PREDICTORS OF LOSS OF RESIDUAL RENAL FUNCTION AMONG NEW DIALYSIS PATIENTS

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Abstract

Residual renal function among patients with end stage renal disease is clinically important as it contributes to adequacy of dialysis, quality of life, morbidity and mortality. The predictors of residual renal function loss were studied in patients initiating hemodialysis and peritoneal dialysis. The adjusted odds ratios (AOR) and p values associated with each of the demographic, clinical, laboratory and treatment parameters were estimated using an univariate analysis and significant variables ($p < 0.05$) were included in a multivariate logistic regression model. Predictors of RRF loss were female gender (AOR=1.45; p<0.001), non-white race (AOR=1.57; p=<0.001), prior history of diabetes (AOR=1.82; p=0.006), prior history of congestive heart failure (AOR=1.32; p=0.03), and time to follow-up (AOR=1.06 per month; p=0.03). Patients treated with peritoneal dialysis had a 65% lower risk of RRF loss than those on HD (AOR=0.35; p<0.001). Higher serum calcium (AOR=0.81 per mg/dl; p=0.05), use of an angiotensin converting enzyme inhibitor (AOR = 0.68; p<0.001) and use of a calcium channel blocker (AOR=0.77; p=0.01) were independently associated with decreased risk of RRF loss. The observations of demographic groups at risk, potentially modifiable factors and therapies have generated testable hypotheses regarding therapies, which may preserve RRF among ESRD patients.

Key Words: residual renal function, dialysis, end-stage renal disease, predictors.

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List of Abbreviations

APD	Ambulatory PD
A-V	Arterio-venous
AOR	Adjusted Odds Ratio
B_2M	Beta $_2$ microglobulin
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCPD	Continuous Cycling Peritoneal Dialysis
CORR	Canadian Organ Replacement Register
CRF	Chronic Renal Failure
CrCl	Creatinine Clearance
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
HCFA	Health Care Financing Administration
HD	Hemodialysis
MDRD	Modification of Diet in Renal Disease
NIDDK	National Institute of Diabetic, Digestive and Kidney Disease
nPCR	Normalized Protein Catabolic Rate
RRF	Residual Renal Function
RRT	Renal Replacement Therapy
PD	Peritoneal Dialysis
QOL	Quality Of Life
UV	Urine Volume

UKM	Urea Kinetic Modeling
USRDS	United States Renal Data System

CO-AUTHORSHIP

The following thesis includes a manuscript co-authored by Port, Orzol, Young, Ostbye, Wolfe, Hulbert-Shearon, Jones, and Bloembergen.

All of the work in the thesis was done by Louise Moist, with the exception of some of the analyses which were performed by Orzol and Hulbert-Shearon.

For copyright releases, see Appendix 1.

CHAPTER 1: EPIDEMIOLOGY AND BURDEN OF ILLNESS IN END STAGE RENAL DISEASE

1.1 Introduction

The objective of this thesis is to highlight the importance of the residual renal function (RRF) among patients on dialysis and to identify parameters that are associated with the loss of RRF.

The epidemiology of end-stage renal disease (ESRD) and its burden of illness on the patient and on society will be reviewed in Chapter 1. The importance of RRF will be discussed in Chapter 2 and the measurement of RRF will be discussed in Chapter 3. Chapter 4 will describe the methodology used in a study conducted to examine predictors of RRF loss among new dialysis patients. Chapter 5 is unique in that it is the actual paper describing the study as well as the results and discussion. *A version of this chapter has been accepted for publication in The Journal of the American Society of Nephrology and is scheduled for publication in the March 2000 issue.* The copyright release is found in Appendix 1. The limitations of this study will be discussed in Chapter 6 and a discussion of the future directions of this work will be discussed in Chapter 7.

1.2 End-Stage Renal Disease

End stage renal disease (ESRD) is defined as the stage of progressive renal failure when renal replacement therapy (RRT), such as dialysis or transplantation

becomes necessary. "End stage" refers to the end of the kidney function. For most patients with progressive chronic renal failure (CRF), the decision to start dialysis is based on a combination of uremic symptoms and laboratory parameters. These symptoms include nausea, vomiting, anorexia, unexplained weight loss, development of malnutrition, decreased mentation, changes in sleeping patterns, peripheral neuropathy, restless leg syndrome, and pruritus [1]. The presence of these signs and symptoms significantly affect the patient's quality of life (QOL). There is usually 5-10% of the kidney function remaining when patients start RRT [2, 3].

1.2.1 Renal Replacement Therapy

The modalities of RRT available for treatment of ESRD include hemodialysis (HD) and peritoneal dialysis (PD). This definition often includes renal transplantation, however, transplantation is not addressed here. Hemodialysis is subdivided into in-centre provided HD, the most commonly used modality, self-care and home hemodialysis. The majority of PD comprises continuous ambulatory PD (CAPD), and automated PD (APD).

1.2.2 Hemodialysis

Hemodialysis removes toxins and excess fluid via extracorporeal circulation of blood through a dialyzer, or so-called "artificial kidney". Treatments are usually scheduled for three times weekly and last three to five hours. A vascular access is required, using an arterio-venous (AV) fistula, an A-V graft, or in-dwelling

vascular catheter. The treatment is performed predominantly as "in-centre HD" in a hospital based dialysis unit.

1.2.3 Peritoneal Dialysis

Peritoneal dialysis uses the patient's own peritoneal membrane as a "dialyzer". It requires placement of a catheter into the abdominal cavity, and repeated installation and drainage of sterile dialysate. PD involves the movement of small solutes and water across the semi-permeable membrane. Toxins move from the plasma to the dialysate, due to concentration gradients during the dwell time while other solutes (eg. calcium and lactate) move in the opposite direction. Fluid is removed by osmotic ultrafiltration using hypertonic glucose containing dialysate solutions. The rate of movement of small solutes, such as creatinine, between blood and dialysate differs from one patient to another and this peritoneal function characteristic is quantified in the peritoneal equilibrium test (PET). Using this test, each patient's peritoneal membrane can be categorized as having a high, high average, low average, or low peritoneal transport characteristics. Patients with high peritoneal transport have rapid clearance of small molecules, but poor ultrafiltration due to dissipation of the osmotic gradient between the dialysate and the blood by glucose absorption. Patients with low transport ultrafiltrate well but have slow equilibration requiring the continuous presence of larger dwell volumes in the peritoneal cavity [4, 5].

Several PD options are available. The most common is continuous ambulatory PD (CAPD). The patient usually performs four or five exchanges with a dialysate volume of two to three liters on a daily basis. Automated PD (APD) includes exchanges with the use of a programmed machine cycler and includes continuous cycling PD (CCPD), a home treatment utilizing several exchanges through a programmed machine cycler, typically every night with one long dwell time throughout the day.

