NUTRITIONAL ANALYSIS AND COMPARISON OF SERUM INSULIN CONCENTRATIONS PRE- AND POST- HEMODIALYSIS IN A DIABETIC END STAGE RENAL DISEASE POPULATION

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BY CHERIE M. CRAFT, B.S.

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ABSTRACT

NUTRITIONAL ANALYSIS AND COMOPARISON OF

SERUM INSULIN CONCENTRATIONS

PRE- AND POST-HEMODIAYSIS IN A DIABETIC

END STAGE RENAL DISEASE POPULATION

AUGUST, 1999

Diabetics comprise a growing percentage of the population with end stage renal disease commencing dialysis therapy. The purpose of this study was to determine the nutritional status and serum insulin concentrations pre- and post-hemodialysis of this population. Sixty-seven adults who received daily insulin injections and attended hemodialysis therapy thrice weekly completed the study. The subjects used high efficiency, high flux and conventional dialyzers.

The serum insulin concentrations were determined in duplicate, using a solid phase ^{125}I radioimmunoassay procedure. Upon comparison, using a Student's paired t test, the total sample's mean post-hemodialysis serum insulin concentration was significantly lower than the mean pre-hemodialysis serum insulin concentration ($p < 0.05$).

The subject's nutritional intake histories were recorded for typical dialysis and non-dialysis days. The records were analyzed, using the Nutritionist IV Dietary Analysis Computer Program, version 3.5. Age and sex appropriate

Recommended Dietary Allowances were used for each subject and the goals were set at 67% of the RDAs. The goals for energy and protein intake were calculated for each subject, based on estimated dry weight. The energy intake goal was 35 kcal/kg/day and the protein intake goal was 1.5 gm/kg/day. There were no significant differences between the mean nutrients intakes on the two typical days. The mean intakes of six nutrients were below the goals on one or both days. For dialysis and non-dialysis days, the mean energy intakes were 60.67 $\pm$ 23.57 (21.23 kcal/kg) and 62.94 $\pm$ 25.67 (22.03 kcal/kg) and the mean protein intakes were 72.07 $\pm$ 31.49 (1.08 gm/kg) and 71.93 $\pm$ 31.49 (1.079 gm/kg), respectively. Both energy and protein intakes were signficantly less that the goal of 100% ($p < 0.0001$).

Vitamin D, calcium and magnesium were significantly less than the goal of 67% of the RDAs on one or both days ($p < 0.02$). Zinc intake was deficient on one day, but not statistically significant. Many nutrients had mean intakes of 0%.

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CHAPTER I

INTRODUCTION

Approximately sixteen million individuals in the United States have diabetes mellitus and the 1999 estimate from the National Institutes of Health, is that over five million are unaware of their diagnosis (1). Almost 800,000 new cases are diagnosed annually (1). The cost of diabetes is staggering, both financially and in human morbidity and mortality. In the United States, direct and indirect costs totaled $98 billion in 1997, which is a six billion increase since 1992 (1,2). Death certificate data for 1996 identified diabetes as a primary or secondary cause of death of 193,140 individuals which is a marked increase over the 169,000 diabetes related deaths in 1992 (1,2). Diabetes mellitus was ranked as the seventh leading cause of death by disease in 1996 and is the major contributing factor to the most prevalent causes of death, heart disease and stroke (1). Frequently observed sequelae of diabetes include cardiovascular disease, hypertension, blindness, neuropathy, amputations, periodontal disease and renal disease (1).

Renal disease associated with diabetes is a progressive, degenerative condition of the blood filtering units of the kidney known as the glomeruli (3). Diabetic glomerlulosclerosis is the term applied to all glomerular lesions

produced by diabetes mellitus (4). There are five stages of the disease process, each evidencing deteriorating structural and functional capabilities (3). While progressing through the first four stages, the individual advances along a continuum on which, initially, they will be asymptomatic but will advance to a point of significant disturbance in lifestyle. The final stage is end stage renal disease (ESRD) and is referred to in the vernacular as kidney failure. While most, if not all diabetics have some glomerular changes, the majority do not develop ESRD (3,5). Diabetes is the most common cause of ESRD and 30,933 diabetic individuals comprised 42.3% of the 73,091 newly diagnosed cases in 1996 (6). Data collected in 1996 and reported in 1998 by the United States Renal Data System, states that 283,932 Medicare funded individuals received treatment for ESRD and 92,211 (32.5%) had the primary diagnosis of diabetes mellitus (6).

End stage renal disease is financially devastating and most individuals in the United States are eligible for federal financial support from the time of diagnosis. Since the institution of Medicare reimbursement in 1973, the enrollment of patients has steadily increased by geometric proportions and diabetics comprise an increasing proportion of these admissions (7). In 1996, a total of $14.6 billion was spent in this country for the provision of ESRD care and Medicare paid $11 billion (75%) of this amount (6). This amount represents a 15% increase over the $9.3 billion spent in 1994 (3). In 1996, the Medicare cost per patient for ESRD was $44,000 and for each individual receiving

hemodialysis, the amount was $55,000 (6). As the population of America continues to increase and as a greater percentage of the population is sixty-five years old and older (therefore with enhanced risk for diabetes mellitus and ESRD), the financial burden of managing kidney disease is projected to increase significantly, if not exponentially.

There are only three options for persons diagnosed with ESRD – dialysis, organ transplantation and death (3). With the shortage of available organs for transplantation, the vast majority of people are left with the option of dialysis as a treatment modality. Many people are not considered candidates for transplantation and not all transplants are successful, so some patients revert back to dialysis therapy. In the embryonic days of hemodialysis, diabetics were not considered acceptable subjects for dialysis, but currently they comprise an increasing percentage of the dialysis patients world wide and particularly in this country (3,8).

The process of dialysis has been greatly refined since its inception in the 1930s, but much remains unknown regarding optimal treatment regimes. This lack of knowledge is magnified and critical for the diabetic who receives dialysis therapy. The microvascular and other metabolic/physiological complications of diabetes continue their rampage despite the life-sustaining effects of dialysis (9,10). The diabetic who begins dialysis has a statistically significant shorter life expectation than the dialysis patient without diabetes (6,9,11).

The Handbook of Dialysis (12) lists "No protein loss to dialysate" as one of the advantages of hemodialysis. The loss of amino acids into the dialysate is well documented, yet the protein insulin, molecular weight 5808, has been assumed to be too large to pass through the dialysis membrane (8,12,13,14,15). Bellomo et al. (16) conducted a study of sixteen traumatized patients, including one diabetic, in an intensive care unit, receiving hemodialysis therapy for acute renal failure. They determined the serum levels of glucose and insulin as well as the glucose and insulin concentrations in the untradiafiltrate prior to and following hemodialysis. The researchers verified insulin losses across the filter into the untradiafiltrate, but not at a level of statistical significance. There is a dearth of scientific information on the effects of dialysis upon serum insulin levels in maintenance hemodialysis patients.

Insulin is required for metabolic utilization of the three energy yielding nutrients: carbohydrates, protein and lipids (17). The relative lack of insulin necessitates the ingestion of a proper diet as the most important component of a diabetic treatment regime. Hypoalbuminemia is a hematological marker of diminished protein stores (18). There are many other predisposing factors to hypoalbuminemia, but inadequate nutritional intake is a prominent dietary concern for uremic individuals (18,19,20,21). The absolute necessity of adequate nutrition is a basic tenet of dialysis care as many ESRD patients are malnourished (12,19,22). Minimal nutritionally related research has been

attempted beyond those studies which have examined protein and/or energy requirements for the uremic diabetic individual.

Statement of the Problem

Diabetics constitute a major proportion of the ESRD population and their morbidity and mortality, as compared with the non-diabetic ESRD group, is significantly greater. Researchers have focused on identifying risk factors such as sex, age, race and the impact of co-morbid conditions in an attempt to explain why diabetics suffer greater consequences. The physiological difference is the pancreas' inability to regulate serum insulin levels in response to food and stressors in the diabetic. Scientists have not determined what, if any effect, hemodialysis has on serum insulin concentrations. Both diabetics and uremic individuals are nutritionally at risk and the effect is magnified in the individual with both diagnoses. There were two goals which served as the focus for this study. The first was to examine the serum insulin concentrations prior to and following hemodialysis to determine if a change of serum insulin concentration occurred that was associated with the process of hemodialysis. The other goal was to identify the current nutritional status of diabetic individuals receiving hemodialysis therapy by documenting the serum albumin concentrations and comparing the reported nutritional intake with the Recommended Dietary Allowances (RDAs).

Purpose of the Study

The purpose of the study was to determine the nutritional status and serum insulin levels pre- and post-hemodialysis in a diabetic ESRD population that receives exogenous insulin injections.

Objectives of the Study

Specific objectives of this study were:

1. to compare serum insulin concentrations pre and post hemodialysis in a diabetic population.
2. to analyze the subjects self-reported nutritional intake on a 'typical dialysis day' and compare the results with the RDAs for the appropriate sex and age group.
3. to analyze the subjects self-reported nutritional intake on a 'typical non-dialysis day' and compare the results with the RDAs for the appropriate sex and age group.
4. to compare the two nutritional analysis reports to determine if a difference exists between the dialysis days and the non-dialysis days.
5. to document the serum albumin concentrations.
6. to identify when the subjects eat in relation to the timing of their hemodialysis therapy.
7. to identify when the subjects take their insulin in relation to the timing of their hemodialysis therapy.

Null Hypotheses

There will be no significant difference in the serum insulin concentrations as measured prior to and following hemodialysis in a diabetic population.

There will be no significant differences between the reported nutrient intakes on a typical dialysis day as compared with a typical non-dialysis day in a diabetic ESRD population.

CHAPTER II

LITERATURE REVIEW

Diabetes Mellitus

History

Diabetes mellitus was first described in the writings of ancient civilizations. The word "diabetes", meaning 'to flow through' was used by the Roman Aretaeus (A.D.70) as he described the symptoms of polydipsia and polyuria. In 1675, a London physician, Thomas Willis, noted the urine's sweet taste and added the word "mellitus" (or 'honeylike') as compared with diabetes insipidus in which the sweet taste was not present in the urine (17). The classic symptoms of polydipsia, polyuria and polyphagia were well documented although there was no effective treatment and the patients died, often having lain for months in what we now know as a diabetic ketoacidotic coma.

Primitive diabetic nutritional therapy regimes recommended carbohydrate replacement for the losses noted in the urine, but the relative lack of circulating insulin prevented successful abatement of the symptoms. Dietary prescriptions have changed radically throughout history and have included recommendations for varied restrictions on carbohydrates and/or proteins, intermittent 24-hour fasts, and the promotion of various carbohydrate sources such as rice, milk,

potatoes and oatmeal (17). When insulin was isolated in 1921, many thought that it was a cure, but time did not bear out this prediction (23).

Metabolic Disturbance

Diabetes is a metabolic disorder that impacts all facets of the individual's physiology, including carbohydrate, protein and lipid metabolism/utilization, with varying degrees of morbidity (17,24). A lack of insulin, total or diminished, coupled with cellular insulin resistance is the causative agent for the domino effect throughout the diabetic's body (25,26). Insulin resistance is an integral component of both types of diabetes and is most evident in hyperinsulinemic states (27). The two classifications of diabetes, Types I and II, are differentiated at the time of diagnosis. The diabetic population is composed of 5 -10% Type I diabetics and 90 - 95% Type II diabetics (3,5,17).

An absolute lack of insulin, resulting from an auto-immune destruction of pancreatic Islet of Langerhans beta cells, is the diagnostic criterion for Type I diabetes mellitus (23,28). The treatment regime for Type I, known as insulin dependent diabetes mellitus (IDDM), requires proper diet, regular exercise and daily insulin injections. If a Type I diabetic chooses to not take insulin, then severe consequences, including death, will ensue. Children and young adults diagnosed with diabetes are always Type I and in rare instances, some mature adults are diagnosed with IDDM (24).

