CORRELATION BETWEEN ADEQUACY OF DIALYSIS AND OVERALL NUTRITION STATUS IN THE END STAGE RENAL DISEASE POPULATION

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I am submitting herewith a dissertation written by Eileen Baugh entitled "Correlation between Adequacy of Dialysis and overall Nutritional Status in the End Stage Renal Population." I have examined this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Nutrition.

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ABSTRACT

CORRELATION BETWEEN ADEQUACY OF DIALYSIS AND OVERALL NUTRITION STATUS IN THE END STAGE RENAL DISEASE PATIENT

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Malnutrition among dialysis patients in the United States has been correlated with increased morbidity and mortality rates. Multiple factors are known to contribute to this problem, although inadequate dialysis (defined by Kt/v levels) has been postulated to be a major factor. One-hundred eighteen subjects were randomized into two groups during a 12 month period from December 1993 to November 1994 to assess the impact of two different Kt/v levels (1.2 vs 1.5) on nutritional parameters (albumin, nPCR, pre-dialysis BUN, total cholesterol) and clinical outcomes (dry weight, number and length of hospitalizations). Dialysis adequacy was measured using urea kinetic modeling. The average dose of dialysis (Kt/v) delivered to both groups was higher than initially targeted, 1.3 ± 0.03 for the control group and 1.6 ± 0.02 for the experimental group. Lab work was completed monthly. Urea kinetic modeling calculations for Kt/v and nPCR were calculated monthly. One hundred eight patients completed the study. No correlation was found between Kt/v and nutritional parameters. A significant correlation

was observed between Kt/v levels and weight ($p < 0.0001$, $r = 0.92$). No association was observed between Kt/v levels and number of days spent in the hospital or number of hospital admissions. An increase number of days for black males vs non black males was observed but not considered statistically significant. While this study showed no significant correlation between experimental group vs control group on nutritional and clinical outcomes, variation in these outcomes between different Kt/v levels may be more obvious over longer periods of time as demonstrated by other studies.

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CHAPTER I

INTRODUCTION

Today more than one million people worldwide are receiving dialysis therapy. One fifth of them are in the United States. In the U.S. 73% of dialysis patients receive Medicare/Medicaid financial assistance from the government through the social security system (1). Consequently, the financial burden placed upon taxpayers from kidney and urologic disease, which often ends up as End Stage Renal Disease (ESRD), is staggering. In 1991, the cost of caring for these patients in the United States was approximately seven billion dollars. This number represents a twenty-one percent increase over 1989 figures. The population of America continues to grow and as a larger percentage of the population which is at risk for ESRD reaches the age of 65, the cost of managing kidney disease is projected to increase significantly. Although kidney transplantation is the treatment of choice, the waiting time for cadaver organs and the low transplantation rate in the aging ESRD populations (55% of the ESRD population are now 60 years or older) will likely ensure that dialysis treatment remains the primary method of renal replacement therapy in the foreseeable future (1-3).

In the United States, dialysis centers have been under severe economic pressure since 1982. This pressure has been in the form of a demand for shorter dialysis treatment

time per patient. The National Cooperative Dialysis Study (NCDS) indicated dialysis time could be shortened safely and has set the stage for a reduction in the dialysis exposure provided to patients (4,5). Unfortunately, a number of experts feel that this has also lead to a diminished quality of care (6-9). Research relating adequacy of dialysis and quality of life is limited.

Despite improvements in dialysis technology over the past decade, annual mortality statistics for American patients have increased remarkably during the past several years. Renal disease related mortality rates for the United States are now estimated at 20 - 24%. When these rates are compared to international rates (7 - 11% in Europe and 6 - 8% in Japan) the figures suggest that significant room for improvement exists in American treatment. These numbers are reinforced by the fact that the average life expectancy of a person receiving dialysis therapy in the United States is about one-fifth that of the general population. Morbidity rates of dialysis patients in the United States are equally high. In 1986, hospitalizations averaged 2.8 days per year for all Medicare patients over 65. However, the median time of hospitalization for patients over 65 who have been on dialysis for one year or more was 15 days per year (1,10-12).

There is increasing evidence that "underdialysis" is contributing to these increased morbidity and mortality rates (10,13-16). Since the origin of chronic dialysis, a way to quantify the therapy and define its adequacy has been sought. Currently accepted methods rely on the mathematical description of urea kinetics by use of an index for dialysis prescription which is referred to as, Kt/v. Adequate dialysis has been

largely defined during the past decade by using data gathered from the NCDS. The dominant interpretation of this study is the one done by Sargent and Gotch (17), who developed the concept of "Kt/v", a dimensionless number that defines the decrease in urea during each dialysis session. The equation is derived by multiplying urea clearance (K) in milliliters/minute, by dialysis time (t) in minutes, divided by the volume of distribution for urea (v) in milliliters/minute.

An adequate dose of dialysis is considered to be the amount of dialysis necessary to keep the patient maintained at a stable level and out of the hospital for the greatest possible length of time. The Kt/v range that Sargent and Gotch suggested for adequate dialysis was 0.9 - 1.4. The average "dose of dialysis" as defined by K/v provided in the United states is 1.0 whereas in Europe and Japan the suggested Kt/v levels are maintained 1.6 or greater (18-21).

Concerns regarding the trend towards reduced dialysis time per treatment fueled by economic factors and patient preference for reduced treatment time, have directed attention to the potential consequences of these actions. Several studies (13,15,16) have confirmed that delivery of dialysis at the upper limits (Kt/v values higher than the NCDS recommendations) have improved patient survival.

Numerous notations in the literature (13,15,16,22-24) have also shown a positive correlation between "underdialysis" (lower Kt/v values) and poor nutrition, as well as high morbidity and mortality rates. This suggests that one of the key effects underdialysis has on these patients and their survival is related to alterations in nutritional stores.

Malnutrition is a common problem among hemodialysis (HD) patients . This problem is characterized by weight loss, abnormal body composition, serum biochemical abnormalities and evidence of altered nutrient metabolism (11,12,24-27).

Investigation over the past twenty years has focused on metabolic abnormalities with respect to malnutrition documentation. Major improvements in dialysis technology and therapy have not resulted in a significant reduction in the frequency and severity of uremic symptoms which play a major role in nutrition related problems. Current estimates indicate 25-50 % of patients with ESRD have clinical malnutrition as determined by customary criteria (10). Causes of malnutrition in this population are multifactorial and may be attributed to numerous components including inadequate dialysis, catabolic processes associated with dialysis, concurrent illness, and dialysis treatment associated symptoms, as well as psychosocial factors.

Malnutrition not only affects the patients ' quality of life, it has been linked to increased morbidity and mortality. This pattern has been shown to occur with the use of a variety of assessment techniques. Acchiarado (22) found a strong correlation between low Normalized Protein Catabolic Rate (nPCR) and an increased number of hospitalizations and mortality rate. Lowrie (28) associated low serum albumin levels with a five fold increased risk of mortality with values less than 4.0 g/dl. Kelly (29) associated weight loss greater than 5% with an increased rate of morbidity and mortality .

Nutrition intervention is a constant challenge. However, the association between optimal nutrition and clinical outcome on dialysis is now well accepted. Unfortunately, oral nutritional supplements are often ineffective due to poor patient tolerance and limited compliance. Funding for nutrition support by Medicare/Medicaid and private insurance companies is nonexistent and the patients usually cannot afford the associated high costs. Fluid and electrolyte restrictions are limiting factors which compound the problem. Intra Dialytic Parenteral Nutrition (IDPN) has been used to treat these patients, however ,there is limited data available on its success, and its cost effectiveness (10,30,31).

Questions that deal with the management of dialysis intensity and the nutrition related components of treatment are now under more intense scrutiny in hopes of attacking the problem from a different angle. The dose of dialysis, as defined by "Kt/v", and utilized as a measure of the adequacy of dialysis, is affected by numerous factors other than nutritional factors, relating to patient compliance and status , staff procedures, and treatment times. There is evidence to suggest a positive correlation between a low Kt/v (<1.0) and protein intake as defined by nPCR levels. Hakim et al (15) showed that patients with a Kt/v of > 1.2 (averaged over a period of one year) had a significantly higher serum albumin and transferrin, and nPCR than those a with Kt/v of < 0.86. Their findings were consistent with observations by Parker, et al (16), but different than

those found by Morgenstern, et al (32), although the study period in the latter analysis was not defined.

It is generally assumed that an increase in Kt/v will clear uremic symptoms, and in turn improve the patients food intake and nutritional status. Controversy exists as to whether attempts to increase nPCR through oral supplementation and/or parenteral nutrition or dietary counseling are effective without first improving Kt/v .

The purpose of this prospective study was to determine if a sustained increase in Kt/v (>1.5) would provide improved clearance of uremic symptoms, in turn resulting in improved nutrition outcomes. The effect of a sustained increase in Kt/v on nutritional parameters (serum albumin, total cholesterol, blood urea nitrogen, protein catabolic rate, weight), and clinical outcome (number of hospital visits, hospital length of stay, mortality rates) and adequacy of dialysis (Kt/v) was evaluated between hemodialysis patients dialyzed to a Kt/v of 1.2 (standard of care) as opposed to a Kt/v of 1.5.

CHAPTER II

LITERATURE REVIEW

Kidney Disease in the United States

The kidney is an extremely complex organ, both structurally and functionally. Because of the importance of the kidney in the body's everyday functioning, diseases of the kidney produce serious consequences. The kidneys have the major responsibility for regulating volume and composition of body fluids. This is accomplished through a filtering and reabsorption process that operates at a flow rate of approximately 125 milliliters of blood per minute (180 liters of blood per day). The kidneys regulate homeostasis by maintaining the functioning of all body cells, primarily by their involvement in the excretion of water and nonmetabolized solutes through highly selective filters. The kidneys are also involved in hormone synthesis. Through this process they play a role in the regulation of bone metabolism, and the formation of red blood cells.

Each year millions of people are affected by kidney disease, and many of these individuals will eventually experience kidney failure. Also known as end stage renal disease (ESRD), kidney failure afflicts people of all ages and from all walks of life. The incidence of ESRD in the United States is currently 180 patients per million

population, and the rate continues to rise by 7.8 percent per year (10). The primary causes of kidney failure are hypertension and diabetes mellitus. In 1990, these two conditions accounted for 63% of the new cases of renal failure and they now account for an even greater percentage (10,12).

End Stage Renal Disease is four times more common among people over 65 years of age. Men suffer a two-fold higher rate of kidney failure than women because men tend not to seek medical care until later in the disease process (10). Black Americans and Native Americans are generally younger at the onset of renal disease and show dramatically higher disease incidence rates than do Caucasians or Asian/Pacific Islanders. This tendency may be related to cultural and social situations. Clinical experts suggest that the incidence of ESRD in Hispanics is greater than in Caucasians although; data from the United States Renal Disease Data System is not sufficient to confirm this clinical impression due to the way racial group data has historically been collected (1,10,12,33). Prior to 1960, ESRD was uniformly fatal. This outcome has changed with the development of the Quinton catheter and Scribner shunt. These methods allowed physicians to permanently access a patient's circulatory system and to help decrease the accumulation of toxins. These and other technological advances launched chronic intermittent hemodialysis as a successful therapy for renal patients.

Treatment Options for ESRD Patients

Following many years of medical research, two primary treatment options are now available for people with ESRD. These options are dialysis and transplantation. The decision regarding which treatment option is appropriate for a particular patient is based on many factors. Important considerations in the decision making process include the patient's medical history, the physician's opinion, patient's/ family's wishes, the patient's lifestyle, and the clinician's ability to educate the patient and/or family regarding certain techniques or procedures. Currently there are two basic treatment options for kidney disease, transplantation and dialysis. Because a patient's physical condition and other factors related to the disease state may change, patients often move from one treatment option to another.

Dialysis

Dialysis is a mechanical filtering process which is used to cleanse the blood of impurities while it draws off excess fluids and regulates the body chemistry. The word "dialysis" is of Greek origin and means "loosening from something else." In

this case, wastes are loosened from the blood. Since it's development in the late 1930's, dialysis treatment has undergone many improvements enabling a greater number of people to receive this procedure.

There are two main types of dialysis procedures. Hemodialysis and peritoneal dialysis are both methods which may be adapted for use in hospitals, dialysis centers, or at home. Hemodialysis is the most commonly employed method with approximately 85 % of the patients on dialysis receiving this form of therapy (10). During hemodialysis, a patient's blood flows through a device called an artificial kidney (dialyzer). The dialyzer has two chambers which are separated by a thin membrane. Blood flows through one chamber , while the remaining chamber contains a cleansing fluid called the dialysate solution. The dialysate solution contains a concentration of electrolytes which are similar to those found in extracellular fluid. When electrolytes and urea are present in greater than normal concentrations in the patient's blood, these solutes are diffused into the dialysate. The membrane separating the chambers is a semi-permeable membrane containing thousands of tiny holes. These holes allow solutes to pass into the dialysate for removal from the body Larger molecules, such as proteins and red blood cells, are too large to pass through the membrane and remain in the blood. The hemodialysis process takes three to four hours, and most people receive treatments three times a week.