1.3 Epidemiology of End Stage Renal Disease

Much of our epidemiological information comes from the United States of America due the completeness of their ESRD registry data. The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about ESRD in the United States. The USRDS contains data on over 93% of all patients treated for ESRD in the United States [6, 7]. Submission of this information is mandatory and linked to reimbursement for patients who are covered by Medicare, who comprise the majority of ESRD patients. The Canadian Organ Replacement Register (CORR) data is submitted on a voluntary basis and it includes 93.3% of all the patients treated for ESRD in Canada [8].

The research study, *Predictors of Loss of Residual Renal Function among New Dialysis Patients*, was based on the United States population. The demographics

of the US ESRD population are reported with reporting of the Canadian demographics for comparison.

1.3.1 The USRDS Data Base

The USRDS is funded directly by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) in conjunction with the Health Care Financing Administration (HCFA). HCFA provides most of the existing data in the USRDS database. This national data system collects, analyzes, and distributes information about ESRD in the United States. It includes comprehensive data needed to describe the incidence and prevalence of treated ESRD, modality of treatment, cause of death, patient survival, hospitalizations, cost and cost effectiveness, and institution providers of ESRD treatment. The University of Michigan, Ann Arbor, was the coordinating center for the USRDS at the time of this study.

1.3.2 The CORR Data Base

The Canadian Organ Replacement Register (CORR) at the Canadian Institute of Health Information (CIHI) is a national information system on organ failure and transplantation, with a mandate to record and analyze the level of activity and outcome of vital organ transplantation and renal dialysis activities. Information is collected from a number of sources including 28 transplant hospitals, 86 dialysis facilities and 8 organ procurement organizations. The most recent data available is from 1996 reported in the 1998 CORR report.

1.4 INCIDENCE AND PREVALENCE OF END-STAGE RENAL DISEASE

1.4.1 Definition of Incidence and Prevalence

Incidence refers to new cases of ESRD during a given time period and is a key population measure of kidney disease and access to renal replacement therapy. Prevalence refers to all patients receiving ESRD treatment at a particular time (point prevalence) or during a given time period (period prevalence) and is a population measure of disease burden and resource requirements. Prevalence is determined by incidence and patient life expectancy.

1.4.2 Measuring Incidence and Prevalence of ESRD

ESRD is defined by treatment with any form of chronic dialysis or renal transplantation. Patients who die of renal failure without first receiving dialysis or a transplant are not considered ESRD patients. Dialysis for acute renal failure is not considered ESRD unless renal function fails to recover. As a practical matter, the degree of renal failure or the reason for initiation of dialysis does not impact the ESRD classification. A patient is considered incident at the time of the first regular dialysis for chronic renal failure. It is possible that incidence is not fully reported, especially for patients who die before chronic treatment is fully established. A patient is considered prevalent if he/she is known to be receiving dialysis or to have a functioning kidney transplant. Point prevalence refers to the number of ESRD patients at a particular point in time (example: on December 31, 1997). Period prevalence refers to the number of patients with treated ESRD

during a period of time, usually a year, and includes patients' point prevalence at the end of the period as well as those who died during that period. Most prevalence statistics reported by the USRDS and CORR refer to point prevalence. Prevalence is a direct function of incidence and survival. Prevalence rates are on average four to five times higher than incidence rates because the average survival time is four to five years for ESRD patients. Changes in prevalence are attributable to changes in incidence, average survival time, or both. Patients who return to dialysis after a failed transplant are not counted as incident ESRD patients. This situation is classified as a modality change. Similarly, patients who stop chronic dialysis and then restart are counted as prevalent, not incident patients. In the USRDS, patients are maintained in the ESRD database until death. Incidence and prevalence will be referred to as rates; incidence is expressed as rate (number per million population per year), while prevalence is expressed as a proportion (number per million population).

Both the USRDS and the CORR databases adjust incidence and prevalence rates to a reference population using a direct method. Use of an adjusted rate accounts for growth and aging of the general population and permits meaningful comparisons across years. In other words, the adjusted rate assumes a constant reference population.

1.4.3 Incidence and Prevalence of ESRD

The ESRD program in the United States has grown from approximately 10,000 beneficiaries in 1973, when the Medicare entitlement became effective, to 86,354 in 1983 to 304,083 patients as of Dec 31, 1997 [6, 7]. The prevalence rate was 1105 per million population, or 1 in every 1000 person is receiving RRT as of December 31,1997. Prevalence growth rates provide important information for determining future ESRD resource needs and it has risen every year, almost doubling during the past decade. Most of the change in prevalence rates is due to change in incidence rates because death rates have been comparatively stable. During 1997, 79,102 new patients started ESRD. The incident rate was 287 per million. The annual percent increase was near 10% at the start of the decade and has fallen to a less than 5% increase in 1997. Despite these data suggesting that the incident rate of ESRD is slowing down, the pattern is still one of continued growth [10].

In Canada, in 1996, the number of patients on RRT was 19,424 reflecting a prevalence rate of 648.2 per million, representing a 5.9% increase from 1995 to 1996 [8]. The total number of new ESRD patients was 3,322, representing an age-adjusted incidence rate of 110 per million and a 3% increase in the number of new patients from 1995 [8]. Table 1 compares ESRD population in Canada and the U.S.A.

1.5 Characteristics of the ESRD Patient Population

In 1997, in the U.S. the average age was 56 for prevalent patients and 61 for incident patients. Incidence increased fastest and most consistently in the oldest (75+) age range. The average age of the prevalent population is lower due to the increased survival and younger age of the transplant population. Males represented 53% of incident patients in 1997. The annual percent increase in incidence rates was similar for males and females. The racial distribution of incident ESRD patients continues to show disproportionately high rates in blacks and Native Americans. In 1997, blacks constituted 29% of new ESRD patients as compared to 12.6% of the US population. Native Americans constituted 1.2% of ESRD patients as compared to 0.8% of the US population. The age–sex adjusted ESRD incidence rates were much higher for blacks (873 per million) and Native Americans (586 per million) than for the Asian Pacific Islander (344 per million) and white (218 per million) populations [11].

The cause of ESRD is subject to a certain amount of uncertainty. ESRD caused by diseases such as polycystic kidney disease and diabetes is easily defined. There is more uncertainty in attributing hypertension as the cause of ESRD, even though the association between blood pressure and ESRD has been established in recent epidemiological studies [12, 13]. Hypertension is often the first clinical sign of CRF and can be a sign of CRF versus the actual cause of the disease. Diabetes is the most common attributed cause of ESRD (41%), followed by

hypertension (28%), glomerulonephritis (11%), and cystic disease (4.0%). Other causes combine to make up 16% of new ESRD.

