Day1	Day2	Day3	Day4	Day5

Medications: ☐ phosphorus binder ☐ Yes ☐ No Type:

Adherence ☐ good ☐ fair ☐ poor

☐ calcium supplement

☐ vitamin D ☐ Oral ☐ IV ☐ Inactive ☐ Active

☐ calcimimetic

Diet issues: Adherence ☐ good ☐ fair ☐ poor

Education: Understands diet ☐ Yes ☐ No

Comments:

Diabetes Management: ☐ N/A *If applicable, complete at each assessment.*

Most current HgB A1C: <Lab Results.Lab Result>

Diet:

Diet controlled ☐ Yes ☐ No

If No: Diabetes medications: ☐ Oral Agents ☐ Insulin
(see medication list for details)

Blood Glucose Monitoring ☐ Yes ☐ No

If Yes: Monitoring Frequency: _____ times/day

Usual blood glucose range: Fasting

Usual blood glucose range: Non-Fasting

Recent or present infection, skin lesion/breakdown, inflammatory diagnosis
(including periodontal disease):

History of amputation:

Diabetes Education:

Comments:

Date:

Initials:

APPENDIX B:
Nutrition Status Criteria

Nutrition Status Criteria

	Malnutrition of Mild Degree	Malnutrition of Moderate Degree	Unspecified Severe Protein Calorie Malnutrition
Albumin	3-3.4 g/dL	≤2.9 g/dL	<2.5 g/dL
Edema	N/A	N/A	May be present
% IBW/UBW or BMI	≤95%	≤92%	≤90% And/or BMI <17
% Weight loss	3-5% in 1 month or 5.5-7.5% in 3 months or 8-10% in 6 months	>5% in 1 month or >7.5% in 3 months or >10% in 6 months	> 15%
Muscle Mass	N/A	N/A	Wasting
Poor PO	Yes	Yes	Possible
Criteria needed	2 of the above	2 of the above	All of the Above