Peritoneal dialysis is the other type of dialysis treatment available to the ESRD

patient. This process uses the peritoneum, which is a semipermeable membrane, as a natural filter. It acts in a similar fashion to the artificial kidney utilized in hemodialysis. An indwelling peritoneal tube, a catheter, is placed into the body surgically. This makes it possible for the patient to connect a piece of tubing to the catheter. The peritoneal tubing, thereby allows for the placement of a dialysis solution into the abdominal cavity. This dialyzing solution contains dextrose and is instilled into the peritoneal cavity where an exchange of solutes and water occurs across the peritoneal membrane. The filling of the peritoneal cavity takes 30 - 40 minutes. The dialysate solution must stay in the abdominal cavity for 3 - 6 hours, depending on the patient's body size and how much waste has to be removed. This time period is called the "dwell time". During this time the patient is free to do whatever he wants. At the completion of the "dwell time", the solution containing waste products and excess fluid is drained through the tube into an empty bag. This process is usually repeated three to five times a day.

Transplantation

Another treatment option for ESRD patients is kidney transplantation. Transplantation is a process whereby a healthy kidney from a donor is placed inside a patient's body to perform the work of the failed kidney. Many people think of transplantation as a cure for kidney failure. A successful kidney transplant can result in a

feeling of well being and freedom from dialysis, but it is still a treatment, rather than a cure. Patients interested in becoming candidates for kidney transplant surgery must first undergo a series of comprehensive medical tests to determine their body's ability to withstand the surgery. An individual's mental attitude and level of expectation are examined to determine their ability to prepare for any possible outcome. Not every person is a good candidate for this surgery, and not all kidney transplants are successful.

Indices of Nutritional Status

Evidence suggests that adequate nutritional status is instrumental in the survival of hemodialysis patients. Surveys have demonstrated that malnutrition is common even in ESRD patients who appear normal and have had a successful clinical course (22,31). The reluctance of many nephrologists to use a large battery of measurements and laboratory determinations to assess nutritional status may be related to current reimbursement issues. Another problem in this regard is that current nutritional assessment techniques and measurements have wide confidence limits. Although the indicators normally used to assess nutritional status are useful epidemiologically, no single measurement is of consistent value for an individual patient. All current clinical, biochemical, and electrophysiological tests provide insight into the problem, but none have proven to be simple, reproducible, sensitive, and inexpensive (10,22). The ideal

determinant of nutritional status in the ESRD population remains elusive. Clinical assessment in conjunction with a diet history and anthropometric measurements seem to be the most useful when properly performed in the serial assessment of the patient. This level of assessment is, however, only adequate for detecting gross changes in nutrition status (34).

Traditional reference standards such as height and weight indices are less reliable when used with the hemodialysis patient due to the difficulty in determining body dry weight. Using body weight as an estimation of lean-to-fat ratio, because of fluid shifts in the kidney patient which are related to diminished urinary output, is of little value. Anthropometric techniques and norms for the chronic hemodialysis population have been published but are limited in application to stable populations (34,35).

Multiple prognostic indices (PNI) exist and are routinely used to evaluate patients nutritional stores when they have either suffered abdominal trauma, or are scheduled for surgical procedures. These predictive tools have been established to a) isolate high risk patients, b) decide upon an appropriate nutritional intervention, and c) evaluate a patient's outcome. A PNI was recently developed for use with the hemodialysis patient population, but has not been clinically validated (29).

Recent studies have demonstrated the feasibility of determining body composition using bioelectrical impedance (BEI) in hemodialysis patients (10). Bioelectrical impedance has been shown to be easily reproducible in the renal

population and has been shown to be valid for determining lean body mass. Because it is noninvasive and causes no discomfort to the patient it can be easily performed in the dialysis center (10,24).

The most convincing link between malnutrition and mortality in the ESRD patient is the range of albumin concentrations (27,28,36). Small decreases in this routinely measured parameter are associated with increased mortality rates. Although serum albumin has been shown to a late indicator of malnutrition, it has been widely accepted as a nutritional marker and has been shown to be a powerful predictor for morbidity and mortality among the dialysis population. For this reason, normal albumin concentrations have been adopted by the Health Care Financing Administration (HCFA) as an indicator of quality patient care. Studies have shown that dialysis patients with serum albumin concentrations in the range of 3.5 to 4.0 g/dl have an increased risk of mortality (two-fold greater) when compared to patients with serum albumin concentrations in the range of 4.0 - 4.5 g/dl.. The mortality risk has been shown to have a two to four fold increase when patients have a low serum albumin concentrations (3.0 - 3.5 g/dl) and a sixteen fold increase when serum albumin concentration levels fall to less than 3.0 g/dl (28). Other studies have shown that increased risk for hospitalization occurs with low serum albumin concentrations (11,22,27,36). Kaminski, et al. (27) demonstrated that as serum albumin concentrations decreased to 2.0 g/dl or less, morbidity and mortality

linearly approached 100%. A low serum cholesterol concentration in the presence of hypoalbuminemia has been shown to be an additional risk factor for morbidity in the dialysis population. Mortality has also been shown to increase when serum cholesterol concentrations fall to between 100-150mg/dl while serum albumin concentrations are also low (24,28,37,38).

Dietary protein intake of patients undergoing dialysis can be monitored via the measurement of their protein catabolic rate (PCR). Protein catabolic rates are calculated by measuring the changes in the serum blood urea nitrogen (BUN) using urea kinetic modeling. However, PCR is not determined in a large number of dialysis centers on a monthly basis. Where it is used, values are often obtained only quarterly and are assumed to be representative of the average for the patient. Since a patient's dietary habits differ on weekends, dialysis days, and non-dialysis days, quarterly nPCR measurements may not represent the true protein intake, and therefore may over or under-estimate actual dietary protein intake. Results from a study by Lindsey, et al (39) suggest that dialyzed uremic patients who do not have extraneous factors (i.e. malignancies or diseases of the gastrointestinal tract) impacting on them, have PCR's which are directly dependent upon the amount and type of dialysis treatment. Early observations from the NCDS study showed that, in spite of intensive dietary counseling and provision of oral protein supplements, patients would not eat well until an adequate dose of dialysis was prescribed. What was thought to be an adequate does of dialysis

during the NCDS study has subsequently been redefined as being too low and it is now being reevaluated with respect to appetite and dietary protein intake (15,16,24,40).

An additional risk factor which has been correlated with mortality in the ESRD patient is serum creatinine concentration (28,40,41). Creatinine concentrations reflect somatic protein mass and low values have been associated with a higher mortality in the ESRD population (17,28,41). Stable serum creatinine concentrations, if viewed as a single nutritional marker, are subject to error since depletion of muscle mass can still allow for constant serum creatinine concentrations if the removal rate decreases. Utilizing serum blood urea nitrogen (BUN) as a sole marker of protein metabolism can also provide a false picture of adequacy of nutrition (40). Blood urea nitrogen concentrations correlate poorly with anorexia in patients receiving dialysis, since a certain concentration of urea can be achieved, either by adequate dialysis and nutrition, or by inadequate dialysis coupled with inadequate nutrition. This is notable because low serum BUN concentrations are sometimes used as a signal to reduce dialysis time. In summary, using blood chemistry levels to assess delivery of dialysis is considered valid to a point but no single assay gives a true picture, especially since blood chemistries are only routinely performed on a monthly basis.

Malnutrition in the ESRD Population

Long term survival and rehabilitation are the most basic goals care providers try to reach with their ESRD patients. To achieve these goals, care providers modify the dialysis prescription to prevent or treat subsequent medical problems that may lead to increased morbidity and mortality. The relationship between malnutrition and increased morbidity and mortality in the renal patient is not simply one of cause and effect since many patients have complicating diseases along with their renal disease (34,42). Malnutrition and cachexia are not listed among the causes of death in the U.S. Renal Data Systems Annual Report; therefore, it is difficult to obtain accurate data about possible relationships between malnutrition and mortality (12).

Today, Americans are expressing more concern about the cost of health care; however, historically the main consideration has been whether the care resulted in a medical benefit to the patient (43). At the current time, regulatory agencies and insurance companies are expecting to see a cost benefit from the care provided, and patients are expected to contribute financially in order to obtain the expected reductions in health care costs. The cost of care for patients with ESRD in 1990 was approximately $7.26 billion but this figure does not include the cost for drugs, medical supplies, disability and social security payments (43). The average annual cost for treating each patient now exceeds $50,000. The renal care industry began

growing in the early 1960's, but it was not until the U.S. Medicare program began to subsidize the cost of the ESRD program (1973), that this industry really began to take root and grow to the size it is today. The hemodialysis industry is now an expensive multifaceted spectrum of goods and services which is designed to confer longevity to patients with ESRD.

Malnutrition has been associated with uremia for sometime, therefore, nutritional status, is thought to be the most important index of dialysis adequacy. A reduction in kidney function is first manifested by anorexia, nausea, and vomiting. These are also the first symptoms which improve following the institution of dialysis or transplantation. A great deal of effort has been made in recent years to a) identify the best determinant of nutritional status among uremic patients, b) find specific and reliable tools which can be used to correlate dialysis dose with nutrition, and c) characterize the conditions that accelerate or potentiate malnutrition in uremic patients (10,23,34,44,45). Interaction between nutritional intake, nutritional status, and morbidity and mortality in dialysis patients has been of particular concern and the subject of recent studies. Virtually every survey over the past 10 years has highlighted protein calorie malnutrition as a major problem for patients undergoing hemodialysis or peritoneal dialysis. Malnutrition has been reported to be "mild" to "moderate" in approximately 33% of the maintenance dialysis population and severe in approximately 6 - 8% (10,23,34). This suggests that the nutritional status of a patient

is a major factor in the outcome of hemodialysis treatment and makes it an important aspect to consider in treatment (10,23,33,34).

Malnutrition is a multifactorial disease which has many causes. Major contributors include inadequate nutrient intake, underlying or concurrent illnesses, alterations in metabolism caused by kidney failure, and the dialysis process itself. Both the health care provider and the patient must want to prevent nutrient deficiencies in order to maintain good nutritional status. By doing this, uremia can be minimized, edema and electrolyte imbalances can be controlled, and renal osteodystrophy can be prevented or slowed. All of this can be accomplished by enabling the patient to eat a palatable, attractive diet which fits into his lifestyle.

Although the prevention of malnutrition is one of the primary goals of treatment for the dialysis patient, researchers are largely ignorant about how to prevent it. Current regimes range from dietary counseling and education to complex therapy which involves the use of intravenous nutrients in the form of intradialytic parenteral nutrition (IDPN). These basic interventions are needed to improve and maintain nutrition stores and reduce overall morbidity and mortality related to malnutrition.

Factors which Affect Nutrition Status of the Hemodialysis Patient

Dietary Restrictions

Dietary restriction is a way of life for chronic dialysis patients who are faced with the exclusion of many commonly eaten foods from their diet. Healthy individuals in industrialized nations have difficulty meeting optimal nutrition guidelines with respect to a balanced diet and recommendations by health agencies; therefore, it is no surprise that malnutrition exists in the dialysis population (10,23,24,34). Diminished nutrient intake caused by anorexia, is probably the most common reason for protein or calorie malnutrition in these patients. Anorexia has multiple causes, including the buildup of uremic toxins, as well as the debilitating effects of concurrent or underlying illnesses or depression (24). Dietary restrictions placed on patients who are admitted to a hospital and placed on a " Renal Diet" may limit the amount and palatability of food. Unpalatable diets are also often prescribed which are marginally adequate in protein and other nutrients and are difficult to prepare. Poverty and cultural factors may also accelerate this problem (24). Provision of adequate nutrition is more the responsibility of the patient than the dialysis center, but the center has control of certain functions that have the potential for enhancing the nutritional status of the patient (45).

Dialysis Factors

Numerous studies have shown that factors used in performing the dialysis procedure impacts the nutritional needs of the ESRD patient. Dialysis membranes, dialysis fluid as well as treatment times can impact on a patients' nutritional status.

Biocompatible Membranes

"Bioincompatibilty" is the term used to describe the reaction chronic hemodialysis patients have to extracorporeal materials. Patients have been shown to develop direct toxic effects to the membrane material used in some dialyzers (13,24,46-49). The membrane's chemicals activate the complement cascade which and stimulates cytokine production in an abnormal manner and induce phagocytosis as well as adhesion of activated granulocytes to pulmonary endothelium. Some studies suggest that there is a 50% fall in incidence of infection when a switch is made to a more biocompatible dialyzer. The effects of these bioincompatible membranes cause side effects such as enhanced rates of infection and accumulation of beta-two-microglobulin amyloidosis (47-51).