Table 1: Epidemiology of ESRD in Canada and USA

	Canada (1996)	USA (1997)
Incidence (per million population)	110	287
Prevalence (per million population)	648	1105
% Transplants	46	28
% HD	36.5	63.3
% PD	17.5	8.7
% Dialysis only HD	67.6	87.9
PD	32.4	12.1
Age Incident (Mean)	60	61
Prevalent (Mean)	55	56
Causes of ESRD % DM	29	41
HTN	17.6	28
GN	16.1	11

In 1996, in Canada, the average age was 60 for incident patients and 55 for prevalent patients. Males form the majority of new patients starting treatment in all age groups, except children under age 15 and individuals over age 75. The four known leading causes of ESRD requiring RRT were diabetes (29%), glomerulonephritis (16%), hypertension, including renovascular disease (18%) [8].

1.6 Renal Replacement Modalities

In 1997, in the U.S., 63% of the ESRD population was receiving HD, 28.1% had a functioning transplant and 8.7% were on PD. As of December 1997 12% of the dialysis population were receiving treatment with PD and 88% were receiving treatment with HD [11].

In 1996, in Canada, 36.5% of the ESRD population was receiving HD up from 32.4% in 1990, 46% had a functioning kidney transplant and 17.5% were on PD. Of the total dialysis population, 67.6% were on HD and 32.4% were on PD [8].

1.7 BURDEN OF ILLNESS IN END-STAGE RENAL DISEASE

1.7.1 Morbidity in the ESRD Population

Patients with ESRD experience significantly greater morbidity, including a substantial decline in QOL compared to aged-matched controls [10]. The frequency and duration of hospitalization has been used as a measure of QOL because of the impact that it can have on the lifestyle of patients [4, 15]. According to the USRDS data, the mean number of admissions for ESRD patients during 1995 was 1.3 for patients younger than 65 and 1.4 for patients older than 65 years. The average number of hospital days per year was 11.4 for ESRD patients older than 65 compared to a mean of 7.1 hospital days per year for non-ESRD patients over the age of 65 years [7, 16].

1.7.2 Mortality in the End-Stage Renal Disease Population

The availability of RRT has allowed the survival of patient with ESRD, previously a fatal illness. Despite improvement in the overall quality of dialysis therapy, the mortality among dialysis patients remains high. The expected lifetime of dialysis patients is 16% to 37% that of the age-, gender-, and race-matched US population. As an example, the mean expected remaining life span is only 9.3 years for a person beginning dialysis at 40 and 4.3 years for a person beginning dialysis at 59 [17]. These values in older patients are only slightly better than those in patients with lung cancer, but much worse than the general population (37.4 and 20.4 years at 40 and 59 years respectively).

1.7.3 Cause of Death in the End-Stage Renal Disease Population

There are three major causes of death in dialysis patients: cardiovascular disease, accounting for approximately 50% of cases, infection, accounting for 15–20%, and withdrawal from dialysis, accounting for 5–10% [17-19]. While a decline in cardiovascular death has recently occurred in the general population, a similar trend has not been seen in the dialysis patient [20]. This may be due to the high prevalence of co-morbid conditions, the inability of dialysis to fully replace the functions of the native kidney, and adverse consequences or side effects of RRT. The average age, of ESRD patients is over 60 years and approximately 16% are over 74; and many have underlying cardiac disease. It is estimated that only 27% of patients about to enter the dialysis regimen have a

normal echocardiogram, while 19% already have severe left ventricular hypertrophy [21, 22].

Although it is not clear if CRF is associated with "accelerated" atherosclerosis, coronary artery disease is very common. Factors that are common in the ESRD population and promote the develop of coronary disease and cardiovascular mortality include hypertension, which is present in approximately 80% of patients at the onset of dialysis, left ventricular hypertrophy, due both to hypertension and chronic anemia, and possibly hyperlipidemia, as the most predominant abnormality in maintenance dialysis is hypertriglyceridemia. Several factors have been associated with increased mortality. These include dialysis time, dialysis clearance or dose, RRF, type of dialyzer, fluid balance, malnutrition, mode of dialysis and calcium/phosphate ratio [23, 24].

1.8 Economic Costs of End-Stage Renal Disease

Total expenditure for ESRD patients in the United States has increased dramatically, as a result of the growing patient population and the increasing costs of treating older and sicker patients [25]. The estimated total US ESRD costs in 1997 was 15.64 billion dollars, reflecting Medicare and non-Medicare payments. Information is available through Medicare payments on per patient year at risk by treatment modality costs. Total Medicare spending per year at risk for dialysis patients averaged $51,000 per year. Hemodialysis averaged $52,000 per year, whereas PD payments averaged $45,000 per year. Annual

costs for ESRD treatment rise steadily with age from a low of $23,000 per person per year for ages 0 – 19, to a high of $57,000 per person per year for ages 75 and older (148% increase between the youngest and oldest age groups) [17].

In Canada, Prichard estimated the cost of RRT using 1988 data, in a tertiary centre. In the first year CAPD cost $31,799, in-centre HD $37,242 and self-care HD $33,774, quoted in Canadian dollars [26]. This data does not reflect the cost of new connections used for PD, cost of erythropoietin nor costs involved with switching modalities. Goeree et al (1995) estimated the cost of dialysis modalities for ESRD using a societal viewpoint. The average cost per patient year in 1993 dollars was $88,585 for in-center HD, $55,593 for home HD and $44, 790 for PD [27].

1.9 Summary

The ESRD population continues to grow in size and severity, challenging the medical community to provide care that will improve patient morbidity, mortality and QOL in a cost efficient manner. The following chapters will discuss the benefits of RRF in the ESRD patient and the measurement of RRF. An epidemiological study to determine the predictors of RRF loss in a national sample of incident patients with ESRD will be presented. Initiatives for a further study in measurement of RRF in the remnant kidney and interventions that may slow the progression of RRF in the native kidney will be discussed.

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CHAPTER 2: THE ROLE OF RESIDUAL RENAL FUNCTION IN END-STAGE RENAL DISEASE

2.1 Introduction

Residual renal function (RRF) is often used as a synonym for glomerular filtration rate (GFR), considered the gold standard measurement of kidney function. However it needs to be emphasized that the kidney is involved with many other functions such as production of erythropoietin [1], calcium, phosphate and vitamin D homeostasis [2, 3], volume control and removal of low and middle molecular weight proteins [4-6]. The value of preserving these functions has been identified for patients with chronic renal failure (CRF). Burgess has recently reviewed this literature and developed evidence-based recommendations on conservative treatment to slow deterioration of RRF in the CRF population [7]. Proteinuria, hypertension, initial serum creatinine and cause of ESRD predicted RRF progression in this population. Tight control of blood pressure, particularly in the presence of significant proteinuria, moderate protein restriction, and treatment with angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers appear to slow the rate of deterioration of RRF in the CRF population [7]. There is minimal evidence looking at the factors that preserve RRF in the ESRD population. This chapter examines the available literature looking at the benefit derived from preserving the RRF in patients on dialysis.