Type II diabetes is a metabolic disturbance that occurs in individuals who are usually at least forty years of age, often are overweight (> 115% of desirable body weight), and have a sedentary life style (24,28,29). The cause of Type II diabetes mellitus has not been fully elucidated, but its physiological effects are due to the combination of three major metabolic disturbances: impaired insulin secretion, peripheral insulin resistance (receptor and post-receptor defects) and increased basal hepatic glucose production. (23,30). Optimal treatment for Type II diabetes requires proper diet and regular exercise. Unlike Type I diabetics, Type II diabetics may maintain glycemic control without medication, but often require oral hypoglycemic medication to stimulate pancreatic insulin production and/or diminish the effects of cellular insulin resistance (3,17). Some Type II diabetics exhibit uncontrolled hyperglycemia, and therefore, require insulin to maintain glycemic control, but they are still properly classified as Type II diabetics (28,31).

Diabetes, as well as other disorders concerning altered insulin and glucose metabolism, are poorly understood, despite years of research (32). There exist aberations in glucose metabolism, unrelated to pancreatic function, in which serum glucose concentrations are beyond the normal range, yet below that which is diagnostic of diabetes (12,33). Glucose intolerance which resembles the pattern of Type II diabetes during a glucose tolerance test (GTT), has been documented in non-diabetic uremic individuals (34). The GTT curves of twelve uremic individuals were compared with those of fourteen age and sex matched

non-uremic controls. Compared with the controls, the uremic subjects evidenced a higher mean fasting glucose, a normal rise, but significantly elevated serum glucose concentrations at 60 minutes ($p < 0.02$) and also at 90 and 120 minutes ($p < 0.001$). These results indicate that the diabetic individual who also is uremic has a dual mechanism of altered glucose metabolism.

Diabetic Nephropathy

Functional diabetic nephropathy is the most serious complication of diabetes (35,36). Diabetic renal disease is a multi-stage condition requiring several years to become clinically evident (5). Most diabetics do not develop nephropathy to the severity of being diagnosed with End Stage Renal Disease (ESRD), yet Diabetes Mellitus has consistently been identified as the leading single cause (35.9%) of ESRD (3,5). Diabetes, as a primary diagnosis of nephropathy, accounted for 42.3% of the total new cases of Medicare funded individuals who began treatment for ESRD in 1996 (6).

Physiological and Functional Alterations

Alterations in the renal hemodynamics of diabetics have been documented by scientists for more than sixty years (37). The basic lesions commence in the microvasculature (37). The progression of diabetic microangiopathy has been delineated as beginning with altered local blood flow followed by progressive reversible dilatation of the small vessels. Periodic arteriole vasoconstriction

interfaces with the formation of sclerotic lesions of the arterioles, small veins and capillaries. The slowly progressive microcirculatory decompensation leads to clinically overt symptoms such as retinopathy and nephropathy (37). The pathogenesis of the microvascular changes is not clearly understood and theories attempting to explain the phenomena discuss metabolic abnormalities, genetic predisposition, hemodynamic alterations and an activated immunological process (38,38).

The five stages of developing chronic renal failure advance along a continuum and the initial physiological damage begins insidiously, often concurrent with or prior to the diagnosis of diabetes (3,40). Functional abnormalities are associated with the microvascular changes found in diabetics (32). Deterioration takes place in and around the glomeruli which are the blood filtering units of the kidneys (3). Damaged glomeruli cannot be restored to their prior level of activity (3). The hallmark of glomerulosclerosis is the thickening of the glomerular capillary basement membranes which eventually leads to the total occlusion of many glomeruli (39,41,56). Glomerulosclerosis is generally believed to be a slow and gradual process (39).

The first functional changes are those of hyperfunction and hypertrophy evidenced by a marked increase in the glomerular filtration rate (GFR) (3,5,40,42). The increased GFR is induced by several mechanisms, but it is generally concluded that it is associated with nephron hypertrophy and specifically

glomerular enlargement (3,39,43,44). A close correlation has been demonstrated between glomerular surface area and GFR (42,45). Upon microscopic examination of both diabetics and control subjects, Kroustrup et al. (46) found an 80% enlargement of the capillary basement membrane ($p = 0.009$) and a 70% increase in the glomerular tuft surface ($p = 0.03$) was verified in the diabetics. Both hypertrophy and hyperplasia are associated with these type of lesions (5,39,47).

Renal dynamic alterations may be hormonally influenced/mediated (43). Hyperglycemia and hyperinsulinemia both predispose compensatory renal hypertrophy (43). Renal tissue growth is influenced by glucose metabolism and insulin can act as a growth factor (48). Research has documented instances of significantly decreased GFR, renal plasma flow and renal hypertrophy following three months of intensive insulin therapy in newly diagnosed Type I diabetics, but reversal of diabetic nephropathy has not been demonstrated (3,32,42).

During the second stage, the GFR remains elevated or returns to a normal rate and microalbuminuria, defined as urinary albumin losses of 20 – 200 mcg/minute, is intermittently present (3). The basement membrane is the only complete anatomic barrier between the plasma and its filtrate (32). Thickening of the glomerular capillary basement membrane diminishes its capability to serve as a selective filter (32). The third stage is marked by urinary losses of albumin and other proteins at rates > 200 mcg/minute (3). Increased glomerular damage evidenced by albuminuria and proteinuria, and elevated serum concentrations of

creatinine and blood urea nitrogen (BUN) are hallmarks of stage three. During stage four, known as Overt or Advanced Clinical Nephropathy, the GFR is decreased to < 75 ml/minute, proteinuria is increased, hypertension is present, and increasingly elevated serum concentrations of BUN and creatinine are noted (3). When the GFR diminishes to < 10 ml/minute, ESRD is diagnosed and the person is in the fifth and final stage of the continuum. The symptoms of renal failure remain covert until kidney function is < 25% normal, but then the decline is relentless (57,58). In comparing diabetic individuals and non-diabetics with glomerulonephritis, both beginning hemodialysis therapy, the diabetics have a higher GFR and more severe proteinuria (49).

Incidence

Thirty to forty percent of Type I diabetics develop clinical nephropathy, identified by a GFR < 75 ml/minute and persistent proteinuria, within fifteen to twenty years following diagnosis of IDDM (3,5,50). The median time span between the appearance of gross proteinuria and the diagnosis of chronic renal failure is seven years, with a range of two months to twenty-two years (5,7,39). An unknown percentage of Type II diabetics develop end-stage renal disease, but it is generally considered to be a lesser percentage, possibly 3 – 8% overall (39,47). Type II diabetics advance to stage four or stage five less often than Type I diabetics, but 60% of diabetics with ESRD are Type II (3). The higher absolute number of Type II diabetics with ESRD is attributed to the ten times

greater number of Type II diabetics as compared to those with Type I.

A retrospective incidence cohort study to identify the incidence of chronic renal failure (CRF) by type of diabetes included 1,832 Type II diabetics and 136 Type I diabetics (7). The incidence of CRF was 28% higher in the Type I diabetics, but the actual number of cases of CRF that developed in the cohort was over eight times higher in Type II diabetics. The type II diabetics seem to exhibit proteinuria sooner after their diagnosis of NIDDM than Type I diabetic individuals, but this may be related to delayed diagnosis of NIDDM (39). Once the diabetic is diagnosed with proteinuria, the rate of decline has been shown to vary little between Type I and Type II diabetics (51). More Type II diabetics have renal disease unrelated to their diabetes when compared with Type I, whose incidence of ESRD is almost entirely a diabetic complication (39,52,53).

Proteinuria

Proteinuria, defined as urinary protein loss at least equal to 200 mcg/minute has been accepted as the hallmark of diabetic nephropathy and progressive renal failure (3,39,41,54). The presence or absence of proteinuria at the time of diagnosis of diabetes has been found to be predictive of the clinical expression of chronic renal failure. In a retrospective incidence cohort study which included 1,832 NIDDM subjects, the subset of 133 with proteinuria at the time of diagnosis with diabetes presented with CRF at 5, 10 and 15 years in the percentages of 7%, 8.4% and 11.6%, respectively (7). The 1,699 Type II

subjects who did not have proteinuria at diagnosis, developed CRF at 10, 15, 20 and 30 years at the rate of 0.3%, 0.5%, 3.2% and 9.4%, respectively. The expression of proteinuria has been attributed to both increased porosity and also to isolated defects in the membrane barrier to protein filtration (54).

Proteinuria is primarily albuminuria (43). Microalbuminuria, a sub-clinical elevation of urinary albumin excretion detected by radioimmunoassay is the earliest expression of and strongest predictor of overt proteinuria (36,39). The rate of decline in the GFR negatively correlates with the rate of urinary albumin losses ($r = 0.58$, $p < 0.005$) (59). The diagnostic clinical criterion for microalbuminuria is the excretory rate of > 20 mcg/minute but < 200 mcg/minute, and some place the lower limit at 10 mcg/minute (3,5,39,41). The normal range for urinary albumin loss is 2.3 – 8.3 mcg/min with a mean of 4.3 mcg/min (39). The incidence of microalbuminuria increases with the duration of diabetes and once diagnosed, it presents a twenty fold greater risk for the expression of clinically overt renal disease for diabetics (5). A significant correlation has been documented between the percentage of global glomerulosclerotic lesions and the log of urinary albumin excretion ($p < 0.001$) (4). Type I diabetics often exhibit microalbuminuria within a year after diagnosis and Type II diabetics frequently present with urinary albumin losses at the time of diagnosis (5). Mogensen (55) followed 76 Type II diabetic patients for nine years who presented with an initial urinary albumin excretion of 30 – 140 mcg/ml. Also included in the study were 129 Type II diabetic subjects with microalbuminuria at rates < 30 mcg/ml.

Twenty two percent of the subjects with excretion rates of 30 – 140 mcg/ml developed clinical proteinuria as compared with 5% of the patients with a urinary albumin loss of < 30 mcg/ml.

Theories

Tight glycemic control is reported to be important in limiting and/or delaying the serious comorbid complications (retinopathy, peripheral vascular disease, neuropathy and nephropathy) associated with diabetes mellitus (3,5,24,38,49,50.60,61,62,63). Seemingly contradictory evidence exists as instances are documented that indicate that these complications occur in those individuals (5% of diabetics) who have maintained very rigid glycemic control while others (20 – 25%) who consistently have hyperglycemia suffer minimal complications (38). While glycemic control has been shown to influence microvascular renal damage in the early stages, research has not verified this benefit in the latter stages. Viberti et al. (64) studied 12 IDDM patients with proteinuria and found that the group (n = 6) with continuous subcutaneous insulin infusion and maintaining tight glycemic control continued their unabated rate of decline of renal function just like the subjects (n = 6) with conventional diabetic control. They propose that once glomerular function has begun to fail, it is a self-perpetuating process and not influenced by glycemic control. The abnormalities of basement membranes are not restored with insulin administration (32).

Two generally accepted theoretical notions have emerged regarding the development of diabetic complications; they are the genetic and the metabolic theories. The work of Siperstein et al. (65) provides support for the genetic theory. They documented that 98% of diabetic adult subjects had significant capillary basement membrane thickening. They also examined thirty normo-glycemic adults, each with two diabetic parents, and verified that 53% had capillary membrane hypertrophy. These findings support the association between diabetes and thickened basement membranes and also indicate that basement membrane hypertrophy may precede any glycemic abnormalities.

The metabolic theory is based on the premise that hyperglycemia is required for the microvascular hypertrophic changes to occur. Mauer et al. (66) examined renal transplant tissue in twelve diabetics and twenty eight non-diabetics. Ten of the twelve diabetics evidenced vascular lesions characteristic of diabetes by the third year post transplant. The non-diabetic patients evidenced vascular lesions in three of the twenty-eight subjects, but not until after five years. Raskin and Rosenstock (38) propose that the miocrovascular complications associated with diabetes are caused by an interplay of both genetic and metabolic influences.