In 1938, the humble artificial sausage skin (cellophane) was first used as a dialyzer membrane. Cuprophane (cupra-ammonium cellulose) was the next modification used for dialysis membranes and resulted in a precipitous fall in white

blood cell count within minutes of starting dialysis. This change in white blood cell count was noted, but generally accepted because there were no other dialyzer membranes available at the time. This reaction was not considered to be detrimental unless the patient had a compromised cardiopulmonary system. (52)

In the early 1980's two new membranes made of polysulfone and polyacrylonitrile were developed. These two membranes did not activate the complement cascade and were therefore regarded as "biocompatible". Both membranes were also better at clearing molecules which were thought to cause long term complications in patients receiving hemodialysis. Unfortunately, these membranes are many times more expensive than conventional dialyzer membranes and so are not widely used except where high flux or high efficiency dialysis is necessary.

Studies by Ikizler, et. al. (53) and Kaplan, et. al. (54) showed that when high flux polysufone (bioincompatible) membrane dialyzers were used, excess amino acid losses were seen in the dialysate fluid. They suggested that chemicals used to clean and reprocess the dialyzers, such as bleach, increase the porosity of the membranes leading to increased amino acid losses. Another clinically important finding associated with the reprocessing of these dialyzer membranes has been the discovery that albumin molecules escape in the dialysate after the sixth reprocessing (53). Because of its size, albumin normally cannot pass through the membrane pores. Current research is ongoing to see if this phenomena is related to specific dialyzer membranes or is common

to all membranes. Further research is ongoing in the area of membrane biocompatabilty and it's relationship to malignancy, cardiopulmonary disease, and malnutrition.

Dialysate Fluid

The two forms of dialysate currently used in the hemodialysis process contain either bicarbonate or acetate. The bicarbonate containing dialysate is preferred because of the improved biocompatibility and concomitant reduction of cytokines (interleukin 1,TNF) which are associated with alterations in immune function (13,48,51). Several studies have documented benefits of bicarbonate over acetate dialysates. Bicarbonate dialysate has been shown to be associated with improved cardiovascular stability and better control of uremic acidosis . The use of acetate as a base in dialysate fluid has been associated with an increased incidence of nausea and vomiting in older individuals with small muscle mass who apparently cannot metabolize acetate efficiently (13,44,54). Although the use of bicarbonate is more expensive than acetate and is associated with a higher risk of bacterial contamination, it is the preferred buffer because of its other benefits to the patient. Although most dialysis units have changed to a bicarbonate dialysate base, acetate is still used in some smaller units (54).

Effect of Missed or Shortened Treatment Times

Monthly urea kinetic modeling (UKM) results used to assess adequacy of dialysis may be influenced by missed or shortened times. Dialysis adequacy measurements, which are based on kinetic modeling, are generally only calculated once a month for each patient. Those measurements are assumed to be the average (usual) for that patient for that month. Results, although based on the current and previous treatment factors, may not reflect actual cumulative clinical effects of missed or shortened dialysis treatment time. This cumulative effect of receiving an inadequate dose of dialysis has been associated in the literature with an increase in the number of hospital admissions and cardiac problems for patients who frequently miss treatments or discontinue their treatment prior to receiving the prescribed dose of dialysis (14). Comorbid complications associated with uremia and osteodystrophy have also been observed with those patients who have a history of long term noncompliance with the dialysis prescription (14).

Hospitalizations

Hospitalizations for dialysis related or non-dialysis related conditions have been identified as stimuli for anorexia in the ESRD patient (24).

The frequency of hospitalizations for the ESRD patient population has been

utilized as an indicator of morbidity by the Health Care Financing Administration and the End Stage Renal Disease Network. Vascular access problems and cardiovascular complications are the most frequently noted reasons for hospital admissions for ESRD patients. Diabetic patients are expected to be hospitalized 25% more often than non-diabetics and account for an average of 75% more days spent in the hospital per year. An increase in days spent in hospitals over a one year period is also seen among older patients and Caucasians versus other racial groups (3,10-12).

Comorbidity

Infection remains the major cause of death in 15 - 30% of dialysis patients. These infections are usually caused by a common organism (Staphylococcus aureus) and are access related. Fifty to sixty percent of all dialysis patients are carriers of this organism, whereas, only 10 - 30% of the general population carry it. The carrier rate among diabetic dialysis patients is thought to be even higher and translates to more frequent hospital admissions.

Currently acidosis is the only identified uremic condition which has been shown to induce protein catabolism and impair nitrogen utilization. Mitch, et al (45) showed that acidosis, rather than uremia, appeared to enhance protein catabolism. When patients consumed a low protein diet or become anorectic, specific metabolic responses

were activated which improved the utilization of dietary protein and minimized the influence of any catabolic stimulus. This metabolic adaptation generally led to a more efficient utilization of dietary protein. Some researchers have suggested that the uremia experienced by chronic renal patients blocks or prevents activation of these responses (24,45).

Researchers have shown that metabolic acidosis is a stimulus for protein catabolism in humans as well as animals (45). In normal subjects, metabolic acidosis increases ammonia excretion by increasing renal glutamine extraction. The glutamine pool, however, is not depleted with acidosis. Consequently, it has been hypothesized that body protein stores are degraded to amino acids which are then utilized to synthesize glutamine. Acidosis has also been shown to increase the production of glucocorticoids which act to regulate protein turnover. This process is beneficial in non- renal failure patients, however, it has been shown to be maladaptive in patients with chronic renal failure. The combination of acidosis and glucocorticoids appears to stimulate the catabolic pathways, which impair normal metabolic responses (45). Other studies have shown that in non-dialyzed chronic uremic patients, nitrogen balance is improved following the correction of metabolic acidosis (45). Uremia itself has also been shown to impair cell mediated immunity. This impairment has been shown to be only partially corrected by dialysis (24).

Cardiovascular disease, when present at the initiation of dialysis, has been shown

to be an important predictor of outcome of dialysis therapy (33,42). This is particularly true when the disease is found in nondiabetic patients with ESRD. Cardiovascular problems, primarily blood pressure abnormalities, and myocardial infarctions, or strokes, account for approximately 50% of the mortality in dialysis patients (34,37,61). Alterations in lipoproteins are also correlated with increased mortality in dialysis patients. The benefit of long term control of lipid abnormalities with lipid lowering drugs has not been validated in this population (34).

Finally, metabolic bone disease is a disorder which eventually affects all patients with ESRD. This condition is affected to a great extent by whether the patient complies with his/her medication and diet. Severity of the osteodrystrophy also can now be controlled to a large extent with the use of a commercial vitamin D supplement (Calcitrol).

Interventions in Malnutrition

The traditional approach to nutrition therapy for the ESRD patient is based on determining nutritional requirements for individual patients, assessment of their of current nutrient intake, and implementing nutrition intervention. Food, food supplements, medications, or more aggressive nutritional support in the form of enteral or parenteral nutrition are types of intervention that have shown little success with dialysis patients

(24,34). Relaxing dietary restrictions has been shown to be more successful in encouraging adequate oral intake in this population. Oral nutritional supplements have been used to enhance the diets of patients who have eating difficulties or are not taking enough nutrients by mouth, unfortunately, some patients are not able to afford the high cost of supplements. The development of "renal" specific oral nutrition supplements also have not proven to be beneficial because they often have a high fat content which leads to early satiety in many patients and they are very expensive.

Current studies have not demonstrated the efficacy of using Intradialytic Parenteral Nutrition (IDPN) with chronic hemodialysis patients to enhance survival of malnourished chronic hemodialysis patients, because of study designs, follow-up and lack of clinical outcome and cost benefit data. The few studies that have shown any benefit from IDPN in terms of increased serum albumin concentrations or of increased dry weight generally required a minimum of 4 months of therapy (10,24,34).

Drug therapy to treat anorexia and other common symptoms in dialysis patients has been of limited benefit (10,24). Many patients suffer from gastrointestinal complications related to diabetes mellitus and uremia, which result in a high rate of prescription medications. Motility stimulating agents, H2 blockers, antacids and anti-HCL secretory agents are a few medications taken by this population (10,24). Research involving the etiology and treatment of these problems has been minimal. Successful treatment of these common problems would improve dietary intake for many patients

(10,24). On the other hand, many patients receiving dialysis therapy have shown improved nutritional status with the use of new hormone therapies. Erythropoetin (EPO) and Recombinant Growth Hormone (rhGH) and have been shown to have a positive effect on nutrition outcome (10,24,34).

Normally, the kidney produces about 85% of the body's erythropoietin, with the remainder being produced by the liver. The major function of this hormone is to regulate red blood cell production by the bone marrow. In the presence of kidney disease, the diseased kidney can no longer produce the necessary circulating levels of erythropoetin and anemia develops. Anemia is the most universal complication in patients who suffer from chronic kidney failure. A commercially available recombinant erythropoietin (EPO) has been approved for use by the Food and Drug Administration. Experience with EPO over the last four years has shown that it has beneficial effects to many patients (i.e. weight gain, better dietary intake , and improved physical performance) (10). The use of EPO has also been shown to have a positive impact on improving protein status as documented by urea kinetic modeling (10).

A potential strategy for increased incorporation of nutrients in dialysis patients is in the use of rhGH (10,24,34). Patients with ESRD have been shown to have multiple growth hormone abnormalities (3). Growth retardation has been identified as a severe complication associated with long term dialysis treatment (10). Research has shown that GH-insulin like factor (IGF-1) axis is disturbed in uremia (10). Mehls, et al (10) found

that rhGH improved food efficiency ratio in uremic animals without a change in spontaneous food intake. Historically rhGH has been used with children, however clinical research is now being done with malnourished adults. Recombinant growth hormone has been shown to generate an anabolic effect in malnourished patients who are being treated with peritoneal dialysis. This has been documented by a decrease in net urea generation (24). Decreases in serum albumin and increases in serum creatinine are thought to be caused by an rhGH induced shift in amino acid metabolism towards peripheral muscle tissue (10,36).

Zinc deficiency has also been noted in patients with kidney failure (10). Deficiencies arise because of dietary protein restriction, decreased intestinal absorption, blood losses from laboratory analysis, and occult gastrointestinal bleeding. Studies have shown some dialysis patients also to have low serum zinc concentrations, but it is questionable as to whether this parameter is indicative of a true dietary deficiency or the result of problems related to blood losses or malabsorption (24). Zinc supplementation has been met with some success in improving taste acuity and anorexia, although this has not been substantiated in clinical trials (10,24,34).

It has been suggested that intervention in ESRD for malnutrition problems which include the development of educational programs for both the patient and the health care team regarding factors that contribute to morbidity and mortality may contribute a better quality of life and improved longevity as well as correction of

comorbid conditions. The National Institute of Health (NIH) has indicated that patient participation is an integral part of the recovery process if it is to be successful. Other areas of future direction for research have been identified by the NIH. These directions encompass: a) evaluating the effectiveness of aggressive nutrition support on morbidity and mortality rates, b) evaluating the benefits of early control of renal osteodystrophy, c) examining the differences in patient morbidity and mortality at different Kt/v levels, d) evaluating the interactions of reuse and biocompatability on nutritional status, and e) evaluating newer methods for early nutrition assessment along with their use as intervention tools (10).

Quality of Life Considerations

Extending survival or life expectancy of the hemodialysis patient is clearly a primary goal of medical care for this population, whereas improving the quality of a patient's life has been secondary goal. There is a growing consensus that understanding the impact of chronic illness and associated treatment on health-related quality of life is critical. Unfortunately, measuring a patient's quality of life is inherently based on a subjective appraisal that cannot be measured (15). In addition, when one tries to interview patient's they differ greatly in the importance they attach to different aspects of their health.

Moody, et al. (56) looked at freedom of choice and health status and found that as freedom of choice was removed with respect to any changes in dialysis modalities the health status of the patient remarkably declined. Sloan, et. al. (57) looked at the impact of the dose of dialysis (Kt/v) and level of nutrition on the way in which hemodialysis patients perceive their health status. They concluded a patients perception of their health status was related to their nutritional status, but a clinical increase in their nutrition status did not significantly change the patient's perceptions of their impaired health status.

Relationship between Nutritional Status and Adequacy of Dialysis

Studies relating to assessing cost and outcome on dialysis are minimal. As technology improves and emphasis is placed on switching from conventional to high flux dialysis and on increasing Kt/v above current standards, cost becomes a significant consideration. Alterations in the hemodialysis prescription may increase or decrease costs as the use of biocompatable membranes requires the use of bicarbonate dialysate, computerized dialysis machines, and increased water usage. In some situations it may be easy to offset the higher cost with shorter treatment times. Analysis of data from the National Cooperative Study and the U.S. Renal Data System has provide new insights into outcomes which may be favorable to previously mentioned changes in the dialysis

prescription including a reduced number of hospital days as well as improved survival rates (5,25).