2.2 Residual Renal Function and Dialysis Adequacy

An adequate dialysis dose can be defined as the dose below which one observes a significant worsening of morbidity and mortality. Urea kinetic modeling (UKM) is a tool for quantifying dialysis dose and nutrition. The model generates the values of Kt/V_{urea}, as an indicator of dialysis dose for small molecules, and the normalized protein catabolic rate (nPCR). Gotch and Sargent introduced Kt/V_{urea} as a measure of HD adequacy, where K is the urea clearance, t the treatment time; and V is the volume of urea distribution [8]. In PD, Kt/V_{urea} and creatinine clearance (CrCl) are used to assess the adequacy of dialysis clearance [9, 10]. The concept of dialysis adequacy could involve topics such as adequate fluid removal, blood pressure control, acid base balance, calcium and phosphate control, adequate nutrition, and prevention of arteriosclerosis; however, this discussion will focus on clearance of urea and creatinine.

Numerous outcome studies have demonstrated a relationship between the delivered dose of HD and patient mortality and morbidity [11–19]. Relationships between dialysis adequacy indices and clinical outcome parameters have also been observed in long-term studies of PD [20–24]. A Kt/V_{urea} of 2.0 per week and a total creatinine clearance (CrCl) of at least 60 L per week per 1.73 m^2 have been recommended for patients on PD and a Kt/V_{urea} of 1.2 per dialysis session is recommended for patients on HD [25, 26].

In all patients who have RRF, adequacy is dependent on the total clearance (the renal clearance i.e. RRF plus the dialysate clearance) of urea and creatinine. The contribution of RRF to total solute and water clearance is significant, especially in the first year of dialysis and is often necessary to attain targets of Kt/V_{urea} and CrCl. In PD, a renal CrCl of 1.0 ml/min will produce a weekly CrCl value of 10 liters representing approximately 17% contribution to the total weekly CrCl values. RRF exerts a greater contribution to CrCl than to Kt/V_{urea} due to the large molecular size of creatinine. Given its important contribution, it is now recommended that RRF be measured on an ongoing basis and considered in the dialysis prescription [22–26].

The total Kt/V_{urea} usually decreases gradually with time, mainly due to the decline in RRF. The relative contribution of RRF to Kt/V_{urea} and CrCl has been addressed in several studies in the PD population. Brunkhorst et al have studied 104 patients treated with CCPD [27]. The more the RRF decreased, the more frequently manual CAPD exchanges became necessary. With complete loss of RRF, CCPD had to be combined with one or two additional CAPD exchanges per day in order to achieve a weekly CrCl of 55 L per week. Teehan et. al. have also demonstrated the importance of RRF when prescribing PD [28]. The presence of RRF was found to have a profound effect on the prescribed dialysis dose. A 70 kg patient with 4.0 ml/min of RRF would need to have to drain 7.6 L of dialysate per day as compared to a patient in the absence of RRF who would require 13.4 L of dialysate per day. In a study of 64 CAPD patients who received CAPD 2

liters x 4 exchanges per day, Heimbürger et. al. found that RRF accounted for 25% of the Kt/V_{urea} and 38% of the CrCl [29]. This agrees with a study of 58 CAPD patients by Tattersall et al. [6], which showed that RRF was the strongest determinant of differences in Kt/V_{urea}.

Several recent studies have identified the importance of dialysis adequacy and in particular the contribution of RRF to patient morbidity and mortality. The CANUSA Study was a prospective cohort study of nutrition and adequacy in CAPD involving 680 PD patients from 14 centres in Canada and the United States. This study showed that Kt/V_{urea} was a strong predictor of patient survival [22]. A decrease of 0.1 units Kt/V per week was associated with a 5% increase in relative risk of death. Further analysis of the CANUSA Study has shown that RRF was responsible for the differences in adequacy and mortality. Every 0.5 ml/min. higher RRF was associated with a 9% lower risk of death; relative risk = 0.91; $p<0.01$ [30]. Maiorca et al looked at the effects of age, pre-treatment risk factors, serum albumin, transferrin, nPCR, Kt/V, normalized weekly CrCl, RRF, and subjective global assessment (SGA) on nutritional status, survival, and morbidity in a three-year prospective study of 68 CAPD patients and 34 HD patients [31]. Low dialysis Kt/V, defined as < 1.1Kt/V per treatment in HD patients and < 1.7 per week in CAPD patients, predicted death with a RR = 6.69; p 0.001. Each ml/min increase in RRF was associated with a 60% lower risk of death; relative risk = 0.40; $p=0.001$ [30]. In CAPD patients, weekly CrCl < 50liters/week was associated with higher mortality than in patients with CrCl > 50

liters/week (p=0.011). Patients with low CrCl had lower RRF. This suggests that loss of RRF leads to under dialysis that significantly affects patient survival. Interestingly, the effect of CrCl on survival in a Cox analysis disappeared when RRF was included in the model. This suggests that the effect of CrCl is mainly due to the RRF and raises the question of whether clearance from the native kidney and peritoneal clearances are really equivalent [31]. Davies et al looked at patients on CAPD between 1990 and 1995 in a prospective, longitudinal, observational study [32]. On entry, and at six monthly intervals, estimations were made of weight, body mass index, plasma albumin, Kt/V, RRF, nPCR, low molecular weight solute transport, and peritoneal protein losses. During the first 18 months of dialysis treatment, there was a rapid and significant decline in total Kt/V, due entirely to the loss of RRF. The loss of RRF was significantly faster in non-survivors compared to survivors ($p < 0.05$).

Tattersall looked at 58 patients undergoing standard CAPD [33]. Urea kinetic modelling was performed for each patient during the first three months. The number and length of any hospital admissions during the six months were recorded, as were deaths and transfers from PD to HD. Total Kt/V was significantly correlated with RRF ($r = 0.79$; $p < 0.001$). There was a significant negative correlation between hospital admissions per year and RRF ($r = -0.32$; $p < 0.05$).

Diaz-Buxo et al looked at 2686 patients receiving CAPD or cyclic PD on January 1, 1994 [34]. Demographic, laboratory, peritoneal, and renal clearances were analyzed for their effect on patient survival. Renal clearances, but not peritoneal clearances, were associated with risk of death. Each ml/min. increase in RRF (equivalent to 10 L per week) was associated with a 12% reduction of odds ratio whether or not adjusted for peritoneal clearance.

Faller and Lameire have reported on 23 patients maintained on CAPD for seven year [35]. Total Kt/V_{urea} declined from 0.88 ± 0.08 during the first years to a minimum value of 0.62 ± 0.07 after seven years. The contribution of RRF to the total Kt/V decreased from 21% to a negligible 3% after seven years. There was a negative correlation between the mean Kt/V_{urea} per year and the number of hospitalization days in that year ($r = -0.23$; $p < 0.01$). It was noted that the RRF in the survivors was much greater than the RRF in the decedents prior to their deaths.

Davies identified 25 PD patients who survived five years or more in an observational study [32]. Longitudinal changes over the first five years of treatment included a loss of RRF, increasing solute transport, and a decline in nutritional status. Patients surviving long-term PD were characterized by prolonged RRF, maintained nutrition, and lower solute transport.