Morbidity and Mortality

The long term outcome for both types of diabetes is determined by the incidence

of ESRD and cardiovascular disease (5). Type of diabetes has not been shown to have a significant impact on the rate of survival (49). Although dialysis has been an accepted therapeutic option for more than thirty-five years, the mortality rate overall is unacceptably high (6,67). Held et al. (68) analyzed the five year survival rate of 4,661 ESRD patients and found that those with diabetes of either type had a 261% relative risk of death compared with those in the reference group with a low risk primary disease, and a low risk to no risk complicating condition(s).

Koch et al. (70) monitored 196 subjects to assess rates of survival at 36 months after initiating hemodialysis and found that 40% of Type I and 43% of Type II diabetics were deceased. At fifty seven months, 43% of the Type I and 62% of the Type II were deceased. No deaths were attributed to the assessment of mal-nourishment, using the Body Mass Index (BMI) wt(kg)/ht(m^2). Type I diabetics' mean BMI was 24.6 and Type II mean BMI was 25.7. Twenty five percent of the subjects were below normal values, but there was no significant difference in regard to nutritional status of those who died of cardiac or non-cardiac causes, such as septicemia.

Despite its obvious life extending value, dialysis does not alter the multi-system involvement of end stage diabetic nephropathy (9,10). When compared with non-diabetic hemodialysis patients, diabetics have more problems with angio-access, hypertension, hypotension, congestive heart failure (CHF), peripheral vasclular disease (PVD), cerebral vascular disease (CVD), progressive

bone disease, retinopathy and increased rates of infection (39). Investigators (69) have verified over an eleven year period that the number of diabetics entering dialysis with one comorbid condition decreased from 60% to 34%. During this same time frame, the number of diabetics entering dialysis with two, three and four comorbid conditions has steadily increased from 30% to 48%. This change has obvious implications for the mortality rate of these individuals. The comorbid conditions identified in the study population include arteriosclerotic heart disease (ASHD), cerebral vascular disease, peripheral vascular disease, cancer and chronic obstructive pulmonary disease (COPD). Acknowledging the complexities of the diabetic ESRD individual, one can understand their greater incidence of mortality as compared with non-diabetic ESRD individuals (69,70).

Nutritional Considerations

For humans to survive and thrive, nutrients must be ingested in sufficient quantities to serve as metabolic fuel and provide resources for tissue growth/maintenance and the regulation of cellular and metabolic processes (18). If an insufficient amount of a macronutrient or essential micronutrient such as an amino acid or vitamin is ingested so that the body's requirement is not met, there will be serious consequences. The time span required for the consequences to become evident is determined by the individual's metabolic needs and nutritional stores. Often the nutritional deficiency will be clinically covert for a prolonged

period of time prior to the appearance of physiological symptoms, and may only be discovered by lab assays or by metabolic experiments. When morbidity occurs, mortality can follow if the deficit is not corrected. Not until morbidity and mortality occur, do vital statistics reflect the nutritional deficiency (18). Physicians fail to formally establish a diagnosis of malnutrition in dialysis patients and this omission has obvious implications for the statistical data (71).

Diabetes and Renal Disease

Appropriate nutritional intake is vital in the clinical management of both diabetes mellitus and renal disease. Kopple stated in his McCollum Award Lecture in 1998 that the nutritional management of chronic renal failure is in its infancy (71). The primary goal of nutritional therapy in both disease states is the prevention of malnutrition (72). Both the pancreas and the kidneys are necessary for optimal utilization of nutrients. Insulin is critical to macronutrient metabolism and the kidney plays a major role in macro- and micronutrient metabolism, and also participates in insulin clearance. The uncontrolled diabetic milieu suppresses protein synthesis while stimulating protein degradation. Metabolic acidosis, a result of poorly controlled diabetes, stimulates protein and amino acid degradation, especially of the branch chain amino acids (20,74,75). The inflammatory process and infection, often observed concurrently with diabetes and ESRD, also stimulate protein degradation (20). The diabetic with ESRD has multiple predisposing factors for nutritional concern, separate and apart from

the effects of the dietary limitations imposed by each disease.

When the diabetic exhibits clinical evidence of renal disease, major metabolic alterations are present and dietary limitations exceed basic glycemic control as the fluid, mineral and protein ingestion are also considered (72). The impaired ability to excrete substances such as water, sodium, magnesium, potassium, acid, phosphorus and nitrogenous metabolites dictate what is restricted in the diet plan (72). Compensating for the minimally or non-functioning kidney takes precedent over rigid glycemic control in nutritional prescriptions. Calorically dense foods are necessary to meet energy requirements and maintain a nutritional state compatible with life (72).

Multiple studies demonstrate that restricting dietary protein, in the early stages of renal decline, to no greater than 0.6 gm/kg/day can retard the progression and expression of diabetic nephropathy (76,77,78,79). Uremic symptoms can be diminished by decreasing the concentration of uremic toxins which are the end-results of protein metabolism. But many individuals remain asymptomatic or ignore their symptoms and, therefore, the disease becomes too advanced for protein limitation to be of benefit.

Less optimistic results were obtained by other scientists (81) who evaluated the effects of protein intake on renal function in 585 subjects with moderate renal decline (GFR = 25 – 55 ml/minute). They found that there was no statistically significant difference in the rate of decline between the subjects who ingested 1.3 gm/kg of protein and those who ingested 0.58 gm/kg. The same

researchers also examined the effects of protein restriction on 255 subjects with more severe renal insufficiency (GFR = 13 – 24 ml/minute). Some subjects ingested a low protein diet of 0.58 gm/kg while others followed a very low protein diet of 0.28 gm/kg. The subjects on the very low protein diet had only marginally slower decline in GFR ($p = 0.07$).

While the low protein diets are deemed nutritionally sound, close monitoring is required and at least half of the protein intake should consist of high biological value protein in order to prevent amino acid and protein deficiencies (74,78,82,83). The low protein diet which concurrently limits the intake of sulfates, phosphates, potassium and sodium, can diminish urinary protein losses, promote the increase of serum proteins, decrease the daily insulin requirement and ameliorate complications of uremia in CRF, such as metabolic acidosis, hyperkalemia and hypertension. (78,80). Lazarus (71) recommends promoting higher protein and energy intakes than often suggested, at the expense of increased potassium and phosphorus intake. This recommendation is based on the belief that malnutrition is a greater risk than hyperkalemia, cardiac arrythmias or metabolic bone disease. Protein energy malnutrition begins before the diagnosis of ESRD and therefore it is recommended that close attention be paid to the nutritional status of those in the early stages of chronic renal failure before dialysis is initiated (84).

Gastroparesis deabeticorum

Gastroparesis diabeticorum, is commonly shortened to simply 'gastroparesis' when discussing the diabetic, uremic population. The condition was first described in 1945 as a component of a generalized autonomic neuropathy and is a physiological complication of diabetes mellitus that affects the nutritional status beyond the effects of altered insulin concentrations (85). This condition is a chronic, relapsing neuropathy which clinically presents as intermittent episodes of nausea and vomiting, often persisting for days and is due to delayed gastric emptying in the absence of gastric outlet obstruction (73,85). Other symptoms include early satiety, epigastric pain/burning, post prandial fullness, weight loss and malnutrition (73,85). Characteristically, liquids empty into the duodenum at a normal rate while solid foods are retained in the stomach (85).

The etiology of this complication of diabetes has not been elucidated, but it has been noted that diabetics with uremia have higher incidence than non-uremic diabetics (85,86). Autonomic neuropathy, gastro-intestinal hormone abnormalities, hyperglycemia, altered insulin and glucagon secretion, medications, electrolyte imbalances, microvascular changes in the stomach and gastric angiopathy all seem to play a contributing role in diabetic gastroparesis (8,85). This complication is estimated to affect 20-50% of diabetics and some require long term nutritional support (85). Part of the nutritional impact gastroparesis is unpredictable nutrient absorption which predisposes the diabetic individual to

episodes of hyperglycemia and hypoglycemia (12).

Malnutrition and Renal Disease

Prior to the availability of renal replacement therapy, nutritional alterations were utilized to help decrease the symptoms of uremia. With the advent of dialysis, attention to nutrition decreased as the dialysis process alleviated many of the physiological symptoms which precipitated nutritional complications (87). Time and experience evidenced that dialysis was not a total replacement for the functioning kidney and poor nutritional states remained prevalent throughout the renal replacement therapy population. Nutritional complications are compounded when the dialysis patient is also diabetic and nutritional wasting tends to be greater in the portion of the ESRD population that has diabetes mellitus when compared with the non-diabetics (73). Understanding and preventing malnutrition will provide a basis for the better management of the nutritional needs for this population (87).

The National Cooperative Dialysis Study (NCDS) provided a longitudinal evaluation of nutritional status in patients receiving dialysis therapy (88). Parameters used to asses nutritional adequacy were five day food intake records (including both dialysis and non-dialysis days), anthropometric measurements and biochemical indices of protein metabolism. The mean caloric intake was 24 kcal/kg/day and the mean protein intake was 0.97 g/kg/day (88). The NCDS

excluded patients over 70 years of age, and those with diabetes, heart disease, uncontrolled hypertension, excessive weight gain and other pathological conditions. The NCDS demonstrated that even those subjects who are generally healthy have clearly defined nutritional deficiencies (88).

The term, 'malnutrition' refers to protein energy malnutrition (PEM) when discussing hemodialysis patients and can be used interchangeably with PEM in this situation. Malnutrition as a contributing factor to the unfavorable outcomes of the hemodialysis treatment for ESRD has been acknowledged for decades. Signs of malnutrition in hemodialysis patient include loss of energy stores (adipose tissue), loss of muscle mass, impaired wound healing, diminished concentrations of albumin, transferrin and other visceral proteins, and abnormal plasma amino acids (18). Malnutrition is rampant in patients with ESRD with the incidence reported as high as 25 – 70% (19,67,89,90). Clinicians must use the words 'associated' or 'related' and not 'cause' when discussing factors related to malnutrition and ESRD as much remains unknown (91). A myriad of predisposing/contributing factors of malnutrition are cited in the literature and may be grouped into the following categories: primary malnutrition, physiological, socio-psychological and iatrogenic (Table 1).

Table1. Factors Contributing to Malnutrition associated with ESRD

Primary Malnutrition

Decreased energy intake
Decreased protein intake

Socio-psychological

Depression
Lassitude
Impaired mental status
Socio-economic status
Family support

Iatrogenic

Protein and amino acid losses
Unpalatable diet prescription
Multiple medications
Recurrent hospitalizations
Inadequate dialysis prescription

Physiological

Anorexia
Nausea
Vomiting
Malabsorption – GI and renal
Co-morbid conditions
Insulin resistance
Acidosis
Constipation
Cytokine effects on CNS
Gastroparesis
Gastritis
Inactivity
Iron deficiency anemia
Fatigue
Impaired taste acuity
Altered dental status
Infection/Inflammation process
Altered protein and amino acid metabolism

(18,19,20,71,73,74,75,90,82,83,91,93,94)

The relative importance of the various factors that cause anorexia and stimulate protein catabolism is not well understood, but anorexia is the most frequently mentioned contributing factor to malnourishment (20). Anorexia is often attributed to the presence of uremic toxins, yet it can also be related to most of the other identified factors (20). It is a common clinical experience that uremic patients develop an improved appetite when they begin dialysis therapy (20). This finding suggests that one or more uremic toxins which promotes anorexia is removed during dialysis (20). Yet, Maroni (96) notes that it is not yet

proven that dialysis improves appetite or nutritional status. Many hemodialysis patients experience nausea and occasional vomiting for several hours following treatment, so increased nutritional intake between treatment days may be an effective measure to counter-balance the losses on dialysis days (73). Ingesting small volumes of calorically dense foods at frequent intervals is an effective therapeutic tactic (73).

Qureshi et al. (97) conducted a cross sectional study of 128 subjects (including 23 diabetics) to assess prevalence of and degree of protein energy malnutrition in hemodialysis patients, using Subjective Global Nutritional Assessment (SGNA). The six components of SGNA are history of weight loss, incidence of anorexia, incidence of vomiting, the presence of muscle wasting, the presence of edema and loss of subcutaneous adipose tissue. The subjects were evaluated and categorized into one of three classification groups. Group I (36%) was assessed to have normal nutritional status, Group II (51%) was determined to be mildly malnourished and Group III (13%) was found to have moderate to severe malnutrition. Sixty four percent of the subjects were determined to have some degree of malnutrition. The researchers found that diabetics composed 41% of Group III as compared with only 11% of Group I ($p < 0.05$).