At present there is controversy regarding the optimal Kt/v level (6,16,24,40,42). The National Cooperative Dialysis Study (NCDS) (8) evaluated urea clearance versus time on dialysis. A correlation was found between the probability of therapeutic failure in hemodialysis, serum BUN levels and dietary protein intake (DPI). These data demonstrate the greatest morbidity for patients when Kt/v and PCR was less than 0.8 g/Kg/day. A Kt/v >1.0 was considered adequate during the NCDS but nutrition management and dietary intake were uncontrolled variables making it difficult to conclude that changing dietary intake would necessarily improve outcome in this study. Kt/v > 1.0 was also not analyzed (10). Another significant factor in comparing NCDS data to current research is that the NCDS study population was not similar to the population which is undergoing dialysis today. The patient population was younger, compliant with care, non-diabetic, and had fewer comorbid complications (16,24). Lindsay and Spanner (39) show a direct correlation between Kt/v and PCR, although they noted a possible variable of urea disequilibrium with use of high-flux dialysis. They also highlighted the importance of membrane biocompatibility as a direct relationship between PCR, Kt/v. Other groups (13,46) document similar findings with cuprophane membranes. Hakim, et al (15) and Levine et al (16) as well as Lowrie (38) more recently have

reached similar conclusions.

Dumler, et al. (58) also show a positive correlation between PCR and Kt/v. The best predictor of increasing PCR is a high Kt/v. Research by Suahail and Cole (59) suggest inadequate dialysis as one factor contributing to increased morbidity in patients whose Kt/v is in the 0.9 - 1.0 range. Hakim, et al (60) correlate increasing mortality with inadequate or inappropriately short dialysis time. Charra's (61) analysis of twenty year actuarial survival concluded that a Kt/v greater than 1.6 contributes to improved survival curves as well as better blood pressure control. Kupin, et al. (62) demonstrate the lowest morbidity and mortality with a PCR of 1.1 - 1.4g/Kg/day. Himmelfarb, et al (23) identified trends for patients with low Kt/v's with lower PCR's although they are not statistically significant. A strong correlation between dose of dialysis and protein intake was evident in a recent study by Hakim, et al (15) and further corroborated by Parker, et al (16).

Sargent and Gotch (4) analyzed the NCDS data, utilizing a mechanistic model vs the statistical model. They concluded that in patients who were adequately dialyzed, with a Kt/v = 1.0, PCR =1.0, prescribing higher levels of nutritional (i.e. more liberal diets) and dialysis parameters is of no apparent clinical value with the cellulose dialyzers. However they did not look at levels beyond 1.0 and had defined optimal dialysis differently than today's researchers.

Keshaviah and Collins (5) demonstrate that optimal clinical outcomes occur

with Kt/v >1.3. Their analysis of NCDS data note an over-exaggeration of significance of PCR on therapy outcome. Their study demonstrated more how "not to" dialyze rather than "how to" dialyze

The controversy raised by studies concerning "adequate" versus "optimal" Kt/v and the relationship to PCR can be attributed to multiple variables. These include demographics of study populations, time of study, method of calculating Kt/v, timing of specimen collection after dialysis and individual estimation of body water.

Over the past decade patients with chronic renal failure have benefited from major advances in dialysis as evidenced by declining mortality. Despite this, the mortality rate is still relatively high. Even today, 38% of those patients who have been on dialysis longer than one year have a Kt/v of less than 1.0, the minimum recommended by the NCDS study, well below the minimum recommendations of 1.2 set by the NIH Consensus conference and that recommended by the Renal Physicians Associations (10).

Many physicians feel that optimal nutritional support is crucial for a positive outcome with dialysis therapy. The difference between the management of the dialysis intensity and the nutrition related dimension is the question put to today's researchers and the impending NIH 5 year multi-center trial. Renal patients suffering from poor nutrition require prolonged or more frequent hospital admissions and also have a higher incidence of mortality (22,27,37). The failure of chronic dialysis

therapy to improve the nutritional status of patients makes the task of preventing malnutrition an even greater (10).

The question remains: Can the dose of dialysis as measured by Kt/v affect the nutritional status of the patient ?

This study will demonstrate that a sustained increased Kt/v will result in an increase in PCR and affect improved nutrition as measured by noted indices and improved clinical outcomes.

CHAPTER III

MATERIALS AND METHODS

Subjects

The subject population used for this study consisted of sixty-five adult male and fifty-three adult female patients who were treated at one of four free-standing outpatient hemodialysis facilities located in the metropolitan area of Ft Worth, TX. The population was similar to the national dialysis population with respect to age, diagnosis and number of years on dialysis. At the time of the study patients were: a) in stable condition, b) had been on hemodialysis for more than a year, and c) had not been hospitalized in the past 3 months. Patients were excluded from the study if they had had a secondary diagnosis of AIDS, cancer, liver failure, or nephrotic syndrome, or had recently been receiving steroids. All patients were recommended for dialysis treatment by their primary care physician who also gave permission to adjust dialysis variables (hours dialyzed, blood flow rate, dialysate flow rate, type of dialyzer membrane) to meet targeted Kt/v levels. All patients were dialyzed via a permanent vascular access. Experimental protocol for the study was approved the Medical Staff at Dialysis Associates (Ft Worth, TX) and Texas Woman's University (TWU) (Denton, TX) (Appendices A and B). All subjects signed a consent form as required by the Human

Subjects Review Committee at Texas Woman's University and Dialysis Associates (Appendix C).

The dialysis centers were staffed by six board certified nephrologists who saw the patients at least two times per week. Two Registered Dietitians were assigned to the dialysis centers and met with patients at least four times a month. There were no changes in the frequency of the visits by the physician or the dietitians during the study period.

Demographic and Kinetic Modeling information pertaining to each patient was maintained in the patient's medical record and in a private data base which was maintained by Dialysis Associates.

Experimental Design

The one-hundred-eighteen patients involved in the present study were randomized into two groups and then studied for a 12 month period. Group 1 (n = 56) was the control group and was initially targeted at a Kt/v of level of 1.2. The experimental group (Group 2; n = 62) was targeted at a Kt/v level of 1.5. Optimal nutrition status for the patient was defined at the beginning of the study according to the classification method shown in Appendix D.

Data Collection

Serum samples were collected by trained nurses who were employed at each of the participating Dialysis Centers. The following serum biochemical components were analyzed (albumin, total cholesterol, BUN). The Pre BUN samples were drawn as part of the monthly Chem 20 assay. This assay required 15 ml of blood which was collected in a Corvac serum separator tube prior to initiation of dialysis. The post BUN samples were collected in a 5 ml serum separator tube. Post BUN samples were collected from patients after the blood in the extracorporeal circuit was returned to the patient at the end of the dialysis treatment.

The serum required for analysis of serum albumin and cholesterol concentrations was collected with the Pre BUN sample. Serum was removed by centrifugation and was analyzed using a Hitachi Autoanalyzer (San Jose, Ca) by trained personnel at LifeChem Laboratory (Norville, New Jersey). Serum albumin and cholesterol were determined utilizing the method of bromcresol green (BCG) and according to Lowrie, et al. (28). Protein Catabolic Rates (PCR) were calculated using a two BUN model according to the method of Teehan, et. al. (Appendix E). Nursing staff also made clinical assessment measurements including, pre and post dialysis weights when each dialysis treatment was performed. Hospitalization data (number days hospitalized and cause of hospitalization) and mortality data were collected by a Registered Dietitian.

Kinetic Modeling

The Kinetic modeling equations which were used were based on a single pool variable-volume pharmokinetic model. The equations and data used with the kinetic modeling calculations were established by Sargent and Gotch (62) (Appendix F).

Dialysis

All dialysis was performed using dialysate which contained bicarbonate and which was adjusted to a dialysate flow rate of 500 ml/min. Blood flow rates varied between 300 ml/min and 400 ml/min. Subjects were placed on dialysis 3 times per week for a period of 3 - 4 hours. Dialyzer membranes were made of polysulfone (F8, F80, Fresenius, Concord, Ca.) and cellulose (T175, Terumo Medical Corp., Somerset, NJ) and were used approximately 10 times. In-between uses they were disinfected using < 1% heated formaldehyde solution and cleaned using a 5% bleach solution. All dialysis machines were volumetric control units (Fresenius, Concord, Ca.) and were able to remove precise amounts of fluid during each dialysis treatment period.

Statistical Analysis

Experimental and control subjects were evaluated using a 2-sample independent t-test for differences in serum albumin concentrations, normalized protein catabolic rates (nPCR), total number of days in the hospital, total number of hospital admissions over the study period, mortality, and weight. Additional 2-sample independent t-tests were used to compare subgroups (diabetics and non-diabetic groups, Black vs non Black racial groups, and gender) in regards to clinical, nutritional and outcome data. Regression analysis was performed on all nutritional and outcome data. Differences in selected variables from the beginning of the study to the end of the study were analyzed using a t-test for dependent samples. Serum albumin and cholesterol concentrations, BUN, PCR, and body weights were analyzed via repeated measures analysis of variance. Values were considered to be statistically significant at $p \leq 0.05$. The Statview computer statistical package (Abacus Concepts, Berkley Ca.) was utilized to analyze data.

CHAPTER IV

RESULTS

Population

The characteristics of the study population are shown in Table 1. Table 2 summarizes overall demographic information and descriptive statistics about the subjects. The initial and final overall nutritional status of both groups are summarized in Table 3 and Table 4.

One-hundred eight subjects completed the study. Eight subjects withdrew from the study before completion. Reasons for withdrawal included: transplantation (n = 1); transferred to another facility (n = 5), transfer to CAPD (n = 1), released from the study because of poor compliance with the dialysis prescription (n = 1).

Changes in Kt/v levels

The experimental group was maintained at mean Kt/v level of 1.6 $\pm$ .02 over a 12 month period while the control group was maintained at a mean Kt/v level of 1.3 $\pm$ .03. Overall group means achieved a higher level than targeted. This was attributed to the numerous variables involved in the calculations as well as individual patient variables.

Table 1: Characteristics of the Study Population

POPULATION CHARACTERISTICS	PERCENTAGE
SEX:	
MALE	56
FEMALE	44
RACE:	
BLACK	39.8
CAUCASIAN	46.6
OTHER	13.6
MEMBRANE COMPATABILITY:	
BIOCOMPATIBLE	81
CONVENTIONAL	19
DIABETICS	39

Table 2: Initial Demographic Data and Descriptive Statistics of Study Population

DESCRIPTIVE STATISTICS				
	MEAN	Std. ERROR	MINIMUM	MAXIMUM
AGE (Years)	59.8	1.5	26.0	87.0
TIME ON DIALYSIS (Hours)	3.7	0.3	3.0	4.0
TIME IN HOSPITAL (Days)	10.7	1.5	1.0	47.0
SERUM: ALBUMIN (g/kg)	3.8	0.3	2.8	4.5
CHOLESTEROL (mg/dl)	178	3.9	92	302
BUN (mg/dl)	65	1.4	28	115
nPCR (g/Kg/d)	1.01	0.02	0.63	1.5
WEIGHT (Kg)	73.0	1.8	31.6	124.0

Table 3: Initial Classification of 108 ESRD Patients on Hemodialysis According to Their Nutritional Status: Results show number of patients (n =)

PARAMETER	OPTIMAL	NUTRITION STATUS MILD	MODERATE	SEVERE
SERUM: ALBUMIN	25	59	22	2
CHOLESTEROL	60			
BUN	65			
nPCR	25	27	34	22
WEIGHT: %IBW* % USUAL	58 108	6 --	1 --	-- --

* Body weight as a percentage of IBW for age,sex,height
> 120% IBW n = 29

Table 4: Final Classification of 108 ESRD Patients on Hemodialysis According to Their Nutritional Status: Results show number of patients (n =)

	NUTRITION STATUS			
PARAMETER	OPTIMAL	MILD	MODERATE	SEVERE
SERUM: ALBUMIN	31	58	17	2
CHOLESTEROL	65	--	--	--
BUN	66	--	--	--
nPCR	15	40	--	53
WEIGHT % IBW* % USUAL	65 101	3 6	1 1	-- --

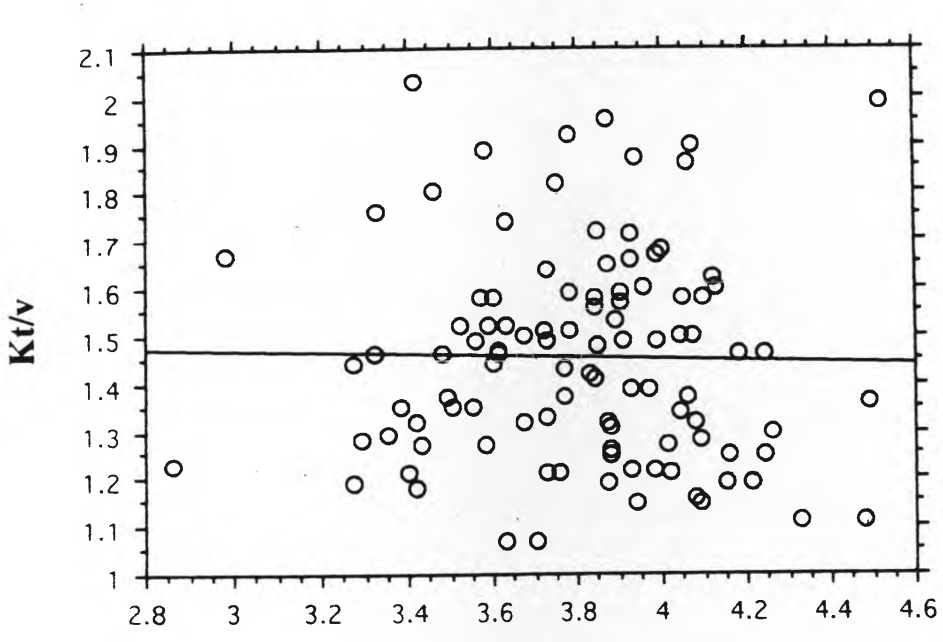
* Body weight as a percentage of IBW for age,sex,height
> 120% IBW n = 39

Nutritional Outcomes

Albumin

Regression analysis revealed no significant correlation between Kt/v levels and serum albumin concentrations (Figure 1). There were no significant differences in serum albumin concentrations observed between the experimental and control group. The mean albumin concentration (averaged over the 12 month study) for the experimental group was 3.79 $\pm$ .04 mg/dl vs 3.84 $\pm$ .05 mg/dl for the control group. When serum albumin concentrations were reviewed with respect to gender and race and split by experimental vs control group, and diabetic status, no significant differences were determined (Appendix G). No significant difference was observed between the number of days each group spent in the hospital days or the number of hospital admissions and serum albumin concentrations (Appendix G). Subjects dialyzing for a greater number of hours per treatment did not achieve a significantly higher serum albumin concentration (Appendix G) although a positive correlation was observed ($p \leq 0.04$, $r = 0.40$). No difference in serum albumin concentrations could be determined between the control group, who had a lower overall average weight and the experimental group (Appendix G). Serum albumin concentrations were not statistically significant when compared to nPCR or between the two groups (Appendix G).