Lowrie (1998) recently reported on data from the patient statistical profile (PSP) system, supported by Fresenius Medical Care, North America [37]. PSP is an industry-supported database designed to detect management changes and support continuous quality improvement. PSP can be viewed as a sub-sample of the USRDS since patients registered with PSP included 23.3% of the USRDS registered patients during the past decade. The authors evaluated measures that were most closely associated with mortality using data from 1991 through 1995. Lower albumin, creatinine, percent ideal weight, and urea reduction ratio, (measure of dialysis dose) and declining RRF increased the odds ratio of death. Interestingly peritoneal clearance did not affect the risk of death. Figure 1 illustrates this information. These profiles suggest again that the equivalence of clearances cannot be assumed and that renal clearance may offer greater benefit to survival.

2.3 Residual Renal Function and Nutrition

A strong association exists between nutritional status and morbidity and mortality in patients with ESRD who are treated with HD and PD [12, 22, 38-45]. The CANUSA Study showed that better nutritional status, as estimated by serum albumin concentration, nPCR, % lean body weight and SGA were also associated with improved outcomes [46]. The study demonstrated a strong association between baseline RRF and each of the estimates of nutritional status at the start of dialysis. Those patients with lower RRF at the start of dialysis had consistently worse nutritional status regardless of the estimate used. This

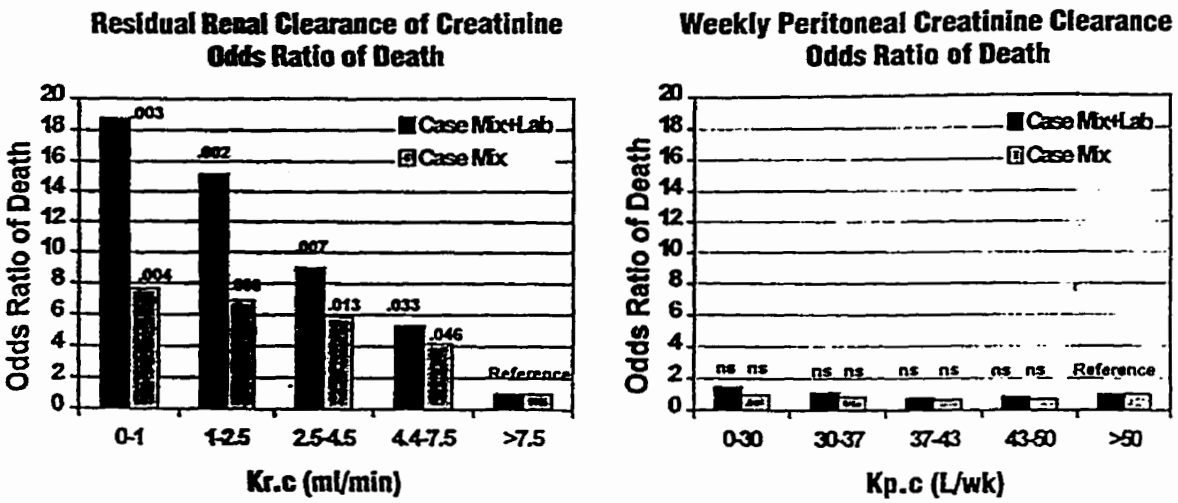

Figure 1. Risk profiles showing the odds of death by residual renal creatinine clearance ($K_{r.c}$) or peritoneal creatinine clearance ($K_{p.c}$) among peritoneal dialysis patients.

Lowrie EG, Zhu X, Lew NL: Primary associates of mortality among dialysis patients: Trends and reassessment of Kt/V and urea reduction ratio as outcome-based measures of dialysis dose. Am J Kid Dis 32;6(Suppl 4):S16-S31, 1998

supports the observation of Ikizler et al, who demonstrated that dietary protein intake begins to decline steadily after CrCl decreases below 50 ml/min. [47].

Caravaca et. al looked at 9 patients with significant RRF at the beginning of PD therapy. The number of peritoneal exchanges was increased as RRF fell to maintain a Kt/V_{urea} equal to 2.0. The mean energy intake normalized for actual body weight decreased significantly after the loss of RRF (37.5 ± 10.1 kilocalories per kilogram per day versus 32.8 ± 8.9 kilocalories per kilogram per day; p=0.02). Loss of RRF led to a reduction in dietary protein and energy intake despite the maintenance of similar Kt/V_{urea} [48].

2.4 The Influence of Residual Renal Function on $ß_2$-Microglobulin Levels

Most of the literature focuses on clearance of urea and creatinine as markers of adequacy in both HD and PD. It is known that chronic retention of proteins of low molecular weight seems to be connected with some of the observed problems of ESRD, such as reduced immune function, amyloidosis, and hormone imbalance [49]. $ß_2$-microglobulin ($ß_2M$), a low molecular weight protein, forms the light chain of the Class 1 major histocompatibility antigens [50]. The concentration in body fluids increases in proportion to loss of kidney function, as it is normally eliminated by the process of GFR followed by reabsorption and catabolism by the proximal tubular cells [50, 51]. Carpal tunnel syndrome, erosive arthropathy, and destructive cystic bone disease are attributed to the deposits of this amyloid substance consisting mainly of $ß_2M$ [52] and are complications of long-term

dialysis therapy. Tielmans et al studied 25 HD and 25 PD patients matched for RRF in duration of dialysis therapy. In both PD and HD, $ß_2M$ was inversely correlated with RRF ($p < 0.001$) [53, 54]. Blumberg et al looked at 52 patients on HD and found the $ß_2M$ level was correlated with time on HD ($r=0.43;p<0.01$) and was inversely correlated to with RRF ($r=0.87$; $p<0.001$). Brown et al studied 34 patients on maintenance HD. Serum $ß_2M$ and alpha 1-microglobulin levels were closely related to daily UV and RRF ($r=0.83$; $p < 0.001$) [55]. Similarly, Amici et al demonstrated the contribution of RRF in determining the $ß_2M$ levels, and it is seemingly more important than $ß_2M$ peritoneal clearance [56].

2.5 Residual Renal Function and Anemia

Anemia related to ESRD contributes to a number of serious problems including, ventricular hypertrophy, angina, and congestive heart failure [57]. These abnormalities reduce quantity and quality of life in the ESRD population [58]. It has been observed that PD patients require fewer transfusions and have better control of anemia than do HD patients [59, 60]. One of the differences observed between PD and HD in these first years of treatment is the presence of a higher RRF in PD. This suggests that RRF may have an influence on anemia in the ESRD population. The GFR in patients with CRF shows a clear relationship with hematocrit levels, but data is less supportive when studying patients already on dialysis [61]. Nolph et al did not find a relationship between hematocrit and RRF [62], however, most of the patients were anuric or had a GFR of < 2.0 ml/min. Opatrny et al followed 22 CAPD patients to study the importance of peritoneal

clearance and RRF on the degree of anemia [63]. A significant correlation between hematocrit and total Kt/V ($r=0.61$; $p < 0.01$) and RRF ($r=0.43$; $p < 0.05$) was demonstrated. In a regression analysis, dividing the total Kt/V into peritoneal and renal components, a significant correlation between hematocrit and renal clearance ($r=0.47$; $p < 0.05$) was found. The authors conclude that the RRF appears to have greater influence on anemia than on the peritoneal Kt/V.