Theoretical Causes of Malnutrition

Baltzan and Shoker (98) propose that there may be two types of protein malnutrition in dialyzed patients, each with a different etiology and response to dialysis. They propose that the presence of comorbid conditions is the cause of one type of malnutrition. These patients exhibit normal protein intake, increased protein catabolism and a lack of response to dialysis. The other type of malnutrition results from uremia and the patients exhibit decreased protein intake per kg of body weight with resultant decreased protein catabolism. This type of malnutrition is reversible by dialysis.

Another view of malnutrition is offered by Bistrian et al. (91) who identified that the two causes of malnutrition were either semi-starvation or a systemic inflammatory response. Anorexia causes decreased protein and/or energy intake which leads to a state of semi-starvation. With either protein or energy deficit, loss of lean body mass (which comprises 75 – 80% of body weight in the two compartment model of body composition) occurs. Morbidity and morality are both related to loss of lean body mass, rather than loss of fat mass. Feeding promotes anabolism by suppressing protein degradation with or without the stimulation of protein synthesis. The net response is a neutral nitrogen balance and preservation of lean body mass (96).

Bistrian et al. (91) has noted that malnutrition is not always alleviated with nutrition repletion therapy, and decided that another predisposing factor must exist. An inflammatory response of a systemic nature has been proposed as a

cause of anorexia and malnutrition in ESRD patients (91). The inflammatory response develops through neuroendocrine responses which result in mobilization of fuel stores: glucose, fatty acids and amino acids. The most sensitive marker of a systemic inflammatory response is depressed serum albumin which results from reduced synthesis, increased catabolism and extravascular extravasation (91).

Nutrient Requirements

Energy

It has been assumed and recorded in the literature that hemodialysis does not appreciably alter the caloric requirements of the renal failure patients (71,82). Ikizler et al. (99) utilized a whole-room indirect calorimeter to determine the resting energy expenditure on dialysis and non-dialysis days of hemodialysis patients as compared with matched controls. Twenty percent of their subjects were well controlled insulin dependent diabetics whose results, when analyzed separately, were found to be similar to the whole group. High flux and conventional dialyzers were used in this study. Paired t-tests were used to determine that there were no differences in the energy expenditure between the two dialyzers.

The chronic hemodialysis patients were found to have a significantly higher Resting Energy Expenditure (REE) both on dialysis days (pre, during and post treatment) and non-dialysis days than the matched controls

($p < 0.01$). These results have greater empirical meaning when one considers that the dialysis patients have no active renal function and functioning kidneys account for 8% of REE in normal individuals. On non-dialysis days, the dialysis subjects' REE was 1.18 $\pm$ 0.15 kcal/min as compared with controls' values of 1.10 $\pm$ 0.16 kcal/min. During the four hours of the dialysis procedure, the REE was 1.32 $\pm$ 0.18 kcal/ min. This level of energy expenditure is significantly greater than the predialysis period ($p < 0.01$) and the post-dialysis period and non-dialysis day REE each ($p < 0.001$). On dialysis days, the REE was 15-20% higher than the controls and on non-dialysis days, the REE was 7.5% higher than the controls. The researchers extrapolated the results of their study and adjusted for light physical activity on non-dialysis days to suggest an energy requirement of 36-39 kcal/kg per day which is higher than other estimates in the literature. For each 0.1 kcal/minute increase in REE, the hemodialysis patients can be expected to lose four to five kilograms of fat tissue from their reserves during a year. This increase in energy expenditure in light of the limited intake may account for at least part of the mal-nutrition found in dialysis patients.

A metabolic balance study to evaluate the effect of energy intake on nutritional status as measured by nitrogen balance, amino acid assessments and anthropometric measurements were conducted by Slomowitz et al. (100). The six clinically stable subjects each consumed diets containing 1.13 $\pm$ 0.02 g protein/kg/day and three caloric intake, 25, 35, 45 kcal/kg/day, each for twenty one to twenty three day periods. A direct correlation between energy intake and

nitrogen balance was confirmed. No statistically significant correlation was found between dietary energy intake and Resting Energy Expenditure. Nitrogen balances were adjusted for unmeasured losses (from skin, nail and hair growth, sweat, respiratory effort, tooth brushing, phlebotomy, and losses in the dialyzers) and were determined to be neutral with the 35 and 45 kcal/kg intakes and significantly negative with the 25 kcal/kg intake. The 25 kcal/kg intake was associated with weight loss, negative nitrogen balance and low plasma amino acid concentrations, increased body weight, neutral nitrogen balance and less abnormal amino acid concentrations were associated with the 35 kcal/kg intake. The highest caloric intake, 45 kcal/kg, was found to promote increased body fat and body weight, positive nitrogen balance and increased plasma amino acid levels. Regression analysis determined that neutral nitrogen balance was associated with a caloric intake, based on desirable body weight, between 32 and 38 kcal/kg/day.

The caloric needs of a dialysis patient are estimated to be 35 kcal/kg dry weight/day, but the range includes estimates of 25 – 40 kcal/kg/day (12,20,73,76,80,89,90,100). The ingestion of adequate calories for energy use is mandatory for maintaining energy stores and optimizing the use of ingested protein (18,80,82,100).

Protein

The protein requirement of hemodialysis patients is not well defined and variables include level of physical activity/inactivity, anemia, infections, metabolic acidosis, chemical abnormalities including endocrine disease (diabetes), inflammatory responses, drug therapy, cardiovascular disease and the hemodialysis procedure. All of the above have been shown to promote a state of net protein catabolism (18,20,22). The increased protein requirement and diminished utilization of ingested protein in hemodialysis patients, as compared with non-uremic individuals, indicates the presence of metabolic factors which are not corrected by dialysis and may enhance net protein catabolism and impair utilization of dietary protein (20).

The estimates of protein requirements for dialysis patients range from 1.0 gm/kg/day to greater than 1.5 gm/kg dry weight/day (14,18,20,73,82,86,88,89,91,102). It has been proposed that the protein needs of these individuals are met before the energy needs due to the bulk of food required to meet the energy needs (93). This notion was expanded to propose that the incidence of low energy intakes take precedence over low protein intakes and that energy malnutrition, independent of protein malnutrition may be a risk for increased morbidity and mortality in the ESRD population (93,101). When giving his McCollum Award speech in 1998, Kopple (72) stated "the single most decisive factor influencing protein-energy status in maintenance dialysis patients is probably their nutrient intake."

Ge et al. (103) assessed the nutritional status of 75 non-diabetic hemodialysis patients by nutritional analysis, anthropometric measurements, and laboratory measurement of serum proteins (albumin, transferrin, fibronectin, immunoglobulins and total lymphocyte count). The results were reported as means $\pm$ 1 standard deviation. The mean protein intake was 1.0 $\pm$ 0.2 gm/kg. Protein intakes < 1 gm/kg were documented for 38.7% of the subjects. Caloric intake was 28.1 $\pm$ 4.6 kcal/kg. Caloric intakes of < 30 kcal/kg were confirmed for 65.3% of the subjects. The researchers propose that energy deficiency may contribute to poor protein utilization. The group with protein intakes greater than 1 gm/kg and kcal > 30 kcal/kg had significant increases in relative body weight, tricep skin fold thickness, and higher albumin, transferrin and fibronectin values than the group with lower protein and energy intakes.

Micronutrients

Despite the minimal data available in the literature regarding micronutrient intake and nutritional status in dialysis patients, these nutrients must be considered in assessing nutritional adequacy. Similar to the macronutrients, insufficient dietary intake, altered metabolism, increased losses from the gastrointestinal tract and losses into the dialysate can predispose an individual to vitamin or mineral deficits (15). Clinicians and researchers concur that some form of supplementation is necessary in dialysis patients (15,73,72,82).

The first consideration is for the water soluble vitamins which all may be found in diminished levels due to the causes previously noted. The water-soluble B vitamins specifically B_6 and folic acid, are uniformly recommended for daily supplementation, at least at RDA doses, to counteract the effects of altered metabolism, dialysate losses and insufficient intakes (15,72,73). Vitamin B_6 intake has been assessed and recorded as 6.8 $\pm$ 3.1 mg/day in a study by Ge et al. which is well over the RDA, but this may not be indicative of the entire dialysis population (103,108). One citation in the literature notes that there is no evidence of lack of thiamin or riboflavin in the dialysis diets and therefore, one may infer, little need for supplementation (15). Vitamin B_{12} is largely bound by protein in the plasma, therefore very little is believed to be removed by hemodialysis (19).

Vitamin C is also at risk for deficiency (72). One study measured intakes of vitamin C at 50.7 $\pm$ 28.5 mg/day (103). There are variances in the recommended amounts of Vitamin C to be supplemented. Levine (73) reports the protocol at New England Deaconess Hospital in Boston suggests supplementing with 70-100 mg of vitamin C daily. Others (82) note that vitamin C may be metabolized to oxalates and may precipitate in the kidneys and other soft tissue, so supplementation is recommended only at the RDA of 60 mg (108).

The fat soluble vitamins do not suffer the same routes of loss as the water soluble vitamins, but there are controversies over supplementation.

With limited to absent renal function, the synthesis of vitamin D and the degradation of vitamin A are both limited, so there may be elevated serum levels of vitamin A and 25 hydroxycholecalciferol, thus negating the need for supplementation according to some researchers (15,82). Another view is that since vitamin D synthesis is inhibited in ESRD, supplementation is indicated due to increased requirements related to azotemia and elevated parathyroid hormone concentration and also, it is effective in treating renal osteodystrophy (73).

The kidneys play a major role in mineral homeostasis as they maintain external balance of calcium and phosphorus, synthesize calcitriol, degrades parathyroid hormone and excretes aluminum (107). Decreased protein intake from meats and dairy products correlates with decreased intakes and potential deficiencies of calcium, iron and zinc, therefore supplementation to the RDA levels is recommended (72,82). In the NCDS study, the daily calcium intake was 419 mg $\pm$ 46 mg and another study reported intake at 383.2 $\pm$ 139.4 mg, both which are less than half of the RDA for adults (88,103,108). The researchers noted that it is particularly difficult to meet the recommended calcium intake and at the same time, keep the phosphorus intake low. This finding supports the need for calcium supplementation (88). Iron supplementation may be desirable secondary to blood losses intrinsic with the hemodialysis process, frequent lab tests, gastrointestinal bleeding, inadequate dietary intake and impaired absorption (73). There is limited knowledge

regarding zinc, copper, chromium and manganese (73).

Hypoalbuminemia

The malnutrition associated with uremia is a complex condition and there is not a single test that stands alone to define malnutrition (102,103). Albumin, total protein and transferrin are serum proteins which are used to evaluate nutritional status (73). Albumin, which is synthesized in the liver, is the most frequently used criterion since it is assumed to reflect visceral protein mass as it comprises about 50% of the plasma proteins (18,21). It is generally accepted that protein malnutrition causes decreased albumin synthesis and this also supports its use as a marker for nutritional status (21). The decreased albumin concentrations found in renal failure may be due to altered amino acid and protein metabolism rather than malnutrition, but improved serum concentrations have been reported in renal patients who receive nutritional supplements (104).

Four physiological situations account for alterations in the serum concentrations of plasma proteins (21). They are changes in rate of synthesis, rate of catabolism, distribution volume and the instances of external loss. Each of these four factors may contribute to hypoalbuminemia, either independently or concurrently.