Figure 1: Correlation Between Kt/v and Serum Albumin Concentrations for 108 ESRD Patients on Hemodialysis



Cholesterol

The final overall mean for all 108 subjects for serum cholesterol was 177 $\pm$ 3.85 mg/dl by the end of the 12 month study. The control group exhibited a slightly higher cholesterol concentration (183.59 $\pm$ 37.59 mg/dl) than did the experimental group (170.89 $\pm$ 36.90 mg/dl), although this difference was not significant. No difference was observed between cholesterol concentrations and serum albumin concentration, nPCR, body weight, or days spent in the hospital (Appendix H). A positive correlation was observed between serum cholesterol and BUN ($p \leq 0.02$, $r = 0.49$). A difference was observed between serum cholesterol levels between Black males vs Caucasian males in the control group ($P \leq 0.05, t = -2.04$), although no other differences were observed between other racial groups or gender.

BUN

The final overall mean for serum BUN was 65.14 $\pm$ 1.43 mg/dl for all 108 subjects. The mean for the experimental group was slightly higher (68.35 $\pm$ 2.86 mg/dl) than for the control group (62.55 $\pm$ 1.80 mg/dl), however, this difference was not significant ($p = .0743$). Overall, a high percentage (43%) of serum BUN values fell below the goal of > 60 mg/dl. There was no significant difference in BUN values

observed between patients according to diabetic status or when adjusted for race and gender between groups (Appendix I). A positive correlation was seen between overall weight and BUN ($p \leq 0.003$, $r = 0.79$) however, that difference was not seen within the individual groups (Appendix I). A positive correlation was observed between the number of hours spent on dialysis during individual patient treatments and differences in BUN concentrations when the experimental group was compared to the control group ($p \leq 0.001$, $r = 0.61$). A strong positive correlation was observed between BUN and nPCR as expected ($p \leq .0001$, $r = 0.92$). An overall difference was observed between Black males vs Caucasian males ($p \leq 0.05$, $t = 2.04$) and Black males vs Caucasian males the control group ($p \leq 0.05$, $t = 2.04$).

Protein Catabolic Rate

The overall mean nPCR for the two groups was $1.01 \pm .02$ g/kg/d. Seventy-seven percent of the patients fell below the nPCR goal of 1.2g/kg/d. Eighty-eight percent of the individual nPCR levels were in the range of 1.0 - 1.2 g/kg/d and another 3% were greater than 1.2. Only 8% of our nPCR's fell below the 1.0 g/kg/d, considered as the minimum amount of protein recommended for ESRD patients in guidelines developed at the 1993 NIH Consensus Conference (10).

Mean nPCR values for the 12 month period were similar for the control group

(1.01 ± .03 g//Kg/d) and the experimental group (1.01 ± .03 g/Kg/d). Normalized Protein Catabolic Rate (nPCR) was similar between the two groups when compared according to race and gender (Appendix J). No significant relationship was observed between Kt/v levels and nPCR (Figure 2) . No significance was observed between the number of days a patient spent in the hospital, the number of hours spent during individual dialysis treatments and diabetic status or race (Appendix J).

Clinical Outcomes

Weight

Comparison of weight losses or gains, and overall weight changes between the two groups showed no significant differences over the course of the study. The mean weight for the control group (Kt/v 1.3) was 65.9 ± 2.00 Kg at the beginning of the study compared to 66.1 ± 2.07 Kg at the end of the study. The experimental group also showed no significant difference in weight from the beginning of the study (84.5 ± 2.41 Kg) until the end of the study (85.9 ± 2.87 Kg). During the 12 month study period, forty-two percent of the subjects lost weight, 28% gained weight, while the remainder (30%) were stable. A positive correlation was observed between weight and Kt/v levels ($p < 0.001$, $r = 0.92$,) (Figure 3) between the experimental vs control group. There was a trend toward a higher individual average weight with the control group.

Figure 2: Correlation Between Kt/v and Normalized Protein Catabolic Rate (nPCR) for 108 ESRD Patients on Hemodialysis

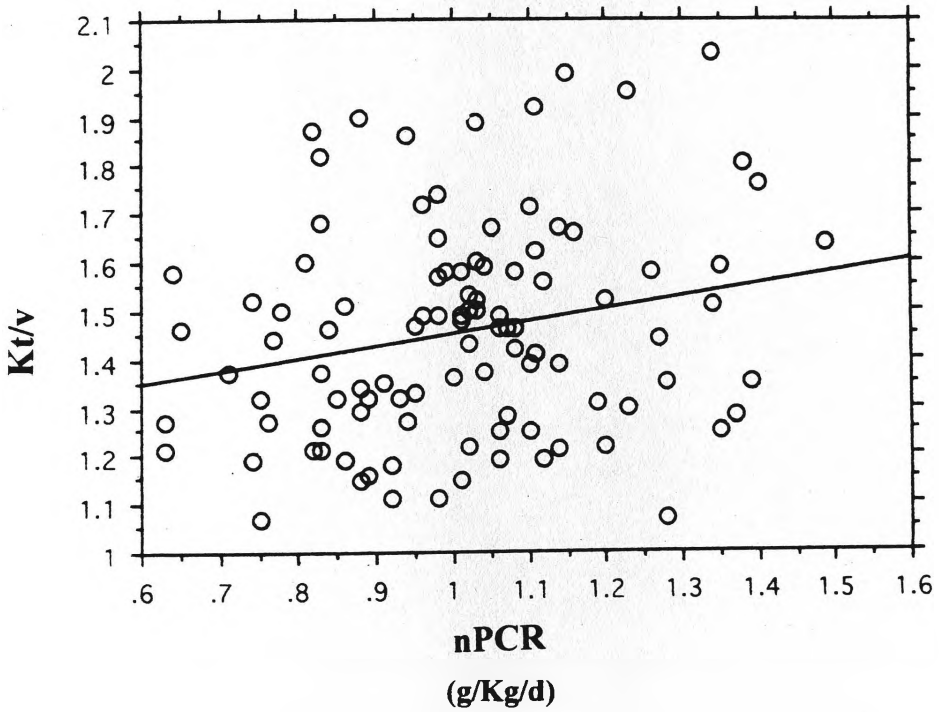
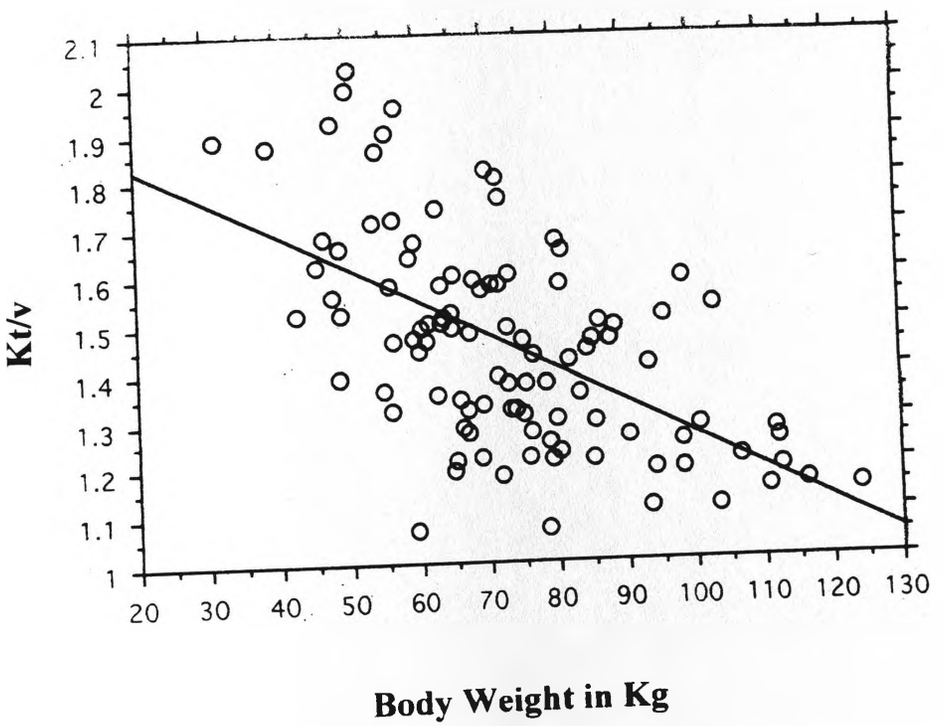


Figure 3: Correlation Between Kt/v and Body Weight for 108 ESRD patients on Hemodialysis



The average weight of the control group was 83.16 $\pm$ 18.0 Kg compared with 64.89 $\pm$ 14.6 Kg for the experimental group. No overall difference was observed between racial groups (Appendix K). A difference was seen in the experimental group between Black females vs Other females ($p \leq 0.03$, $t = 2.43$) and between Black males and Other males ($p \leq 0.04$, $t = 2.18$) (Appendix K).

Hospital Days/Admissions

Forty-nine patients (41.5 %) enrolled in the study were hospitalized during the 12 month study period. Thirty- two percent of the total number of hospital admissions involved patients who had problems which were related to access failures. No correlation was observed between the number of days patients spent in the hospital and overall Kt/v levels (Appendix L). There also were no differences in the number of hospital admissions between patients in the experimental and the control groups when adjusted for diabetic status (Appendix L). The average number of days spent in the hospital for both groups was 10.6 $\pm$ 1.5. The mean number of days spent in the hospital was 11.1 $\pm$ 1.1 for the experimental group vs 10.1 $\pm$ 2.1 days for the control group. The relationship between number of hospital admissions and Kt/v was not significant except during the month of July when one patient had an admission for a

psychiatric diagnosis and remained there all month. There was a trend toward an increased number days spent in the hospital for Blacks as compared to patients of other races but not considered significant (Appendix L). The mean length of hospitalization for Black males was 21 days vs 12.2 days for Caucasian males and 6.6 for other (Asians, Mexican-Americans) although this did not prove to be statistically significant ($p \leq 0.07$). Fifty- three percent of the subjects were hospitalized over the course of the study. No significance was observed between days spent in the hospital and albumin and total cholesterol concentrations, serum BUN, nPCR, weight, age, or time on dialysis (Appendix L). Significance was also not observed when the data were adjusted for gender and race (Appendix L).

Mortality

Seven subjects (5.9%) enrolled in the study died within the study period. Causes of death were: cardiomyopathy (n = 3), Cerebrovascular Accident (n = 2), unknown (n = 1); withdrew from dialysis (n = 1).

The mean Kt/v levels calculated for the patients who died ($1.4 \pm .02$) were the same as the patients who survived ($1.4 \pm .02$). Mortality rates were not significantly different between the control group and the experimental group (experimental group; n = 4; control group; n = 3). No trends were identified between any nutritional parameters and mortality.

CHAPTER V

DISCUSSION

Malnutrition among dialysis patients has been correlated with an increase in morbidity and mortality (23,24,34). Although multiple factors are known to contribute to malnutrition among this population, inadequate dialysis has been postulated as a major contributor (13,16,42). The quantity of dialysis delivered to the patient is one factor to be considered in overall patient care. If the patient is to feel the benefits of dialysis, the optimal dialysis prescription must include measures that promote patient comfort and quality of life as well as those that reduce morbidity and mortality (40).