2.6 Residual Renal Function and Other Benefits

Aluminum accumulates in patients undergoing dialysis contributing to osteomalacia, encephalopathy, and anemia. The principal source of this aluminum is the water used to prepare the dialysate and aluminum-containing phosphate binders. Altmann studied 106 HD patients to look at the effect of RRF on aluminum concentrations [64]. In a multiple-regression analysis, urine volume (UV) was correlated to serum aluminum levels significantly at $r=0.70$; $p < 0.001$.

Phosphate excretion is altered in ESRD due to reduced nephron mass. Phosphate retention contributes to secondary hyperparathyroidism, calcifications, pruritus and further loss of RRF [65]. Block et al reported on data from the USRDS looking at phosphate as a predictor of death in the ESRD population [66]. The relative risk of death for those with a serum phosphate > 6.5mg/dl was 1.27 and was not diminished by statistical adjustment for coexisting medical conditions, delivered dose of dialysis, nutritional parameters or markers of non-compliance. López-Menchero et al followed calcium phosphate metabolism and

found a significant relationship between RRF and serum phosphate level (r^2=0.19; p<0.05) in the ESRD population [67].

Pregnancy is often difficult to achieve among women on dialysis. The registry of European Dialysis and Transplant Association collected information on successful pregnancies in women treated with dialysis and transplantation. Sixteen successful pregnancies occurred in women on dialysis, all of who had RRF [68].

2.7 Residual Renal Function and Quality of Life

Merkus et al has recently reported on the quality of life (QOL) of patients three months after the start of dialysis [69]. Patients' self-assessment of QOL was measured using the SF-36, a 36-item short form health survey questionnaire encompassing eight dimensions. One hundred and twenty HD patients and 106 PD patients completed the SF-36. A higher number of co-morbid conditions, a lower hemoglobin level, and a lower RRF were independently related to poorer QOL. They found that patients with a lower RRF reported a worse QOL, while no effect of dialysis Kt/V could be demonstrated, suggesting that clearance achieved by the native kidneys is superior to clearance obtained by dialysis. In addition, deteriorating RRF and decrease in the UV may give rise to a worse perception of QOL by a growing awareness of the complete dependence on dialysis [69].

Most of the above reported studies have either retrospectively looked at the contribution of RRF to dose, nutrition, etc. or have added it as a secondary outcome to the study objectives. In a recent publication, Lopez-Menchero et al prospectively studied the influence of RRF on dialysis dose, nutritional parameters, anemia, and calcium-phosphate metabolism in 37 PD patients [67]. Residual renal function was measured as the average clearance of creatinine and urea and assessments were done at 1 month, 12 months and 24 months after study start. In a multiple regression analysis RRF was shown to be the most important factor in terms of total CrCl (r^2=0.94;B=0.999), total Kt/V (r^2=0.8; B=0.489), nPCR (r^2=0.53; B=0.446), albumin (r^2=0.25; b=0.229), hemoglobin level (r_2=0.28; B0.407) serum phosphate levels (r^2 = 0.19; b=-0.594). This provides stronger evidence supporting the benefits of RRF and reinforces the need to identify predictors of RRF loss and preserve the RRF in patients on dialysis.

2.8 Summary

RRF is directly related to total dialysis dose, nutritional markers, $ß_2M$ levels, anemia control, phosphate and serum aluminum levels and QOL. Dialysis dose, nutritional factors, and phosphate control are related to patient morbidity and death. We, therefore, can conclude that RRF is also an important contributor to modifying patient morbidity and mortality. Measures that can be identified as associated with better preservation of RRF should have a beneficial effect on patient morbidity and mortality.

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CHAPTER 3: MEASUREMENT OF RESIDUAL RENAL FUNCTION

3.1 Introduction

The usefulness of any diagnostic test is based on its accuracy (comparison to a standard), precision (related inversely to the variability of measurements), and convenience [1]. In clinical practice, physicians use test results to characterize the degree of functional abnormalities in the individual patients. Tests are then repeated to assess changes in individuals over time. In clinical trials, investigators use test results to characterize a study population and repeated evaluations are performed to assess changes in the population over time. The decision to use a particular test depends on features of the test, features of the subjects to be tested and the setting in which the test is used.

The available methods for measurement of residual renal function (RRF) and the advantages and disadvantages will be discussed in the following chapter. The use of urine volume (UV) will be discussed in detail to support its role as a measure of RRF in ESRD patients.

3.2 Glomerular Filtration Rate

The glomerular filtration rate (GFR) is considered to be the best overall measurement of renal function in health and disease. Advantages of the GFR as an index of renal function are that it is a direct measure of renal function, it is reduced prior to the onset of symptoms of renal failure and the impairment in

GFR is associated with the structural abnormalities observed in CRF. Determination of the GFR requires the utilization of a substance that is freely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubule. Inulin, a fructose polysaccharide, exhibits these characteristics and is generally considered the gold standard for GFR measurement [1]. Inulin must be administered intravenously, requires frequent analyses of blood and urine samples and is not readily available. Other radio-labeled chelating compounds (e.g. ^{99m}Tc-DTPA), have been used to measure the GFR however, they too can be difficult to perform accurately, are time consuming, expensive, and often impractical [1,2]. GFR can be relatively insensitive for detecting early renal disease, estimating its severity and monitoring its progression.

Because GFR varies directly with renal size, which in turn varies with body size, GFR is conventionally factored by body surface area. In normal humans, GFR is approximately 125ml/min/1.73m^2. The value of 1.73m^2 reflects the average value for men and women. Despite adjustment for body surface area, however, the normal GFR for women is approximately 8% lower than for men.

Other tests, such as serum creatinine, creatinine clearance (CrCl), urea clearance, the average of creatinine and urea clearance, and urine volumes (UV) have been used to assess RRF in the CRF population. Levey and Walser have reviewed this literature [1, 2].