Using logistic regression analysis with greater than 12,000 subjects, (31.2% diabetics), serum albumin concentrations have been designated as the

single most important predictor of increased death risk in hemodialysis patients by Lowrie and Lew (22). They found that the mortality risk for those individuals with albumin concentrations of 2.5 – 3.0 mg/dl is seven times greater than for those with serum concentrations greater than 4.0 mg/dl. Yet, albumin with its relatively long half life, is not as sensitive an indicator as proteins with shorter half-lives, such as pre-albumin (86). While albumin may not be the ideal marker of nutritional status, its concentration may reflect comorbid conditions which may lead to increased mortality and herein may lie its predictive powers (67,72). It has been ascertained that the causes for albumin reduction are more responsible for the morbidity and mortality than the reduction per se (21,95).

Iseki et al. (105) studied 1,243 subjects in a prospective study and also found serum albumin concentrations to be a strong predictor of morbidity and mortality. In the study population, 58% were hypoalbuminemic (< 4.0 gm/dl) and 2.8% were severely hypoalbuminemic (< 3.0 gm/dl). Though the very low values may be predictive of severe consequences, they found that of the multiple predictors of mortality, serum albumin was correctable.

Serum albumin concentration is affected by many non-nutritional factors such as: a normal decrease associated with age, inflammation, inhibition of albumin synthesis, increased albumin catabolism, albumin losses from the body, altered concentrations between the intravascular and extravascular compartments due to increased capillary permeability, trauma, intestinal disease, liver disease, hydration status, inflammation and the dilutional factors of each compartment

(20,21,67,95,106). Although nutritional factors are implicated in hypoalbuminemia, there are scientists who support the notion that the decreased serum values appear to be more closely related to inflammation than to inadequate diet (106).

Insulin

It has been known since 1935 that they kidney removes insulin from the blood (109). The kidney is the most important extrahepatic site of insulin degradation and therefore plays a role in regulating circulating levels (109). Insulin is removed by kidney at the rate of 7.3 U/day for healthy subjects, 4 U/day for those with moderate renal disease and 0.17 U/day by those with severely diseased kidneys. The type of renal disease has not been shown to influence these rates (110).

The kidney is vital in the regulation of serum insulin concentrations, so diabetics with ESRD have significant complications with their glycemic control. The kidney sequesters, degrades and excretes insulin (110). In diabetics who take exogenous insulin, it is absorbed into the systemic rather than the portal circulation (as from the pancreas) and this magnifies the importance of the kidney in renal extraction and destruction, therefore many ESRD patients need less insulin (110).

Rabkin et al. (110) did renal vein catheterizations to investigate the renal handling of insulin in 13 subjects (including two diabetics) with severe renal

insufficiency (GFR < 6 ml/min). They found decreased uptake of insulin by the damaged kidneys which would account in part for the decreased insulin required with diabetics with glomerulosclerosis. Yet, all renal uptake of insulin cannot be explained by the glomerular filtration alone.

Chamberlain and Stimmler (111) examined the renal handling of insulin in seventeen subjects with normal renal function and seven subjects with renal disease. None of the subjects were diabetic. They found that insulin is totally filtered at the glomerular level and then almost completely reabsorbed or destroyed within the tubule. The implication for diabetics with glomerulosclerosis is one of significant metabolic disturbance from which there may be no recovery.

CHAPTER III

METHODS

Approval

Approval for this study was granted by the Human Subjects Review Committee of Texas Woman's University, Denton, Texas (Appendix A). Written informed consent was obtained from each subject before data collection (Appendix B).

Subjects and Methodology

The subject population for this study was drawn from four free standing dialysis facilities in the metropolitan Ft. Worth, Texas area. The medical director was approached to gain approval for participation in this study (Appendix C). Upon gaining the approval at each facility, all diabetic patients (Type I and Type II) who were at least eighteen years of age, currently taking daily exogenous insulin injections and receiving hemodialysis therapy three times weekly were identified from the patient files by the facility staff. The potential subjects were approached during their usual dialysis therapy time by the principal investigator or a Registered Dietitian for the purpose of explaining the proposed

study and gaining their informed consent. Potential subjects were informed that there currently exists minimal to no data on which to base recommendations of when to eat meals or take insulin in relation to dialysis treatments. Nor is data available regarding the possible changes in serum insulin concentrations in relation to hemodialysis therapy.

Sixty-seven subjects met the criteria, agreed to participate in the study and signed the consent forms. The investigator retained the original signed Informed Consent, the subject received a copy and the third copy was filed in the patient medical record at the respective facility. A date was mutually agreed upon between the investigator and the subject for the blood samples to be drawn and the diet records to be obtained: this was usually on the next regularly scheduled hemodialysis day. As each Informed Consent was obtained, the subject's name was recorded on a Subject Master List, a Subject Number was assigned which was used on all documentation and for labeling samples. The unheparinized blood collection tubes used for serum analysis were labeled and available at each subject's dialysis station prior to their scheduled appointment. The letters A and B were used as suffixes with the Subject Number to denote pre- and post-hemodialysis blood samples, respectively.

On the established day, each subject's pre-dialysis blood sample was obtained after the venous and arterial ports were accessed as per usual routine by the dialysis facility staff member. The blood was allowed to clot for 30 minutes at room temperature and then centrifuged to separate the serum. Taking

proper protective precautions, the serum was aliquoted into cryogenic tubes and refrigerated at 2 - 8 °C until the post-hemodialysis samples were obtained. The subjects' hemodialysis proceeded as usual and upon completion, just before decannulization, a sample of blood was obtained in the B tube, following the same procedure as the A tube. The serum was obtained as previously identified and placed in labeled cryogenic tubes. The blood was transported, maintaining the temperature at 2 – 8 °C to Texas Woman's University where it was stored at -80° C, in the Department of Nutrition and Food Science for no greater than 60 days. Samples were thawed at room temperature just prior to analysis and gently swirled to ensure proper mixing.

Serum insulin concentrations were determined using a solid-phase ^{125}I radioimmunoassay procedure designed for the quantitative measurement of insulin in serum. The analysis was done using Coat-A-Count Insulin kits (Diagnostic Products Corporation, Los Angeles, California). In the Coat-A-Count Insulin procedure, ^{125}I labeled insulin competes with insulin in the patient sample for sites on insulin-specific antibody immobilized to the wall of a polypropylene tube.

All reagents were allowed to reach room temperature before use, and the buffered ^{125}I Insulin, insulin calibrators and controls were reconstituted according to kit instructions. Four plain (uncoated) polypropylene tubes were labeled T (total counts) or NSB (non-specific binding), each in duplicate. Fourteen of the insulin antibody coated tubes were labeled in duplicate, A – G, for each of the

seven calibrators (0,5,15,50,100,200,400 micro IU/ml). The calibrators were prepared in processed human serum to ensure full compatibility with patient serum samples. Into the NSB and A tubes, 200 microliters of the 0 calibrator was pipetted. To each of the remaining calibrator, control and patient sample (unknown) tubes, 200 microliters were added, pipetting directly to the bottom of the tube, per the instructions. To every tube, 1.0 ml of the buffered ^{125}I Insulin was added and then vortexed. The T tubes were covered with parafilm to prevent possible contamination. All tubes were arranged in a sponge rack and allowed to incubate between 20 and 24 hours at room temperature.

All tubes, with the exception of the T tubes, were decanted thoroughly and allowed to drain in an inverted position for at least two to three minutes. To ensure all possible moisture was removed, the tubes were sharply tapped onto absorbent toweling to shake out all residual droplets. All tubes were counted in a gamma counter (Riastat-5410, Piper Instruments, Meridien, CT.) for one minute.

The reported nutritional histories were obtained per personal interview during the subjects' hemodialysis therapy time and were recorded on the Nutritional Intake Form (Appendix D). Probing questions were asked during the interview to obtain as accurate a report as possible. In the pursuit of accuracy, brand names of food products were recorded as were the names of specific restaurants where the subjects dined. If the food were made at home, the subject was asked to list the ingredients with amounts. As an example, " I ate a toast for breakfast," would solicit the following questions: number of toast(s)?,

type and brand of bread?, type and brand of butter or margarine (regular or light and tub or stick)?, and type of jelly or fruit spread and amount ingested? After gathering the data, the investigator went to the local grocery store to read labels, clarify and verify amounts in measurable increments to accurately input the reported intakes into the Nutritionist IV Dietary Analysis Computer Program, version 3.5. The investigator also performed measurements with the food products to determine amounts such as how much mustard or mayonnaise was required to cover a slice of bread and what portion of chopped tomatoes would usually be found in a tossed salad. The principal investigator performed all the nutritional analysis herself to help ensure consistency and accuracy in recorded amounts.

Prior to nutritional analysis, the investigator calculated caloric and protein goals for each subject based on estimated dry weight provided by the dialysis center. The estimation of dry weight is based on the individual's case history including nutritional intake of fluids and sodium, pre- and post-hemodialysis blood pressures and the presence and degree of edema present upon physical examination (92). The caloric goal was calculated at 35 kcal/kg and the protein goal at 1.5 gm/kg. These goals were set per the recommended amounts from the dialysis centers. Calorie intake had to be adequate to support efforts towards nitrogen balance thereby preventing negative nitrogen balance (80). Each subject's nutritional analysis profile was customized with these two goals prior to analysis. All other Recommended Dietary Allowances (RDA) goals were allowed

to remain in accordance with the established RDAs for age and sex (108). To measure adequacy of nutrition, the parameters were set at a minimum of 67% of the RDA for every nutrient except protein and energy. Protein and caloric goals were set at 100% because 67% of the established protein goal of 1.5 gm/kg would be 1 gm/kg and 67% of the 35 kcal/kg would only be 27 kcal/kg and both amounts are below that which is acceptable.

During the process of recording the dietary intakes, subjects were asked when they ate in relation to their dialysis therapy appointments. It was also recorded when they took insulin in relation to their mealtimes and their dialysis therapy appointments. Serum albumin concentrations, measured within a two week time frame from the date of nutritional and hematological data collection, were transcribed from the medical record.

Data Analysis

The mean pre- and post-hemodialysis serum insulin concentrations were statistically compared using the Student's paired t test (112). To determine if a statistically significant difference existed between the mean percentage intake of each nutrient on a dialysis day and the mean intake on a non-dialysis day, paired t-tests were used (112). One sample t tests were used to compare the average nutrient intakes with the 100% goal for protein and calories and with the 67% RDA goal for all other nutrients (112). Values were considered to be statistically significant at $p \leq 0.05$. The subjects' reports of the timing of insulin

administration and food ingestion in relation to the timing of their dialysis therapy were reported as descriptive data. The serum albumin concentrations were reported as descriptive data. The BMDP computer statistical package (BMDP Statistical Software, Inc., Los Angeles, CA) was utilized to analyze data.

CHAPTER IV

RESULTS

Subject Population

The characteristics of the study population are shown in Table 2. Sixty-seven subjects completed the study. One subject was omitted as the post-dialysis blood was not drawn before the vascular access was removed and obtaining the blood would have required another venipuncture.

The racial and sex composition of the subject population was not controlled as all potential adult subjects were approached to participate in the study. Nor was the type of dialyzer utilized a matter of selection or control as all subjects proceeded with their therapy without intervention by the researcher. The subjects were divided by age and sex for the purpose of nutritional analysis using sex and age appropriate RDAs.

Table 2. **Characteristics of Study Population**

		Age in years		**Type of Dialyzer**		
Sex	**n**	**25 – 50**	**50+**	**High Flux[1]**	**High Effic[2]**	**Conv[3]**
Male	**26**	5	21	3	16	7
Female	41	13	28	5	24	12
Total	**67**	**18**	**49**	**8**	**40**	**19**
Percentages		27%	73%	12%	60%	28%

[1] High flux dialyzer
[2] High efficiency dialyzer
[3] Conventional dialyzer

Serum Insulin Concentration Results

The serum insulin concentration samples were analyzed in duplicate and Coefficient of Variation data are in Appendix E. The means of the pre- and post-hemodialysis serum insulin concentrations were used for statistical analysis. The serum insulin concentration data were divided into groups according to the type of dialyzer (high efficiency, high flux and conventional). The sample sizes of the three groups were unequal with eight, forty, and nineteen subjects in the high efficiency, high flux and conventional groups, respectively. Data from five subjects were excluded from data analysis due to extreme values. This adjustment removed four subjects from the high flux group and one subject from the conventional group, leaving the subject count for each group as: high efficiency with eight subjects, high flux with thirty six subjects and the conventional with eighteen subjects. The descriptive data with the pre-dialysis means $\pm$ SD and post-dialysis $\pm$ SD are in Table 3.