Nutritional Outcomes

Serum albumin has been shown to be a strong predictor of nutritional risk and measure of nutrition stores in the hemodialysis population (36). A surprising lack of correlation between serum albumin concentration, hospitalizations, and weight loss was found in this study. Acchiardo, et al. (22) identified malnutrition as a primary factor in morbidity and mortality as reflected by low nPCR values. Owen, et al. (63) showed a

positive correlation between increased doses of dialysis and serum albumin levels. These findings have been corroborated by Canadian investigators (64), Markman (26), and others (28,34). However consistent with this present study, Hemmelfarb, et al. (23) found no statistical difference in serum albumin concentrations with the lower Kt/v group (< 1.3) vs a higher Kt/v group (> 1.3). This phenomena could be attributed to the short study period when compared to other investigations. The relationship of an increased Kt/v was also thought to diminish the importance of serum albumin as an independent predictor of mortality. The lack of correlation in our study may have also been attributed to the narrow range of Kt/v values studied. The average nPCR value of 1.0 g/kg/d may also have been a factor. Although 1.2 g/kg/d of protein has been recommended as the "ideal" intake for patients receiving hemodialysis, there are no clinical studies to confirm this level. The NIH Consensus Conference in 1993, only recommended liberalization of protein to 1.0 g/kg/day for hemodialysis patients (10).

Low cholesterol concentration, another index of malnutrition has been correlated with increased mortality in two separate studies when found in conjunction with decreased serum albumin concentrations (24,28), however, no correlation was observed in this study. A statistically significant difference was found between serum cholesterol concentrations and serum BUN concentrations ($p \leq 0.02$, $r = 0.49$) which could be

related to a higher protein intake, although a similar increase in nPCR values and serum albumin concentrations were not observed. This could be related to the fact that monthly blood work does not representing a fasting state.

A strong positive correlation was observed ($p \leq 0.0001$, $r = 0.92$) between Predialysis BUN and PCR values indicating a higher protein intake with higher BUN concentration. This relationship has also been found in numerous other studies and is related to urea generation rate and protein intake. The average BUN for the control group (65 mg/dl) was slightly lower than the experimental group (68 mg/dl). The reverse was expected because the control group had a higher overall weight than the experimental group and was therefore assumed to have a higher protein and energy intake. The overall difference between Black males and Other males was attributed to the higher overall weight and probable muscle mass in the later group. A difference was seen between Black males vs Caucasian males in the control group ($p \leq 0.05$) although no explanation could be found.

Several methods have been used to evaluate the protein intake of patients undergoing hemodialysis therapy. Normalized Protein Catabolic Rate (nPCR) through UKM is one of the most accepted method. When a patient is not catabolic or anabolic, net protein catabolism as measured by urea appearance is approximately equivalent to

dietary protein intake. Inadequate dietary protein intake has been shown to positively correlate with PCR (24). Numerous factors may affect the protein intake and metabolism during dialysis. An adequate nPCR level of 1.3 -1.4 g/kg/d has been suggested as needed to maintain lean body mass (11). However, assessment of DPI is difficult owing to patient problems and financial constraints. Evaluating the patients intake of DPI by dietary recall with the dietitian is neither practical nor reliable because of the high patient to dietitian ratio in most dialysis centers. Measuring PCR by UKM has been shown to avoid the pitfalls related to the patient's inability to recall food eaten or provide written food diaries. It also represents a more objective measure by which to assess the patient.

Several studies correlate PCR with adequacy of dialysis (15,23,65). Our study found no significant correlation between nPCR and Kt/v values. Blake, et al (11), were also unable to find a relationship between Kt/v and nPCR, hospitalization and death. Morgenstern, et al (32) suggested that a low Kt/v may be significant only if correlated with patients who had a low PCR. Analysis of low PCR values (< 0.8g/kg/day) with Kt/v levels showed no relationship to morbidity and mortality in this study. Hakim, et al (15) found a statistically significant correlation between nutrition factors (albumin, transferrin and PCR) and higher Kt/v levels when viewed over a 4 year period of

time. Their study found that patients whose Kt/v averaged ≥ 1.2 over the study period had a significantly higher nPCR than those patients whose average Kt/v level over the course of the study was ≤ 0.86. They concluded that increases in Kt/v levels correspond with an increase in dietary protein intake. This phenomenon supports other studies in which patients who were considered inadequately dialyzed ($Kt/v < 0.8$) by currently accepted standards ($Kt/v \geq 1.2$), showed improvements in nutrition parameters when Kt/v levels were increased (15,16). This study failed to demonstrate a correlation between a low PCR value (≤ 0.8 g/kg/d) and Kt/v levels. In other studies where patients were dialyzed to higher Kt/v's (1.6 - 2.6) levels, the correlation with PCR was found to be linear (zero slope), suggesting no further benefit in nutritional parameters or outcome measures when dialyzing to higher levels. A similar study demonstrated no further improvement when Kt/v level was increased beyond 1.2 (2). Additionally some studies suggest that since Kt/v and PCR (measured by UKM) are mathematically related, increasing Kt/v levels will automatically result in increases in PCR values. However, this relationship is still being debated (13).

A strong negative correlation was shown to exist between a patient's weight and Kt/v levels ($p \leq 0.0001$, $r = 0.92$) for both the experimental vs the control group. The control patients average weight was 20 Kg higher than the experimental groups

average weight. However, despite an increase in the average individual dialysis treatment time for the experimental group (3.5hours) with the higher weight vs the control patient's group (4.0 hours) with the lower weight, the control group had a lower overall Kt/v. This could be related to decreased compliance by the patient with the prescribed dialysis prescription or an inadequate dialysis prescription (i.e. dialyzer with lower than needed clearance, low blood flow rate, or dialysate flow rate). The same relationship was seen when overall Kt/v levels were compared to time spent with individual dialysis treatments (hours dialyzed). This suggests that we may be dialyzing patients more by convention and formula than by individual patient needs (i.e. looking at individual patient weight, compliance with dialysis time and prescription, etc. we just look at the numbers). There was also a tendency to accept a lower but passable Kt/v level (i.e. Kt/v level = 1.18, 1.17; minimum goal for Kt/v = 1.2), without adjusting dialysis variables to meet the minimum goal. Adjustments in the dialysis prescription often took several months months to be implemented.

Additional analysis of patient's weight ranges between the control group vs the experimental group (Appendix K) noted a higher number of heavy patients ($\geq$ 90 Kg) in the control group and a correspondingly high number of low weight ($\leq$ 50 Kg) patients in the experimental groups, which may have skewed the results.

Clinical Outcomes

Hemodialysis patients in the United States have the higher mortality compared to other industrialized nation (10,16). Suggested reasons for this include the Medicare reimbursement schedule, patient demographics, patient preference, and inadequate quantity of dialysis (BB). Using multivariate analysis, Held, et al. (42) found adequacy of dialysis to be the dominant factor.

The overall mortality in this study deviated from that reported by others (15,16). This difference in mortality could be attributed to the short period of time of the study when compared to previous studies. Other factors include differences in the Kt/v values reviewed (High initial Kt/v levels compared to other studies 1.2 in this study vs $\leq$ 1.0 in other studies) and the type of membranes used in the dialyzers (81% biocompatible membranes utilized in this study).

Studies on morbidity and mortality in Europe have shown an improved morbidity and mortality rate with higher Kt/v levels ($\geq$ 1.5) however, the Europeans also dialyze their patients for longer periods of time (6 - 8 hours) and have used the dialyzers with the more biocompatible membranes for many years. They also have more

restrictive dialysis policies eliminating poor compliance by the patient with the dialysis prescription.

Morbidity and mortality are highly influenced by age and diabetes, these parameters were evaluated in this study, however, no correlation in Kt/v levels was found. The lower diabetic population in Europe and Japan may also contribute to the lower mortality and morbidity rates in diabetic patients which are thought to influence both nutrition and clinical outcomes. Although one would expect to see a correlation between increased age and number of hospitalizations and days spent in the hospital, this study did not find one. The overall age of this study population was high (59.8 ± 1.5 years) and therefore could have accounted for the lack of findings in this area.

Although no correlation could be found between nutrition outcomes and morbidity, a difference in gender and race was noted. A review of reasons for hospital admissions indicated Black males were admitted more frequently for reasons which might be attributed to noncompliance with dialysis; such as CHF and access problems. No statistical significant difference was seen between the control group when compared to the experimental group regarding differences in the number of admissions to the hospital per patient and the total number of days spent in the hospital by each patient.

Several groups have identified serum albumin concentrations as a strong

predictor of morbidity and mortality (23,28,36). Morgenstern, et. al (32), found a negative correlation between serum albumin concentrations and mortality, although they did not find any statistical significance. In this study, only one of the patients who expired had a serum albumin concentration of < 3.5 g/dl for several months prior to death.

Acchiardo, et al. (22) found that a progressive increase in BUN concentration and nPCR correlated with a decrease in the number of hospitalizations, suggesting higher protein intake and assumed increase in nutrition parameters. In their study, patients with a nPCR value of < 0.9 g/kg/d were hospitalized four times as long as those with a PCR > 1.0 g/kg/d. Again, this could be related to the low percentage of patients with PCR < 0.9 g/kg/d compared with other studies. Acchiarado, et al (22) also found a strong correlation between PCR values and morbidity and mortality. They considered the low PCR (< 0.8g/kg/d) to be a high nutrition risk owing to the marginal intake of dietary protein of the subjects. Little success was seen in their study in the improvement of nutrition status as evidenced by increases in nPCR values, despite aggressive nutrition intervention . They attributed it to the low socioeconomic status and eating, habits which are difficult to change. The ethnicity breakdown, 91% Black was considered a contributing factor. This study had a 39% Black population. This study

found no correlation between those individual patients with low PCR averages (< 0.9 g/kg/d), Kt/v and increased number of hospitalization per patient or total number of days spent in the hospital. Again this could be attributed to the reasons for hospitalizations and the short period of time of the study. Reasons for hospitalizations relating to non compliance with the dialysis prescription (CHF, hyperkalemia) and access related admissions usually do not impact nutrition parameters over the short period of time of this study.

Numerous studies have correlated increased mortality rates with Kt/v levels < 1.0. Higher Kt/v levels are thought to improve appetite and increase both DPI and urea generation rate. Lowrie, et al. (37) have shown the relative risk of mortality's decrease as Kt/v increases from 1.3 to 1.6 although that relationship was not seen in this study. Parker, et al (16) suggested a greater improvement in mortality in terms of maximum urea removal, by improving values of Kt/v which are < 1.0 to Kt/v values > 1.0. They also indicate diminishing returns as Kt/v levels increase beyond 1.5. Hemmelfarb, et al (23) found that patients with a Kt/v < 1.3 have a higher rate of mortality when compared with a Kt/v > 1.3. However, it was not clear what range of values were included in the high and low groups.

CHAPTER VI

SUMMARY AND CONCLUSIONS

In conclusion, many of the factors that contribute to morbidity and mortality in the dialysis population may be preventable. The patient, as well as the health care team must take an active role in prevention of these problems. Attention to factors which affect the dialysis prescription (i.e. lab procedures and techniques, delivery of prescribed dialysis time) and the way the information and data is collected by the staff and patients is paramount to reducing the risk of morbidity and mortality.

The influence of the dose of dialysis on nutrition status has been assessed in only a few studies. In many of these the Kt/v level was low (< 1.0). Increasing the dose of dialysis to > 1.0, was shown to clear uremia better and thereby improve appetite and food intake (13). The question remains as to whether increases in Kt/v levels above currently accepted standards (1.2), will lead to further increases in protein and calorie intake. Moreover it is not known whether increases in protein intake will a) increase significantly to cause a substantial increase in nutritional status, b) the effect will occur in a large portion of the dialysis population, and c) whether it will ultimately effect outcome parameters. Additionally, it is not known if increasing Kt/v levels ≥ 1.5 and in theory eradicating the uremic condition, will effect the severity of the patients

comorbid conditions, and appetite and oral intake. Current research is ongoing in this area.

Although one could say there is still a higher overall mortality in the U.S. than in other industrialized nations, the differences in hypothesized inadequate time spent during individual dialysis treatments as addressed by compliance issues, blood and dialysis flow rates, and membrane compatibility use between these nations is being reviewed (10).

While this study showed no significant correlation between the control and the experimental group, differences in outcome between different Kt/v levels may be more obvious over a longer period of time as demonstrated by studies in Europe and Japan. Cost of health care remains a concern especially with the increasing population of ESRD patients. At what level, there is a decreasing cost: clinical benefit ratio to increasing Kt/v is yet to be determined. Issues related to reimbursement and outcome remain to be settled. This and other questions are being investigated in a recently initiated NIH 5 year, multi-center study. It is well documented that malnutrition increases health care costs. Ongoing assessment of nutrition status in these patients is warranted to identifying the risk factors for developing malnutrition and provide both medical and nutritional therapy.

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APPENDICES

APPENDIX A

Institution Approval

nmc Dialysis Services Division
National Medical Care, Inc.

Bio-Medical Applications of Fort Worth
Tarrant County Nephrology Center
1408 St. Louis
Fort Worth, Texas 76104
(817) 921-5191

2/28/94

To: Graduate School
Texas Woman's University

From: J. Patrick Brennan
President: Dialysis Associates

Approval has been granted to conduct research on "The Correlation Between Adequacy of Dialysis and Overall Nutritional Status in the ESRD Patient." As outlined in the attached prospectus by Eileen Baugh. It has been reviewed and approved by the Medical Staff.