3.3 Serum Creatinine and Creatinine Clearance as a Measure of RRF

The creatinine clearance is the most widely used test to estimate the GFR. The use of serum creatinine as an exogenous filtration marker was first reported in 1926 [3]. Creatinine is derived from the metabolism of creatinine in skeletal muscle and from dietary meat intake. Like inulin, creatinine is freely filtered across the glomerulus and is not reabsorbed or metabolized by the kidney, however approximately 15% of urinary creatinine is derived from tubular secretion [4]. Creatinine clearance, therefore, usually tends to exceed the GFR by the 10 to 15 percent, because of the urinary creatinine that is derived from tubular secretion. The CrCl is usually determined from a 24 hour urine collection, since shorter collections tends to give less accurate results. There are two major errors that can limit the accuracy of the CrCl, an incomplete urine collection and increasing creatinine secretion. Figure 2 shows results from a representative study by Shemesh and colleagues, in which simultaneous measurements of GFR by inulin clearance, CrCl, and serum creatinine level were made in patients with glomerular disease and a GFR between 1- 170ml/min [4]. It is clear from these data that neither the CrCl nor the serum creatinine level accurately estimates GFR. The sensitivity (proportion of true positives) of a reduced CrCl or elevated serum creatinine level in detecting a reduced GFR is only 75% and 61% respectively. Both the CrCl and the reciprocal of creatinine have been shown to be unreliable markers of renal function in chronic renal failure and ESRD [5, 6]. Nonetheless, the serum creatinine concentration is

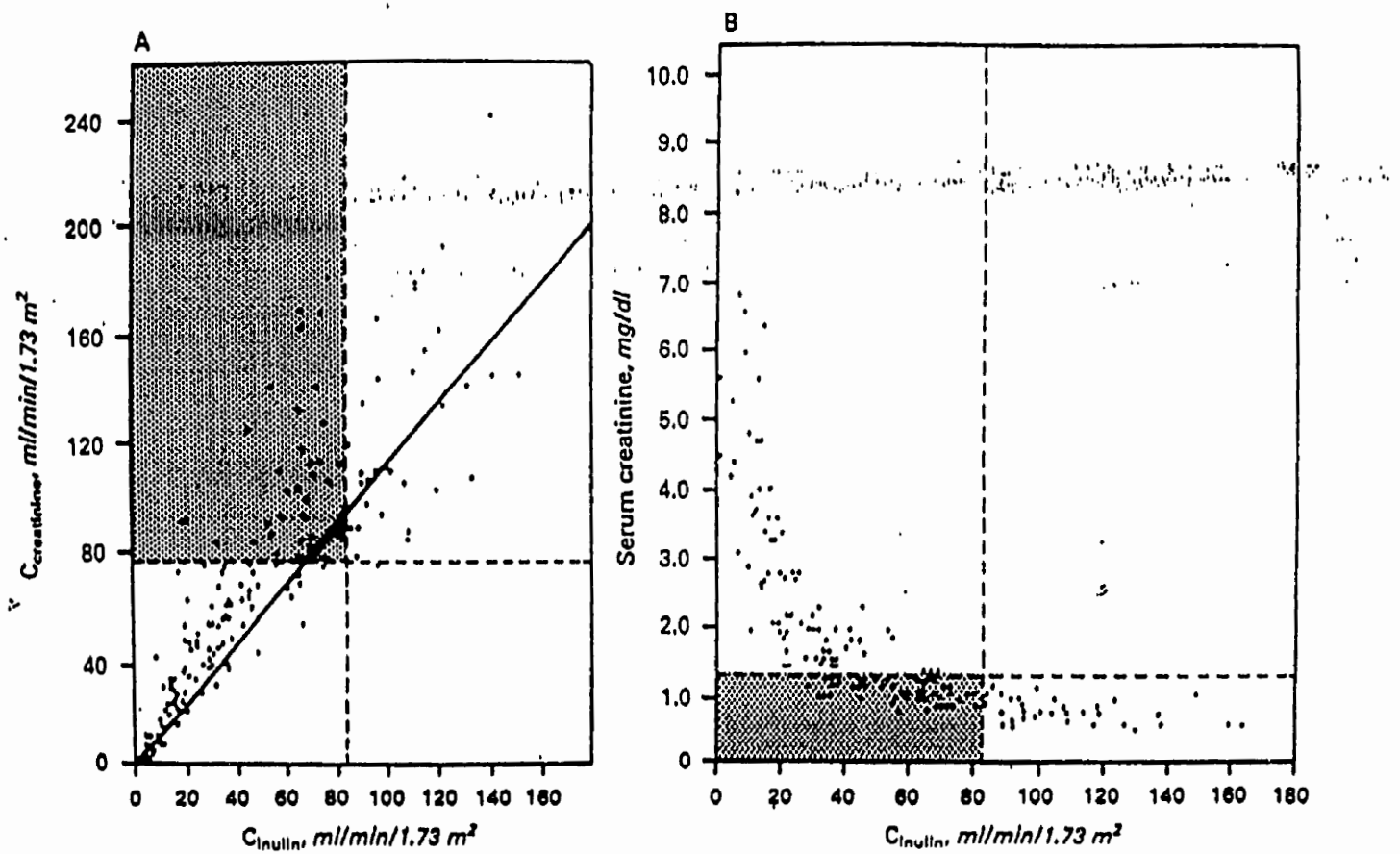

Figure 2. *Relationships between GFR, C_{cr} and P_{cr} in patients with glomerular disease.* Vertical dashed lines in A and B correspond to the lower limit for inulin clearance (82 ml/min/1.73 m^2); the horizontal line in A corresponds t the lower limit for creatinine clearance (77 ml/min/1.73 m^2); the horizontal line in B corresponds to the upper limit for the serum creatinine concentration (1.4 mg/dl). The shaded areas include values for patients in whom inulin clearance is reduced but creatinine clearance (A) or serum creatinine concentration (B) remains normal.

Shemesh O, Golbetz H, Kriss JP, Myers BO: Limitation of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 28:830-838, 1985

widely used to measure progression of renal disease in clinical practice whereas the CrCl is more commonly used in clinical trials.

3.4 Predictive Equations to Estimate Creatinine Clearance and GFR

A number of different formulae have been developed to estimate CrCl and GFR in patients with CRF without timed urine collections [7 – 9]. These formulae were developed and validated on a population with CRF. The Cockcroft Gault formula estimates CrCl and includes age and weight with a correction factor for gender [7]. The Walser formula estimates GFR and was developed in 85 patients with established CRF with serum creatinine concentration > 177 *m*mol/L. The glomerular filtration rate (^{99m}Tc-DTPA) and serum creatinine were determined and a prediction equation was developed which included creatinine, age, and weight with a correction factor for gender [8]. Levey, from the Modification of Diet and Renal Disease group (MDRD), recently published a formula for estimation of normalized GFR from serum creatinine [9]. This formula was developed on 1070 patients from the MDRD study. They performed a cross-sectional study of GFR (Iohexal clearance), CrCl, serum creatinine concentration, and demographic and clinical characteristics in patients with CRF. A simplified prediction equation to estimate the normalized GFR included serum creatinine, age, gender, serum urea nitrogen levels, and serum albumin. The equation explained 90.3% of the variance in the logarithm of GFR in the validation sample, representing a strong correlation. The equations used to estimate GFR and CrCl are found in Appendix 2.

Unfortunately these equations have not been validated in a sufficiently large population of patients near the onset of ESRD. None of these formulae have been used to assess RRF in patients on dialysis because they depend on the native renal function as the sole mechanism for solute removal and CrCl, i.e. without dialysis.