Table 3. **Descriptive Data on Insulin Concentrations**

Type of Dialyzer	n	Pre – Dialysis Mean $\pm$ SD	Min – Max Means[1]	Post – Dialysis Mean $\pm$ SD	Min – Max Means[1]
High Eff[4]	8	30.63 $\pm$ 28.65	9.52 – 85.09	27.47 $\pm$ 16.96[2]	10.05 – 51.35
High Flux[5]	36	45.55 $\pm$ 33.07	5.86 – 135.82	29.58 $\pm$ 18.49[3]	2.20 – 71.08
Conven[6]	18	96.57 $\pm$ 108.90	15.75 – 383.75	88.47 $\pm$ 100.71	14.65 – 336.23

[1] Minimum and maximum mean scores
[2] Mean serum insulin levels differ from mean conventional serum insulin levels ($p < 0.05$)
[3] Mean serum insulin levels differ from mean conventional serum insulin levels ($p < 0.01$)
[4] High efficiency dialyzer
[5] High flux dialyzer
[6] Conventional dialyzer

One of the objectives of this study was to compare the pre- and post-hemodialysis serum insulin concentrations. The post-hemodialysis mean serum insulin concentrations were overtly lower than the matched pre-hemodialysis mean serum insulin concentrations in the total study population as well as in each of the three dialyzer subject groups, separately. A paired t test was used to compare the means of the sample's pre-hemodialysis and post-hemodialysis serum insulin concentrations. The results are shown in Table 4. Adjusted means were reported as each sample group (pre- and post-hemodialysis insulin concentrations) had extreme scores. In conjunction with the adjusted means, second minimum and maximum scores are also reported. The results demonstrate a statistically significant difference in the pre- and post-hemodialysis mean serum insulin concentrations ($p < 0.05$).

Table 4. **Total Sample Mean Pre- and Post- Hemodialysis Serum Insulin Concentrations in Micro IU**

Insulin Sample	n	Mean ± SD	Minimum	Maximum
Pre-Dialysis	62	53.89 ± 68.23[1,2]	6.39	280.46
Post-Dialysis	62	42.31 ± 61.59[1,2]	6.00	304.08

[1] Adjusted mean scores with second minimum and maximum values
[2] $p < 0.05$ paired t test of pre- and post-hemodialysis mean insulin concentrations

The pre-dialysis means and the post-dialysis means of the three dialyzer subject groups could not be compared statistically due to unequal sample sizes. A statistical covariance test did not meet the assumption of equal slopes. Failing

to meet this assumption required that an analysis of variance be performed on the post-dialysis serum insulin concentration means. The unequal sample sizes among the three dialyzer subject groups necessitated that a test for Equality of Means or Equal Variance be performed. The assumption of equal variance for the pre- and post-hemodialysis serum insulin concentration means was not met. A Scheffe post-hoc test was performed on the post-dialysis means. The Scheffe test demonstrated the following statistically significant results: the high efficiency group differed from the conventional group ($p < 0.05$) and the high flux group differed from the conventional group ($p < 0.01$). The post-dialysis serum insulin concentration means of the high efficiency and high flux groups were not statistically different.

Nutritional Analysis Results

The mean nutrient intakes, expressed in percentages of the RDAs for each subject's age and sex, are presented in Tables 5 and 6 for a typical dialysis day and a typical non-dialysis day, respectively. The only exceptions to the standard RDAs were the energy and protein goals. In accordance with the literature and facility policy, the energy requirement was calculated at 35 kcal/kg dry weight and the protein at 1.5 gm/kg dry weight. There were no statistically significant differences between the nutrient intakes on dialysis days when compared with non-dialysis days, using the Student's paired t test.

Table 5. **Mean Percentage of Recommended Nutrient Intakes by Subjects (n = 67) on Dialysis Days**

Nutrient	Mean Percent Intake ± SD[3]	Minimum-Maximum Scores (%)
Energy[1]	60.67 ± 23.57	10 – 117%
Protein[2]	72.07 ± 31.49	7 – 152%
Vitamin A[4]	77.34 ± 71.61	6 – 313%
Vitamin D	47.85 ± 39.96	0 – 165%
Vitamin E	80.39 ± 48.92	6 – 266%
Vitamin K[4]	138.37 ± 211.05	0 – 899%
Vitamin C	134.10 ± 103.03	0 – 438%
Thiamin [4]	126.40 ± 76.39	35 – 313%
Niacin	147.75 ± 68.99	21 – 350%
Riboflavin[4]	102.98 ± 315.03	31 – 263%
Folate[4]	102.77 ± 309.15	20 – 287%
Vitamin B6	84.66 ± 46.76	8 – 261%
Vitamin B12	189.04 ± 142.68	15 – 760%
Iron	115.12 ± 57.22	10 – 291%
Calcium	54.37 ± 27.70	6 – 141%
Phosphorus	105.61 ± 44.09	18 – 284%
Magnesium	57.46 ± 23.66	10 – 107%
Zinc[4]	64.98 ± 39.11	16 – 188%

[1] Goal for energy intake – 35 kcal/kg
[2] Goal for protein intake – 1.5 gm/kg
[3] Other nutrient intake goals – RDAs for age and sex
[4] Adjusted means and second minimum/maximum scores

Table 6. **Mean Percentage of Recommended Nutrient Intakes by Subjects (n = 67) on Non-Dialysis Days**

Nutrient	Mean Percent Intake[3] ± SD	Minimum – Maximum Scores (%)
Energy[1]	62.94 ± 25.67	1 – 139%
Protein [2]	71.93 ± 33.71	1 – 155%
Vitamin A[4]	85.88 ± 103.71	8 – 298%
Vitamin D[4]	56.51 ± 45.40	0 – 150%
Vitamin E	83.01 ± 56.24	0 – 259%
Vitamin K	88.13 ± 72.99	0 – 327%
Vitamin C	122.40 ± 98.85	0 – 471%
Thiamin[4]	118.66 ± 84.05	21 – 289%
Niacin	135.00 ± 61.01	2 – 307%
Riboflavin	101.75 ± 38.05	1 – 194%
Folate	107.66 ± 74.64	0 – 380%
Vitamin B6	81.48 ± 43.60	0 – 254%
Vitamin B12	188.21 ± 125.52	0 – 558%
Iron	117.63 ± 51.66	2 – 248%
Calcium	56.54 ± 34.61	2 – 168%
Phosphorus	107.78 ± 42.81	0 – 202%
Magnesium	58.60 ± 25.15	0 – 157%
Zinc	74.54 ± 40.54	0 – 181%

[1] Goal for energy intake – 35 kcal/kg
[2] Goal for protein intake – 1.5 gm/kg
[3] Other nutrient intake goals – RDAs for age and sex
[4] Adjusted means and second minimum/maximum scores

The six nutrients which were ingested in deficient amounts on either or both days include: energy, protein, Vitamin D, calcium and magnesium and zinc. The mean caloric intakes of 60.67% on the typical dialysis day and 62.94% on

intakes of 60.67% on the typical dialysis day and 62.94% on the typical non-dialysis day yielded energy intakes of 21.23 and 22.03 kcal/kg/day, respectively. The mean protein intakes of 72.07% on the typical dialysis day and 71.93% on the typical non-dialysis day yielded protein intakes of 1.08 and 1.079 gm/kg/day, respectively. Both amounts are significantly below the recommended amounts ($p < 0.0001$).

Table 7. **Subjects' Mean Daily Energy (Kcal) and Protein Intakes**

Day	Kcal/kg	% of goal[1]	Protein g/kg	% of goal[2]
Dialysis	21.23	60.67 %[3]	1.08	72.07%[3]
Non-dialysis	22.03	62.94%[3]	1.079	71.93%[3]

[1]Kcal goal – 35 kcal/kg
[2]Protein goal – 1.5 gm/kg
[3] $p < 0.0001$ for kcal and protein intakes, compared with goal of 100%

The remaining nutrient intakes of concern are Vitamin D, calcium, magnesium and zinc as noted in Table 8.

Table 8. **Subjects' Nutrient Intakes of Concern**

Nutrient	Dialysis Day Mean Percent Intake ± SD	Non-Dialysis Day Mean Percent Intake ± SD
Vitamin D	47.85 ± 39.96[1]	56.51 ± 45.40[3]
Calcium	54.37± 27.70[1]	56.54 ± 34.61[2]
Magnesium	57.46 ± 23.66[1]	58.60 ± 25.15[2]
Zinc	64.98 ± 39.11	74.54 ± 40.54

[1] $p \leq 0.002$
[2] $p < 0.02$
[3] Adjusted mean

The ingestion of calcium and magnesium, on both typical dialysis and non-dialysis days, and Vitamin D on the typical dialysis day, were all below the 67% RDA goals to a level of statistical significance. The minimum mean percentage intakes of these three nutrients were below 10% of the RDA on both dialysis and non-dialysis days. The mean zinc ingestion on the typical dialysis day was below 67% RDA, but not at a level of statistical significance.

Timing of Insulin Administration and Food Ingestion In Relation to Hemodialysis Therapy

The timing of the self-regulated insulin administration and food ingestion was recorded as reported by subjects. The data were divided by the dialysis shift times in order to illuminate their 'real-life' schedules. Each dialysis shift lasted approximately four hours, but the subjects were in the facility longer to allow for the pre- and post-therapy care regimes.

Shift one began early in the morning, between 0600 and 0700 hours, so subjects who received therapy at this time were often awake by 0500 hours. The second shift began between 1100 and 1230 hours and lasted until mid to late afternoon. The third shift commenced approximately between 1700 and 1800 hours and the subjects were ready to go home by 2130 to 2230 hours. The self-reported timing of insulin administration and food ingestion by the subjects was recorded in Table 9.

Table 9. **Timing of Insulin Administration and Food Ingestion in Relation to Dialysis Therapy**

Shift	n	Insulin Prior[1]	Insulin After[2]	Food Prior[3]	Food After[4]
1	29	15	14	19	10
2	25	20	5	21	4
3	13	13	1	13	0
Total	**67**	**47**	**20**	**53**	**14**

[1] Insulin administered prior to dialysis therapy
[2] Insulin not administered until after dialysis therapy
[3] Subject ate prior to dialysis therapy
[4] Subject did not eat prior to dialysis therapy

Table 10. **Summary of Timing of Insulin Administration and Food Ingestion in Relation to Dialysis Therapy**

Shift	N	Insulin & Food Prior[1]	Insulin Prior / Food After[2]	Insulin After/ Food Prior[3]	Insulin & Food After[4]
1	29	12	3	7	7
2	25	18	2	3	2
3	13	12	0	1	0
Total	**67**	**42**	**5**	**11**	**9**

[1] Subject took insulin and ate prior to dialysis therapy
[2] Subject took insulin prior to dialysis therapy, but did not eat until after therapy
[3] Subject ate prior to dialysis therapy, but took insulin after the therapy
[4] Subject neither took insulin nor ate prior to dialysis therapy

In each group, by shift, the majority of the subjects took insulin and ate prior to their dialysis therapy. Subjects in shift one evidenced almost a 50% split between those who took insulin before dialysis and those who waited until afterwards. Also in shift one, almost two-thirds ate prior to arrival at dialysis. For the six subjects who attended shifts two and three and did not take insulin prior to therapy, they spent many morning hours without insulin in their systems. A

maximum of four subjects reported having been instructed when to take their insulin in relation to the timing of their therapy and the instructions were for both "before" and "after". It is also noted that four subjects who attended shift two did not eat until after therapy, which meant that they fasted until mid to late afternoon.

The most revealing information is found in Table 10. It was reported that five subjects on the first two shifts took insulin prior to dialysis, but did not eat until afterwards. Eleven subjects ate prior to therapy, but did not take insulin until afterwards. No subject expressed concern that they were eating without the benefit of insulin to help in the utilization of the energy ingested. The most interesting subject in this group of eleven was the one on the third shift who took insulin late in the evening after therapy.