J. Patrick Brennan, MD

APPENDIX B

Human Research Committee Approval

TEXAS WOMAN'S UNIVERSITY

DENTON/DALLAS/HOUSTON

HUMAN SUBJECTS REVIEW COMMITTEE

OFFICE OF
RESEARCH AND
GRANTS ADMINISTRATION
P.O. Box 22939
Denton, TX 76204-0939
Phone: 817/898-3375

May 16, 1994

Eileen Baugh
C/O Dr. George Liepa
Nutrition & Food Sciences

Dear Eileen Baugh: Social Security #: 547-96-7509

Your study entitled "Correlation between Adequacy of Dialysis and Overall Nutritional Status in the End Stage Renal Disease Population" has been reviewed by a committee of the Human Subjects Review Committee and appears to meet our requirements in regard to protection of individuals' rights.

Be reminded that both the University and the Department of Health and Human Services (HHS) regulations typically require that agency approval letters and signatures indicating informed consent be obtained from all human subjects in your study. These are to be filed with the Human Subjects Review Committee. Any exception to this requirement is noted below. This approval is valid one year from the date of this letter. Furthermore, according to HHS regulations, another review by the Committee is required if your project changes.

Special provisions pertaining to your study are noted below:

___ The filing of signatures of subjects with the Human Subjects Review Committee is not required.

___ Other:

_X_ No special provisions apply.

Sincerely,

Chair
Human Subjects Review Committee - Denton

cc: Graduate School
Dr. George Liepa, Nutrition and Food Sciences
Dr. Dorice Czajka-Narins, Nutrition and Food Sciences

APPENDIX C

Consent Form

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN A RESEARCH PROJECT

Tittle of Study: Correlation of Kt/v and it's Relationship to Nutritional Status

Institution: Tarrant County Nephrology Center; West Fort Worth
Dialysis Center, Cleburne Dialysis Center

Patient Name: _____

Investigators:	Office Phone Number
Eileen Baugh RD	921 - 5191
J. Patrick Brennan MD	921 - 5191
Michael Stoltz MD	921 - 5191
Richard Mauk MD	921 - 5191
Charles Andrews MD	738 - 8703
Rubina Khan MD	921 - 5191
Douglas Meyers MD	738 - 8703

1. Nature and Purpose of study:
I understand I am being asked to volunteer to take part in a research study which will assess if a improved dialysis clearance (represented by a increase in my "Kt/v: of 1.5 or greater from the usual 1.2, which is standard in the renal community) will improve my overall nutritional status and enable better long term control of uremic symptoms. No procedures involved are considered experimental.

2. Explanations of the procedures to be followed:
Calculation of dialyzer clearance during a dialysis treatment will be measured. Based on measurement, dialyzer type, blood flow rate, dialyzer flow rate, dialyzer time will be adjusted to reach a minimum "Kt/v" of 1.5.

3. Foreseeable risks and discomforts:
I understand that the procedures outlined involve no discomfort to me. There may be a change in the length of my dialysis treatment and/or a change in the type of dialyzer I use. No risks are involved above those for hemodialysis.

4. Benefits:
I understand the possible benefits of the study are as follows:
Improved overall nutritional status; better long term control of uremic symptoms.

5. Removal from study:
I understand the physician in charge of the study can remove me from the study without my consent for the following reasons:
--failure to comply with dialysis prescription
--acute problem requiring hospitalization
--initiation of Intradialytic Parenteral Nutrition

6. Offer to answer questions about this study:
If I have any questions during this study, I should contact my physician or the dietitian. I will be made aware of changes made as a result of all laboratory work done.

7. Withdrawal:
I understand I am free to withdraw my consent and discontinue my participation in this study at any time. I understand that such a decision on my part will not influence the availability of future medical care.

Any offer to answer all my questions regarding the study has been made and I have been given a copy of the dated and signed consent form. A description of the possible attendant discomforts have been discussed with me. I understand that I may terminate my participation in this study at any time. I have read, or have had read to me in my first language, the above information. The content and meaning have been fully explained to me. I herby voluntarily consent and offer to take part in this study.
I agree the results of my treatment, including laboratory tests may be published for scientific purposes, provided my identity is not revealed. I understand the information contained in these records will be kept confidential. If you have any questions or concerns about the way this research has been conducted, contact the Texas Womans University Office of Research and Grants Administration at 817-898-3375. I understand that no medical service or compensation will be provided to me by the University as a result of injury from participation in research.

_____ _____
Patient's signature Date

_____ _____
Investigator's signature (RD) Date

_____ _____
Investigator's signature (MD) Date

APPENDIX D

Categorization of Optimal Nutritional Status

Categorization of Optimal Nutritional Status for Study Population of Study Population

	NUTRITIONAL STATUS			
PARAMETER	**OPTIMAL**	**MILD**	**MODERATE**	**SEVERE**
SERUM:				
ALBUMIN (g/dl)	**> 4.0**	**3.5 - 3.0**	**3.0 - 3.4**	**< 3.0**
CHOLESTEROL (mg/dl)	**> 160**	**--**	**--**	**--**
BUN (mg/dl)	**> 60**	**--**	**--**	**--**
nPCR (g/kg/d)	**1.2 - 1.4**	**1.0 - 1.1**	**0.8 - 0.9**	**< 0.8**
WEIGHT:				
% IBW	**80 - 100**	**60 - 80**	**40 - 60**	**< 40**
% USUAL	**90 - 100**	**80 - 90**	**70 - 80**	**< 70**

Reference: Lowrie,E Lew,N. Death Risk in hemodialysis patients: the predicitive value of commonly measured variables and an evaluation of the death rate differences between facilities. Am J Kid Dis. 42:15 (5): 458-482,1990.

APPENDIX E

Calculation of Protein Catabolic Rate

CALCULATIONS FOR PROTEIN CATABOLIC RATE

$PCR = (6.25) (U_{Ur} + F_{Ur} + 11.86 + 0.196 + W (kg)$

U_{Ur} = urine urea nitrogen (in anephric patients = 0) (g/day)
F_{Ur} = dialysate urea loss to protein breakdown
6.25 converts nitrogen loss to protein breakdown
11.86 is the mean losses of protein in amino acids into dialysate
0.194 X weight represents the mean loss of miscellaneous nitrogen compounds

$nPCR = PCR/W (kg)$

Teehan B,Brown J,Schleifer C. Clinical Dialysis (2nd edition).
Nissenson A, Fine R,Gentile D. (eds).Appleton and Lange 1990:319-329.

APPENDIX F

Kinetic Modeling Calculations for Kt/v

KINETIC MODELING CALCULATIONS FOR Kt/V

Calculation: 1. $Kt/V = -1n\ (1- \frac{URR}{100})$

This formula can be fit statistically to general form.

2. $Kt/V = B_1\ 1n\ (1- \frac{URR}{100})$

Where Bs are statistical coefficients. The best fit values are $B_1 = 1.309$ and $B_2 = 102.07$.

3. Therefore, the modified formula for Kt/V is:

$$Kt/V = - 1.309 \text{ X } 1n\ (1 - \frac{URR}{102.7})$$

Reference: Lowrie E, Lew N. The urea reduction ratio (URR). Contemporary Dialysis and Nephrology 1991, Feb:11-19.

APPENDIX G

Relationship Between Serum Albumin Concentrations and Various Clinical and NonClinical Parameters

Relationship Between Serum Albumin Concentrations, Racial Groups and Gender

Serum Albumin Concentrations Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Serum Albumin Concentrations and Various Clinical and Non Clinical Parameters

PARAMETER COMPARED	VALUE
Kt/v	$p \leq 0.80$
Diabetic Status	$p \leq 0.75$
Weight	$p \leq 0.32$
Cholesterol	$p \leq 0.11$
BUN	$p \leq 0.04$ $r = 0.40$
PCR	$p \leq 0.67$
Number of Days Hospitalized	$p \leq 0.86$
Time on Dialysis	$p \leq 0.04$ $r = 0.40$
Age	$p \leq 0.41$
Experimental vs Control Group	$p \leq 0.57$

Relationship Between Serum Albumin Concentrations, Racial Groups and Gender

PARAMETER COMPARED	VALUE
Race:	
Black vs Caucasian	**$p \leq 0.53$**
Black vs Other	**$p \leq 0.75$**
Caucasian vs Other	**$p \leq 0.44$**
Race:	
Control group	
Black vs Caucasian	**$p \leq 0.80$**
Black vs Other	**$p \leq 0.88$**
Caucasian vs Other	**$p \leq 0.98$**
Experimental group	
Black vs Caucasian	**$p \leq 0.64$**
Black vs Other	**$p \leq 0.57$**
Caucasian vs Other	**$p \leq 0.30$**
Gender	
Control Group	
Black Female vs Caucasian Female	**---**
Black Female vs Other Female	**$p \leq 0.15$**
Caucasian Female vs Other Female	**---**
Black Male vs Caucasian Male	**$p \leq 0.14$**
Black Male vs Other Male	**$p \leq 0.33$**
Caucasian Male vs Other Male	**$p \leq 0.97$**
Experimental Group	
Black Female vs Caucasian Female	**$p \leq 0.64$**
Black Female vs Other Female	**$p \leq 0.51$**
Caucasian Female vs Other Female	**$p \leq 0.73$**
Black Male vs Caucasian Male	**$p \leq 0.08$**
Black Male vs Other Male	**$p \leq 0.77$**
Caucasian Male vs Other Male	**$p \leq 0.33$**

Serum Albumin Concentrations Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Racial Group & Sex	(averaged over 12 months of study) Mean (g/dl)
Albumin overall	3.8 ± 0.03
Experimental Group,Black Female	3.7 ± 0.06
Experimental Group, Black Male	4.0 ± 0.15
Experimental Group, Caucasian Female	3.8 ± 0.06
Experimental Group,Caucasian Male	3.8 ± 0.07
Experimental Group, Other Female	3.8 ± 0.15
Experimental Group, Other Male	3.8 ± 0.25
Control Group, Black Female	3.5 ± 0.08
Cotrol Group, Black Male	3.9 ± 0.07
Control Group, Caucasian Female	3.9 ± 0.01
Control Group, Caucasian Male	3.8 ± 0.09
Control Group, Other Female	3.8 ± 0.07
Control Group, Other Male	3.8 ± 0.19

APPENDIX H

Relationship Between Serum Cholesterol Concentrations and Various Clinical and NonClinical Parameters

Relationship Between Serum Cholesterol Concentrations, Racial Groups and Gender

Serum Cholesterol Concentrations Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Serum Cholesterol Concentrations and Various Clinical and Non Clinical Prameters

PARAMETER COMPARED	VALUE
Kt/v	$p \leq 0.79$
Diabetic Status	$p \leq 0.35$
Weight	$p \leq 0.07$
Albumin	$p \leq 0.44$
BUN	$p \leq 0.62$
PCR	$p \leq 0.44$
Number Days Hospitalized	$p \leq 0.82$
Time on Dialysis	$p \leq 0.46$
Age	$p \leq 0.59$
Experimental vs Control Group	$p \leq 0.20$

Relationship Between Serum Cholesterol Concentrations, Racial Groups and Gender

PARAMETER COMPARED	VALUE
Race	
Black vs Caucasian	$p \leq 0.32$
Black vs Other	$p \leq 0.86$
Caucasian vs Other	$p \leq 0.34$
Race:	
Control Group	
Black vs Caucasian	$p \leq 0.07$
Black vs Other	$p \leq 0.89$
Caucasian vs Other	---
Experimental Group	
Black vs Caucasian	$p \leq 0.96$
Black vs Other	$p \leq 0.73$
Caucasian vs Other	$p \leq 0.66$
Gender	
Control Group	
Black Female vs Caucasian Female	---
Black Female vs Other Female	$p \leq 0.89$
Caucasian Female vs Other Female	---
Black Male vs Caucasian Male	$p \leq 0.05$ $t = -2.04$
Black Male vs Other Male	$p \leq 0.43$
Caucasian Male vs Other Male	$p \leq 0.10$
Experimental	
Black Female vs Caucasian Female	$p \leq 0.51$
Black Female vs Other Female	$p \leq 0.60$
Caucasian Female vs Other Female	$p \leq 0.31$
Black Male vs Caucasian Male	$p \leq 0.73$
Black Male vs Other Male	$p \leq 0.97$
Caucasian Male vs Other Male	$p \leq 0.66$

Serum Cholesterol Concentrations Separated According to Final Grouping (Experimental vs Control) Racial Group and Gender

Racial Group ad Sex	(averaged over 12 months of study) Mean (mg/dl)
Cholesterol Overall	177 ± 3.85
Experimental Group, Black Female	187 ± 10.9
Experimental Group, Black Male	187 ± 26.5
Experimental Group, Caucasian Female	178 ± 8.3
Experimental Group, Caucasian Male	186 ± 12.6
Experimental Group, Other Female	199 ± 17.7
Experimental Group, Other Male	175 ± 17.6
Control Group, Black Female	174 ± 15.2
Control Group, Black Male	160 ± 7.1
Control Group, Caucasian Female	194 ± 0.1
Control Group, Causian Male	186 ± 10.2
Control Group, Other Female	170 ± 16.5
Control Group, Other Male	145 ± 25.2