Serum Albumin Concentrations

The serum albumin concentrations covered a wide range in this group of subjects, from 2.5 to 4.5 mg/dl. The results were recorded in Table 11 for individual increments of serum albumin and in Table 12 as physiological groupings. The two subjects below 3.0 mg/dl were at a level of protein depletion indicative of serious protein store depletion and/or illness. It was of note that the mean protein intake was below the desired level, and yet there were seventeen subjects (25.4%) who had albumin concentrations at least equal to 4 gm/dl. The mode was 3.8 mg/dl (n = 13); this could be attributed to the fact that the dialysis

center goal for serum albumin concentrations was 3.8 mg/dl. Interventions were implemented for all persons with concentrations below that level with the goal of reaching 3.8 mg/dl.

Table 11. **Serum Albumin Concentrations and Percentage of Subjects**

Albumin Mg/dl	Number of Subjects	Percentage of subjects
2.5	1	2
2.6	1	2
3.0	1	2
3.1	3	4
3.2	3	4
3.3	1	2
3.4	3	4
3.5	5	7
3.6	7	10
3.7	6	9
3.8	13	19
3.9	6	9
4.0	9	13
4.1	4	6
4.2	1	2
4.3	2	3
4.5	1	2
Totals	**67**	**100%**

Table 12. **Subjects' Serum Albumin Concentrations**

Serum albumin (mg/dl)	Number of subjects	Percentage of subjects
< 3.0	2	3%
3.0 – 3.4	11	16.4%
3.5 – 3.9	37	55.2%
≥4.0	17	25.4%
Totals	**67**	**100%**

CHAPTER V

DISCUSSION

Subjects

The subject population for this study was composed of diabetic individuals with ESRD who received exogenous insulin daily and also underwent hemodialysis therapy three times weekly to sustain life. The literature evidences a lack of information regarding the optimal treatment regime(s) for these individuals. This study was conducted in an attempt to increase the body of knowledge regarding the status of serum insulin concentrations before and after hemodialysis and the reported/actual nutritional intake status, as compared with the RDAs, of these individuals. The subject selection criteria did not control for sex, type of dialyzer used nor type of diabetes as this has not been shown to be relevant in ESRD.

Insulin Concentrations

Insulin losses into the dialysate during hemodialysis in instances of acute renal failure have been documented (16). A dearth of information exists regarding the actual retention or loss of serum insulin during the hemodialysis process for those individuals who have chronic renal failure and receive

maintenance hemodialysis. The protein insulin has been assumed to be too large to be "dialyzed off" along with the uremic toxins. The literature asserts that the loss of protein during hemodialysis is minimal at most, but there may be conflicting evidence.

The present study of maintenance hemodialysis patients concurs with a previous study of acute renal failure patients on hemodialysis (16), in that the post-dialysis serum insulin concentrations were overtly decreased. The small sample size (n = 16) of the acute renal failure study may have inhibited its ability to show statistical significance. The current study, with sixty-two subjects, demonstrated a statistically significant decrease from the pre- to the post-hemodialysis serum insulin concentrations. Because of the fluid disposal systems at the dialysis centers, it was not possible to measure the insulin concentrations in the dialysate, but one may infer that a loss into the dialysate is a valid possibility.

When divided into groups based on the type of dialyzers used, the group sizes were markedly uneven, but this was not a variable that was controlled in sample selection. There were eight subjects who used a high efficiency dialyzer, forty who used a high flux dialyzer and nineteen who used a conventional dialyzer. The inequality of the group sizes prevented statistical comparison of the pre- and post-hemodialysis mean serum insulin concentrations among the three groups. In each instance (Table 3), the post-dialysis mean serum insulin concentrations were less than the pre-dialysis mean serum insulin

concentrations. The largest of the three groups was the high flux dialyzer group with thirty-six subjects. In this group, the means were 45.55 ± 33.07 and 29.58 ± 18.49 for the pre- and post-hemodialysis serum insulin concentrations, respectively. This is a difference of thirty-five percent.

These data indicate a need for more research, establishing the type of dialyzer used as a subject selection criterion and having larger and more equally numbered groups. These study design changes would allow for a comparison of the change in serum insulin concentrations between or among the type of dialyzers used. This information could influence when subjects, using different types of dialyzers, would take their insulin in relation to their dialysis therapy schedules. If a significant portion of the insulin were being removed during hemodialysis, then the diabetic may benefit by either splitting their doses or waiting until after dialysis, depending on their dialysis time, eating schedule and type of insulin used (short or intermediate onset and peak characteristics).

Nutritional Analysis

Diet histories were recorded as reported by the subjects for typical dialysis and non-dialysis days. The range of daily intakes included one subject who ingested only four cans of Nepro (dietary supplement for renal patients) and a subject who reported consuming a 24 ounce steak, baked potato with "all the trimmings", salad with dressing, bread and two large glasses of iced tea the previous evening. Two subjects reported the grams of carbohydrate in each meal in conjunction with the actual foods eaten. Another subject reported eating

"honey buns" for breakfast and keeping a bag a gummy bears close by at all times for snacking purposes. Some subjects reported being exhausted and nauseated after dialysis, but many identified their favorite hamburger or barbeque stop on the way home. More than a few subjects reported regular intakes of carbonated soft drinks, without any apparent interest in the amount of phosphorous contained in these beverages. Consumption of white bread was more often reported than whole wheat bread. Sausage, especially the Jimmy Dean brand, was reported as a favorite. The investigator made every effort to not express surprise or any form of judgement in soliciting the diet histories, so as to obtain as accurate a report as possible and most, if not every subject seemed to speak freely.

Examining individual subject's reported intakes on typical dialysis and non-dialysis days revealed instances of overt differences in the amounts of food eaten. The total samples' mean percent intakes showed no statistically significant differences between the two days. Comparing the mean percent intakes of individual nutrients, there was not a pattern of higher values on one type of day as opposed to the other. The mean percent energy intake on a typical non-dialysis day was higher than on a dialysis day, but the mean percent protein intake was higher on the dialysis day when compared with the intake on the non-dialysis day.

The mean percent energy intakes were significantly below the 35 kcal/kg goal on both days. The mean percent intakes converted to calories revealed that

the subjects ingested 21.23 kcal/kg/day and 22.03 kcal/kg/day on dialysis and non-dialysis days, respectively. The 35 kcal/kg goal was below the 36 – 39 kcal/kg estimated energy need which was identified by Ikizler et al. (90). This would indicate that the actual intakes were more deficient than the statistical analysis reported. The intakes of the subjects in the current study, were closer to (although below) the subjects who ingested 25 kcal/kg in the study reported by Slomowitz et al. (100). Those subjects were found to exhibit weight loss and a state of negative nitrogen balance with caloric intakes of 25 kcal/kg and protein intakes of 1.13 $\pm$ 0.02 gm/kg. Based on these results, the energy intakes by the subjects in the present study were below those reported intakes, so one could question the protein-sparing status of the current study's subjects' dietary intakes. One could also question the subjects' ability to attain and maintain a state of neutral to positive nitrogen balance with their current energy intakes. Ge et al. (103) reported an average energy intake of 28.1 $\pm$ 4.6 kcal/kg of dialysis subjects which was 23% higher than the average intake of the subjects in the current study.

The protein intakes were also significantly below the established goal of 1.5 gm/kg. The mean percentage protein intakes converted to grams of protein ingested were 1.08 gm/kg and 1.079 gm/kg on typical dialysis and non-dialysis days, respectively. These were similar to the protein intake of 1.0 $\pm$ 0.2 gm/kg reported by Ge et al. (103). The mean percent protein intakes were 72.07 gm/kg and 71.93 gm/kg on dialysis and non-dialysis days, respectively. These percent

intakes were higher than the energy mean percent intakes (60.67% and 62.94%) which supported the notion that protein needs were met before energy needs, due to the amount of food required to meet the energy needs (93). The deficit in energy intakes reported by the subjects of this study may have had deleterious effects on the protein usage efficacy in these subjects.

The intakes of eight nutrients exceeded the RDAs on both days. Vitamin C, thiamin, niacin, riboflavin, folate, vitamin B_{12}, iron and phosphorus were all ingested in more than sufficient amounts. The amounts ingested, while exceeding the RDAs, may in fact not be found in values within normal ranges in the blood, due to the potential for losses into the dialysate fluid. Water soluble vitamins are routinely supplemented in the dialysis centers which participated in this study. A study to compare the amounts of ingested vitamins and the serum levels would give more support for interpreting the adequacy of ingested nutrients. It must be understood that the RDAs were established for reasonably healthy individuals and some, if not many ESRD patients may not fit this classification (108).

Three nutrients were significantly below 67% of the RDA on one or both days. Vitamin D, calcium and magnesium were the nutrients that were ingested in inadequate amounts. Renal insufficiency has a serious impact on the synthesis of Vitamin D. There is controversy regarding the supplementation of Vitamin D and a decision for supplementation would need to be made on an individual basis, with consideration to parathyroid hormone concentrations and

the bone density (73). In the dialysis centers involved in this study, serum parathyroid hormone concentrations are monitored quarterly and 1,25 di-hydroxycholecalciferol supplementation is prescribed accordingly. Low calcium intake is a concern because of the role the functioning kidney plays in homeostasis and also because of the limitations on dairy products integral in the renal diet plan. Calcium is routinely given for its supplementation value as well as its ability to function as a phosphate binder. The mean percent calcium intakes were 54.37% and 56.54% and these percentages were higher than the values reported in the NCDS study and the study by Ge et al., which were both less than half of the RDA for adults (88,103).

The nutritional intake of diabetic dialysis patients is a concern which has many levels of impact. Nutritional deficits are related to a multitude of other physiological functions, as well as morbidity and mortality. There are so many unanswered questions regarding the most effective nutritional therapies for this population that research must continue to increase the knowledge base supporting the efficacy of nutritional therapy.

The timing of insulin administration and food ingestion in relation to dialysis therapy times is not addressed in the literature. The descriptive data reported in this study may provide a basis for future research. When the fate of serum insulin concentrations during dialysis is known, then appropriate teaching may be offered to the diabetic with ESRD regarding the most advantageous timing of insulin administration. Many of the subjects in this study demonstrated

no knowledge of the appropriate timing of insulin administration and food ingestion. Although some subjects reported taking their insulin and eating within a thirty minute time frame, others reported eating first and then taking their insulin at a later time. There were five subjects in this study who took insulin prior to their dialysis, but did not consume food until after their therapy. Of course, there was glucose in the dialysate, but the time lapse between insulin administration and the commencement of dialysis may have been significant. Most of the subjects took insulin and ate prior to dialysis but nine subjects performed neither task until after dialysis. The single subject who received dialysis late in the evening and did not take insulin until after returning home was of interest. If this person slept during the daylight hours and stayed up all night, then this routine may have been effective, but it would have been of interest to know how many, if any, hypoglycemic episodes this individual experienced in the early morning hours. A wide diversity in schedules was the most valid statement one could make regarding the timing of insulin administration and food ingestion in this study population.

Serum Albumin Concentrations

There are many factors that influence serum albumin concentrations. It is used as an indicator of visceral protein status and therefore is nutritionally related, but many non-nutritional factors are important. Lowrie and Lew (22) are frequently cited in the literature for their position that serum albumin is the

strongest predictor of mortality in a dialysis population. The descriptive data reported from this study revealed a wide range of serum albumin concentrations, from 2.5 to 4.5 mg/dl. Three percent of the subjects had values of < 3.0 mg/dl. Greater than twenty five percent of the subjects had values ≥ 4.0 mg/dl. When evaluated in light of the mean percent protein intakes, the lower serum albumin concentrations may have been predicted. This study made no attempt to document comorbid conditions which have been reported to influence serum albumin values.