APPENDIX I

Relationship Between Serum BUN and Various Clinical and NonClinical Parameters

Relationship Between Serum BUN, Racial Groups and Gender

Serum BUN Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Serum BUN Concentrations and Various Clinical and Non Clinical Parameters

PARAMETER COMPARED	VALUE
Diabetic Status	$p \leq 0.88$
Weight	$p \leq 0.003$ $r = 0.79$
Albumin	$p \leq 0.09$
Cholesterol	$p \leq 0.62$
nPCR	$p \leq 0.001$ $r = 0.61$
Number Days Hospitalized	$p \leq 0.51$
Time on Dialysis	$p \leq 0.56$
Experimental vs Control	$p \leq 0.001$ $r = 0.61$

Relationship Between Serum BUN Concentrations According to Final Grouping (Experimental vs Control), Racial Group and Gender

Racial Group & Sex	(averaged over 12 months of study) Mean (mg/dl)
BUN Overall	65 ± 1.4
Experimental Group, Black Female	64 ± 3.6
Experimental Group, Black Male	66 ± 7.0
Experimental Group, Caucasian Female	63 ± 3.1
Experimental Group, Caucasian Male	58 ± 3.3
Experimental Group, Other Female	57 ± 4.5
Experimental Group, Other Male	65 ± 9.1
Control Group, Black Female	65 ± 5.4
Control Group, Black Male	75 ± 4.1
Control Group ,Caucasian Female	78 ± .01
Control Group, Caucasian Male	72 ± 4.7
Control Group, Other Female	72 ± 4.7
Control Group, Other Male	76 ± 2.3

Relationship Between Serum BUN Concentrations, Racial Groups and Gender

PARAMETER COMPARED	VALUE
Race:	
Black vs Caucasian	**$p \leq 0.05$ t = 2.04**
Black vs Other	**$p \leq 0.70$**
Caucasian vs Other	**$p \leq 0.30$**
Race:	
Control group	
Black vs Caucasian	**$p \leq 0.13$**
Black vs Other	**$p \leq 0.67$**
Caucasian vs Other	**$p \leq 0.14$**
Experimental group	
Black vs Caucasian	**$p \leq 0.42$**
Black vs Other	**$p \leq 0.54$**
Caucasian vs Other	**$p \leq 0.93$**
Gender	
Control Group	
Black Female vs Caucasian Female	**---**
Black Female vs Other Female	**$p \leq 0.59$**
Caucasian Female vs Other Female	**---**
Black Male vs Caucasian Male	**$p \leq 0.05$ t = 2.04**
Black Male vs Other Male	**$p \leq 0.90$**
Caucasian Male vs Other Male	**$p \leq 0.15$**
Experimental Group	
Black Female vs Caucasian Female	**$p \leq 0.95$**
Black Female vs Other Female	**$p \leq 0.70$**
Caucasian Female vs Other Female	**$p \leq 0.73$**
Black Male vs Caucasian Male	**$p \leq 0.25$**
Black Male vs Other Male	**$p \leq 0.71$**
Caucasian Male vs Other Male	**$p \leq 0.11$**

APPENDIX J

Relationship Between Normalized Protein Catabolic Rate and Various Clinical and NonClinical Parameters

Relationship Between Normalized Protein Catabolic Rate and Racial Groups and Gender

Normalized Protein Catabolic rate According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Normalized Protein Catabolic Rate (nPCR) Calculations and Various Clinical and Non Clinical Parameters

PARAMETER COMPARED	VALUE
Kt/v	$p \leq 0.49$
Diabetic Status	$p \leq 0.98$
Weight	$p \leq 0.07$
Albumin	$p \leq 0.29$
Cholesterol	$p \leq 0.32$
BUN	$p \leq 0.0001$ $r = 0.92$
Number Days Hospitalized	$p \leq 0.54$
Time on Dialysis	$p \leq 0.97$
Age	$p \leq 0.38$
Experimental vs Control Group	$p \leq 0.79$

Relationships Between Normalized Protein Catabolic (nPCR) Separated According to Final Grouping (Experimental vs Control), Racial Groups and Gender

Racial Group & Sex	Mean (g/Kg/d)
nPCR Overall	1.00 ± .02
Experimental Group,Black Female	0.99 ± .05
Experimental Group,Caucasian Female	1.01 ± .04
Experimental Group, Other Female	0.90 ± .06
Experimental Group, Black Males	1.02 ± .11
Experimental Group, Caucasian Males	0.98 ± .06
Control Group, Black Female	1.02 ± .09
Control Group,Caucasian Female	---
Control Group, Other Female	1.01 ± .14
Control Group, Black Male	0.99 ± .05
Control Group, Caucasian Male	0.97 ± .05
Control Group, Other Male	1.11 ± .03

Relationship Between nPCR, Racial Groups and Gender

PARAMETER COMPARED	VALUE
Race:	
Black vs Caucasian	**$p \leq 0.79$**
Black vs Other	**$p \leq 0.62$**
Caucasian vs Other	**$p \leq 0.76$**
Control	
Black vs Caucasian	**$p \leq 0.71$**
Black vs Other	**$p \leq 0.22$**
Caucasian vs Other	**$p \leq 0.15$**
Experimental	
Black vs Caucasian	**$p \leq 0.61$**
Black vs Other	**$p \leq 0.73$**
Caucasian vs Other	**$p \leq 0.44$**
Sex	
Control Group	
Black Female vs Caucasian Female	**---**
Black Female vs Other Female	**$p \leq 0.72$**
Caucasian Female vs Other Female	**---**
Black Male vs Caucasian Male	**$p \leq 0.72$**
Black Male vs Other Male	**$p \leq 0.22$**
Caucasian Male vs Other Male	**$p \leq 0.19$**
Experimental Group	
Black Female vs Caucasian Female	**$p \leq 0.27$**
Black Female vs Other Female	**$p \leq 0.33$**
Caucasian Female vs Other Female	**$p \leq 0.06$**
Black Male vs Caucasian Male	**$p \leq 0.70$**
Black Male vs Other Male	**$p \leq 0.84$**
Caucasian Male vs Other Male	**$p \leq 0.53$**

APPENDIX K

Relationship Between Weight, Racial Groups and Gender

Weight Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Weight Measurements, Racial Groups and Gender

PARAMETER COMPARED	VALUE
Race	
Black vs Caucasian	**$p \leq 0.99$**
Black vs Other	**$p \leq 0.64$**
Caucasian vs Other	**$p \leq 0.43$**
Race :	
Control group	
Black vs Caucasian	**$p \leq 0.31$**
Black vs Other	**$p \leq 0.81$**
Caucasian vs Other	**$p \leq 0.67$**
Experimental group	
Black vs Caucasian	**$p \leq 0.62$**
Black vs Other	**$p \leq 0.69$**
Caucasian vs Other	**$p \leq 0.43$**
Gender	
Control Group	
Black Female vs Caucasian Female	**---**
Black Female vs Other Female	**$p \leq 0.51$**
Caucasian Female vs Other Female	**---**
Black Male vs Caucasian Male	**$p \leq 0.94$**
Black Male vs Other Male	**$p \leq 0.43$**
Caucasian Male vs Other Male	**$p \leq 0.44$**
Experimental Group	**$p \leq 0.66$**
Black Female vs Caucasian Female	
Black Female vs Other Female	**$p \leq 0.39$**
Caucasian Female vs Other Female	**$p \leq 0.03$ $t = 2.43$**
Black Male vs Caucasian Male	**$p \leq 0.13$**
Black Male vs Other Male	**$p \leq 0.04$ $t = -2.18$**
Caucasian Male vs Other Male	**$p \leq 0.24$**

Weight Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Racial Group & Sex	(averaged over 12 months of study) Mean (Kg)	Range (Kg)
Mean Overall Weight	73.0 + 1.8	
Experimental Group,Black Female	66.7 ± 3.4	46.5 - 85.7
Experimental Group, Black Male	56.8 ± 7.6	39.0 - 83.3
Experimental Group, Caucasian Female	62.5 ± 3.3	31.6 - 95.6
Experimental Group,Caucasian Male	71.8 ± 3.2	60.2 - 102.8
Experimental Group, Other Female	50.4 ± 2.9	42.7 - 55.8
Experimental Group, Other Male	72.5 ± 10.0	50.5 - 98.5
Control Group, Black Female	72.8 ± 6.6	80.9 - 106.5
Control Group, Black Male	85.1 ± 4.2	59.3 - 124.0
Control Group, Caucasian Female	112.0 ± 0.0	112.0 - 112.0
Control Group, Caucasian Male	85.1 ± 4.2	60.1 - 116.3
Control Group, Other Female	63.3 ± 6.0	57.3 - 69.3
Control Group, Other Male	92.5 ± 8.6	75.2 - 112.5

APPENDIX L

Relationship Between Total Number of Days Hospitalized and Various Clinical and NonClinical Parameters

Relationship Between Total Number of Hospital Days, Racial Groups and Gender

Total Number of Hospital Days Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Relationship Between Total Number Days Hospitalized and Various Clinical and Non Clinical Parameters

PARAMETER COMPARED	VALUE
Diabetic Status	$p \leq 0.12$
Weight	$p \leq 0.46$
Albumin	$p \leq 0.86$
Cholesterol	$p \leq 0.37$
BUN	$p \leq 0.45$
nPCR	$p \leq 0.38$
Time on Dialysis	$p \leq 0.96$
Age	$p \leq 0.78$
Experimental vs Control Group	$p \leq 0.76$

Relationship Between Total Days Hospitalized and Racial Group and Gender

PARAMETER COMPARED	VALUE
Race	
Black vs Caucasian	$p \leq 0.18$
Black vs Other	$p \leq 0.23$
Caucasian vs Other	$p \leq 0.53$
Race :	
Control group	
Black vs Caucasian	$p \leq 0.81$
Black vs Other	---
Caucasian vs Other	---
Experimental group:	
Black vs Caucasian	$p \leq 0.11$
Black vs Other	$p \leq 0.21$
Caucasian vs Other	$p \leq 0.80$
Gender	
Control Group	
Black Female vs Caucasian Female	---
Black Female vs Other Female	---
Caucasian Female vs Other Female	---
Black Male vs Caucasian Male	---
Black Male vs Other Male	$p \leq 0.66$
Caucasian Male vs Other Male	---
Experimental Group	
Black Female vs Caucasian Female	$p \leq 0.43$
Black Female vs Other Female	$p \leq 0.56$
Caucasian Female vs Other Female	$p \leq 0.88$
Black Male vs Caucasian Male	$p \leq 0.17$
Black Male vs Other Male	$p \leq 0.36$
Caucasian Male vs Other Male	---

Total Number of Days Hospitalized Separated According to Final Grouping (Experimental vs Control), Racial Group and Gender

Racial Group & Sex	(averaged over 12 months of study) Mean (days/year)
Number of Hospital Days Overall	10.7 ± 1.5
Experimental Group,Black Female	15.7 ± 4.9
Experimental Group, Black Male	21.0 ± 13.6
Experimental Group, Caucasian Female	10.9 ± 3.3
Experimental Group,Caucasian Male	6.7 ± 3.7
Experimental Group, Other Female	9.5 ± 8.5
Experimental Group, Other Male	6.7 ± 2.3
Control Group, Black Female	8.7 ± 5.6
Control Group, Black Male	12.4 ± 5.1
Control Group, Caucasian Female	9.0 ± 0.0
Control Group, Caucasian Male	10.1 ± 2.7
Control Group, Other Female	1.0 ± 0.0
Control Group, Other Male	---

APPENDIX M

Definitions

Definitions

BFR = Blood Flow rate: amount of blood that flows through the dialyzer per minute of dialysis time.

DFR = Dialysate Flow Rate: speed at which the dialysate flows through the dialyzer.

BUN = a blood test which measures urea nitrogen levels in the serum in mg/dl.

PCR = Protein Catabolic Rate: the rate at which protein is catabolized into urea (g/day), during the modeling period.

nPCR = PCR normalized to the patients body weight (PCR divided by the patients in kilograms).

UKM = Urea Kinetic Modeling: mathematical model that attempts to simulate the amount of urea from, to, and within the body during and between hemodialysis; tool to measure the effectiveness of dialysis and to examine certain patient variables that are difficult to measure by other means; provides a sensitive test of actual dialysis outcome compared with expected dialysis outcome.

Uremia: refers to a variety of nonspecific complaints and physical symptoms that manifest as a patient's renal function falls below 5% of normal.

Creatinine: produced from muscle from an irreversible dehydration of unstable creatinine phosphate.

Urea: end product of nitrogen metabolism in mammals.

Middle molecules: molecular weight in the 350 - 500 dalton range that are poorly dialyzed across a conventional cellulostic membrane.