Hypotheses

There were two null hypotheses for this study. The first null hypothesis was that there would be no significant difference in the serum insulin concentrations as measured prior to and following hemodialysis in the diabetic population. Based on the results of this study, a statistically significant difference between the pre- and post-hemodialysis mean serum insulin concentrations, this hypothesis was rejected. The second null hypothesis stated that there would be no significant differences between the reported nutrient intakes on a typical dialysis day as compared with a typical non-dialysis day in a diabetic ESRD population. Based on the results of this study, which demonstrated no statistically significant differences in the nutritional intakes of dialysis and non-dialysis days, this hypothesis was accepted.

CHAPTER VI

SUMMARY AND CONCLUSIONS

The purpose of this study was to determine the nutritional status and serum insulin concentrations pre- and post-hemodialysis in a diabetic ESRD population that received exogenous insulin. The subjects were sixty-seven adult subjects who took daily exogenous insulin injections and received hemodialysis therapy three times weekly. No effort was made to control for sex, type of diabetes or type of dialyzer used.

There were seven objectives for this study. The first objective was to compare the serum insulin concentrations pre- and post-hemodialysis. Upon comparison, using the Student's paired t test, the total sample's post-hemodialysis mean serum insulin concentration was significantly lower than the total sample's pre-hemodialysis mean serum insulin concentration ($p < 0.05$).

When the subjects were divided into groups by the type of dialyzer they used, three subject groups were formed. Upon inspection of the data, it was noted that in each of the three groups, the post-hemodialysis mean serum insulin concentration was lower that the pre-hemodialysis mean serum insulin concentration. It was not possible to statistically compare the pre- and post-hemodialysis mean serum insulin concentrations among the three groups due to

unequal group sizes. The post-hemodialysis mean serum insulin concentration of the high efficiency dialyzer group was significantly different from that of the conventional dialyzer group ($p < 0.05$) and the high flux mean serum insulin concentration was significantly different from that of the conventional dialyzer group ($p < 0.01$). The high efficiency and high flux dialyzers post-hemodialysis mean serum insulin concentrations were not significantly different.

This study does not provide proof of the loss of insulin into the dialysate, but it documents a statistically significant decrease in the total subjects' mean serum concentration upon the post-dialysis measurement. To determine if the type of dialyzer impacts the serum insulin concentration, research is needed with larger and equal sized subject groups to compare the serum insulin concentrations using high efficiency, high flux and conventional dialyzers.

The nutritional analysis component of this study included the analysis of and comparison of self-reported nutrient intakes on a typical dialysis day and a typical non-dialysis day. The results of the nutritional analyses were expressed as the mean percent of the nutrient goals which were 100% for energy and protein and 67% of the RDA for all other nutrients. There were no statistically significant differences between the mean intakes on the typical dialysis day and the typical non-dialysis day. The mean intakes of six nutrients were below the nutrient specific goals on one or both of the days. The energy and protein mean percent intakes were significantly below the 100% goal on both days ($p < 0.0001$).

The mean percent intakes of Vitamin D, calcium and magnesium were significantly less than 67% of the RDAs on one or both days intake analyses. On the typical dialysis day, the zinc mean percent intake was less than 67% of the RDA, but not to a degree of statistical significance. The minimum percent intakes of three vitamins (C, D and K) were 0% on a typical dialysis day. The minimum percent intakes of ten nutrients (vitamins C, D, E and K, B_6, and B_{12}, folate, phosphorus, magnesium and zinc) were 0% on the typical non-dialysis day. These 0% intakes of the identified nutrients indicate that some subjects have potential for significant nutrient deficits. This portion of the nutritional analysis fulfilled three of the objectives which were, in summary, to analyze the self-reported nutrient intakes on typical dialysis and non-dialysis days and to compare the mean percent intakes to determine if a difference existed between the two days.

Since there are no data available in the literature regarding the optimal timing of food ingestion and insulin administration in relation to dialysis therapy appointments, this study's objectives were to document when the subjects actually ate and took insulin on dialysis days. The vast majority of the subjects responded that they had never received instructions on the timing of their food intake and insulin injections with their dialysis times and those who had received instructions, were inconsistent with each other. Of the sixty-seven subjects, sixty-three percent ate and took insulin prior to arriving at the dialysis clinic, but thirteen percent did not eat or take insulin until after arriving home from dialysis.

Sixteen percent ate prior to dialysis, but waited until after their therapy to administer their insulin. Seven percent took their insulin before dialysis, but did not eat until afterwards. The most interesting subject was the one on the third shift, which was not concluded until late evening, who did not take insulin until after dialysis.

Serum albumin is a hematological marker for protein stores and thus for protein energy malnutrition. Reviewing the nutritional intake data, many subjects ingested limited amounts of protein. Protein provides the amino acids for the hepatic production of albumin, so the serum albumin concentrations are of interest as an indicator of nutritional adequacy. The range of serum albumin values, expressed in mg/dl, was 2.5 to 4.5. When grouped into physiological value groups, 3% were below 3.0 gm/dl. The 'low normal' serum concentration is 3.5 mg/dl and a fifth of the study population were below acceptable normal concentrations. The total percent of subjects with serum albumin values within the normal range was 80.6%. There were seventeen (25.4%) with serum albumin concentrations $\geq$ 4.0 mg/dl.

Vitamins and some minerals are routinely supplemented in the dialysis patient's diet. This appears to be a good practice for most individuals as intakes, previously identified, are inadequate of nutrients. Malnutrition in the diabetic ESRD population has been documented in many ways. This study, with the comparison of the nutrient intakes to the RDAs is unique and should be followed with more research concerning the nutrients identified herein as 'at risk'.

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APPENDICES

APPENDIX A

Human Research Review Approval

TEXAS WOMAN'S UNIVERSITY

DENTON/DALLAS/HOUSTON

HUMAN SUBJECTS
REVIEW COMMITTEE
P.O. Box 425619
Denton, TX 76204-3619
Phone: 817/898-3377
Fax: 817/898-3416

May 6, 1997

Ms. Cherie Craft
2421 N. Bell #224
Denton, TX 76201

Dear Ms. Craft: Social Security # 450-08-1648

Your study entitled "Analysis of Pre and Post Hemodialysis Serum Insulin Levels between High Flux and High Efficiency Dialyzers" 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 consent forms and an annual/final report (attached) are to be filed with the Human Subjects Review Committee at the completion of the study.**

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. If you have any questions, please feel free to call the Human Subjects Review Committee at the phone number listed above.

Sincerely,

Chair
Human Subjects Review Committee

cc. Graduate School
Dr. Betty Alford, Department of Nutrition & Food Sciences

APPENDIX B

Informed Consent

TEXAS WOMAN'S UNIVERSITY
SUBJECT CONSENT TO PARTCIPATE IN RESEARCH

Title of Study: Assessment of Nutritional Status and Analysis of Pre- and Post- Hemodialysis Serum Insulin Concentrations in a Diabetic ESRD Population

Investigators:

	Office Phone Number
Cherie Craft, RN	(940) 591-0886
Betty Alford, PhD	(940) 898-2636
Andie Hsueh, PhD	(940) 898-2636
Myra Barber, RD/LD, PhD	(817) 921-3431
George Liepa, PhD	(313) 487-3303
Eileen Baugh, RD/LD, PhD	(817) 921-5191
J. Patrick Brennan, MD	(817) 921-5191

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 there is a difference in serum insulin values before and after hemodialysis. I understand that I must have the diagnosis of Diabetes Mellitus to participate in this study. I will also be asked to report my 'typical' food intake and time and dosage of insulin both for a day which I receive hemodialysis therapy and for a day I do not have hemodialysis. No procedures involved are considered experimental.

2. Explanation of the procedures to be followed:
   I understand that blood will be taken from my dialysis tubing immediately before and immediately after hemodialysis. There will not be an extra needle stick for me as the blood will be taken from the tubing. I understand that the total amount of blood taken will not exceed 15 cc or 1 tablespoon. I also understand that during my usual time on dialysis, I will be asked to recall my 'typical' food intake and insulin dosage/time for a day which I have hemodialysis and a day I do not have hemodialysis. Participation in this study will not extend the time I spend in the Dialysis Center nor will my usual dialysis routine be changed.

3. Forseeable risks and discomforts:
   I understand that the procedures outlined involve no discomfort to me. There may be a small risk of infection because the blood samples will be taken from the tubing, but sterile technique will be used to prevent the risk of infection. I understand that a code number rather than my name will be used on my blood samples and my food report. My name will not be published. The information from the study will be securely stored for seven years in the

Tarrant County Nephrology Center and at the end of seven years, all documents will be shredded.

4. Benefits:
   I understand the possible benefits of the study are as follows: an opportunity to participate in research and add to the body of knowledge which may help me and those who follow me; an opportunity to learn my blood insulin levels; an opportunity to receive a copy of the nutritional analysis of my reported food intake; an opportunity to have a copy of the final results of the study.

If I have any questions about the research or about my rights as a subject, I should ask the researchers: their phone numbers are at the top of this form. If I have any questions later, or wish to report a problem, I may call the researchers or the Office of Research and Grants Administration at (817) 898-3377.

The researchers will try to prevent any problem that could happen because of research. I should let the researchers know at once if there is a problem and they will help me. I understand, however, that TWU does not provide medical services of financial assistance for injuries that might happen because I am taking part in this research.

5. Voluntary participation:
   I understand that my participation in this study is voluntary. I may refuse to participate or withdraw my consent and discontinue my participation in this study at any time. In understand that such a decision on my part will not cause any penalty nor influence the availability of future medical care.

6. Offer to answer questions about this study:
   An offer has been made to answer all my questions regarding the study.

I have been given a copy of the dated and signed consent form for my personal records. I agree the results of this study may be published for scientific purposes, providing my identity is not revealed.

_____
Subject's Name

_____
Subject's Signature/Date

_____
Investigator's Signature/Date

APPENDIX C

Institution Approval

TARRANT COUNTY NEPHROLOGY CENTER
Fresenius Medical Care
1408 St Louis
Ft Worth, Texas 76104

12/13/96

To: Graduate School
Texas Woman's University
From: J Patrick Brennan MD
President: Dialysis Associates

Approval has been granted to conduct research entitled "Analysis of Pre and Post Hemodialysis Insulin Levels Between High Flux and High Efficiency Dialyzers". as outlined in the attached prospectus by Cheri Craft. It has been reviewed by the Medical Staff.

J. Patrick Brennan MD

APPENDIX D

Nutrition Intake Form

NUTRITION INTAKE

24 HOUR DIETARY RECALL

Subject #_____ Age_____ Dialysis_____

Sex_____ Non-dial_____

Insulin Dose (s)/ time(s)_____

Supplements taken_____

Fluid limit_____ Dialysis time_____

TIME FOOD/AMOUNT/DESCRIPTION

APPENDIX E

Coefficients of Variation on the Insulin Data

Coefficients of Variation on the Insulin Data

Dialyzer and Sample	Mean ± SD	Coeff of Var	Min- Max Values
High Efficiency Pre 1	30.74 ± 29.75	.97	8.39 – 89.78
Pre 2	30.53 ± 27.66	.91	10.65 – 80.41
Post 1	27.55 ± 16.72	.61	9.98 – 50.10
Post 2	27.38 ± 17.24	.63	10.13 – 52.61
High Flux Pre 1	45.25 ± 33.23	.73	6.46 – 135.71
Pre 2	45.85 ± 33.23	.71	5.09 – 135.92
Post 1	29.74 ± 18.66	.63	2.09 – 71.21
Post 2	29.41 ± 18.33	.62	2.30 – 70.95
Conventional Pre 1	96.19 ± 108.27	1.13	15.88 – 381-25
Pre 2	96.96 ± 109.58	1.13	15.62 – 386.25
Post 1	89.17 ± 102.27	1.15	14.85 – 337.09
Post 2	87.78 ± 99.17	1.13	14.45 – 335.36
Total Sample Pre 1	58.16 ± 68.02	1.17	6.46 – 381.25
Pre 2	58.71 ± 68.49	1.17	5.09 – 386.25
Post 1	46.71 ± 62.42	1.34	2.09 – 337.09
Post 2	46.10 ± 60.75	1.32	2.30 – 335.36