3.5 The Average of Creatinine and Urea Clearance as a Measure of RRF

An average of creatinine and urea clearance, using 24-hour urine collections, has shown to be a better estimate of GFR in the ESRD population [11–15]. As GFR declines, urea absorption is reduced and is less dependent on the state of hydration. The fraction of reabsorbed urea is approximately the same as the fraction of excreted creatinine that is derived from tubular secretion. Consequently, in a patient with a GFR of < 15 ml/min per 1.73 m^2, the average of the urea and creatinine clearance is a closer approximation of GFR than creatinine clearance alone [1-15].

Lubowitz et al [11] compared inulin clearance, considered the gold standard of GFR measurement, to average clearance of urea and creatinine. Inulin clearance values for this group range from 20.3 ml/min to < 1 ml/min with an average of 10.68 ml/min. CrCl was greater than inulin clearance in all 15 patients, while urea clearance was less than inulin clearance in all patients except one. In Figure 3, the average of the creatinine and urea clearance, for each patient, is plotted as a function of the inulin clearance value. The points are

clustered about a line having a slope of 1.0. The equation for the linear regression line transcribed by the experimental points using the method of least squares is $y = 1.034x + 0.24$.

Van Olden et al looked at RRF among ten patients receiving chronic PD [12]. Two 24-hour clearance periods were investigated. Creatinine, urea, and an average of the creatinine and urea clearance were compared to inulin clearance with and without the administration of cimetidine. The administration of cimetidine blocks the secretion of creatinine and provides a closer estimate of the GFR. The average of the creatinine and urea clearance approximated the GFR as measured with inulin, $r = 0.98$; $p < 0.001$ [12]. Lavender et al looked at 100 simultaneous clearances of inulin, ^{51} Cr-labelled Edetic acid (EDTA), creatinine, and urea in 28 patients with CRF [13]. Comparison was made between the average of the urea and creatinine clearances and inulin clearances in patients with inulin clearances < 15 ml/min. There was a good agreement between these two measurements ($r = 0.993$; $p < 0.001$). Bauer et al looked at 31 patients with inulin clearance < 20 ml/min/1.73m^2 who underwent simultaneous timed creatinine, urea, and inulin clearances [14]. The average of the creatinine and urea clearance correlated positively with the inulin clearance and was the best clinical indicator of GFR, ($r = 0.85$; $p < 0.001$).

The National Kidney Foundation Dialysis Outcomes Quality Initiatives (NKF – DOQI) recommends using the mean of the creatinine and urea clearances to

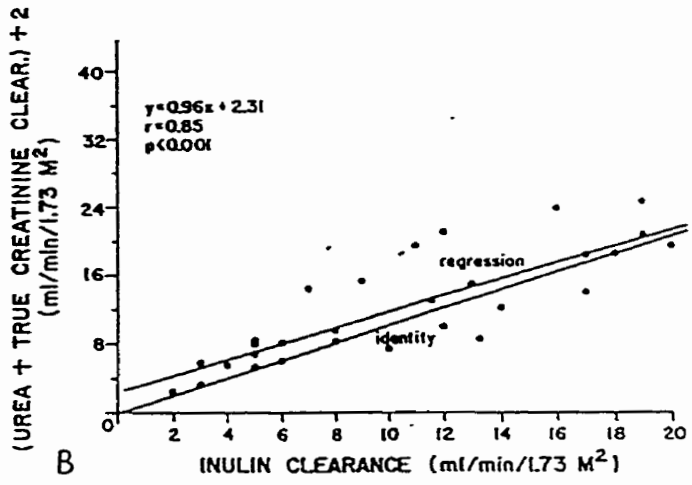

Figure 3. Relationship between average of the urea and the true creatinine clearance and inulin clearance.

Lavender S, Hilton P, Jones NS: The measurement of GFR in Renal Disease. Lancet 2:1216-1218, 1969

determine the RRF component of CrCl and as an estimate of GFR in the PD population [16].

3.6 Urine Volume As A Measure Of Residual Renal Function

Urine volume (UV) was used as the measure of RRF in the study of predictors of RRF loss among patients on dialysis. The causes of variation in UV as well as its relative merits and weakness as a marker of RRF will be discussed.

Although the GFR is very low in patients with ESRD, the UV is variable. These findings are due to the fact that UV is determined by the difference between the GFR and the rate of tubular reabsorption. It is likely that volume expansion, due to sodium retention, and urea osmotic diuresis play a more important role in the persistent UV [17]. Volume expansion alters hormonal milieu causing an increase in atrial natriuretic peptide and a decrease in aldosterone, which promotes sodium excretion despite the very low GFR. In comparison, water intake plays a relatively small role in regulating the UV in CRF. These patients can neither dilute nor concentrate their urine normally. The range of urine osmolality that can be achieved may vary from a minimum of 200 *m*osmol/kg to a maximum of 300 *m*osmol/kg, as compared to 50–1200 *m*osmol/kg in the normal subject [17]. The net effect of this anti-diuretic hormone (ADH) resistance is that variance in ADH release and response to changes in water intake has relatively little effect on the UV.

In spite of these shortcomings, UV has been correlated to GFR in a number of studies [18 – 21]. Milutinovic et al simultaneously compared measured clearances of iothalamate, DTPA, inulin, endogenous creatinine, urea, and urine volume in patients receiving repetitive HD with a GFR < 5 ml/min. Data on UV and GFR were reported. Pearson correlation coefficient for inulin clearance and UV was calculated and the correlation was significant for each individual patient ($r = 0.71$; $p < 0.01$). In other words, once the relationship between the UV and CrCl is accurately determined, changes in 24-hour volume can be used for approximate calculation of clearances, as both decrease with time [18].

Tzamaloukas collected clearance studies including urine volume and dialysate volume on 108 CAPD patients. Urine volume predicted the total dose delivered to the patient [19]. An algorithm was developed from the urine volume to ensure adequate dosing was maintained. Van Olden measured RRF in 13 chronic HD periods in two interdialytic periods. Plasma sodium, chloride, potassium, urea, creatinine, albumin, osmolality, and inulin were measured at the beginning and the end of the interdialytic interval. Urine volume, sodium, chloride, potassium, urea, creatinine, protein, osmolality, and inulin were measured in daily collections during the complete interdialytic interval. There was a strong relationship between the change in UV and GFR for individual patients ($r = 0.82$; $p < 0.005$). They concluded that a change in UV during the interdialytic interval in HD patient is dependent on the change in GFR.

Urine volume has also predicted QOL in patients treated with chronic dialysis [23, 24]. Ravid et al looked at 38 patients with ESRD being treated with HD. They had all been established on chronic HD patients for 12 – 18 hours weekly for one to six years, and their course was relatively stable throughout the observation period. Patients' RRF was calculated as CrCl and UV was recorded. QOL was based on three clinical criteria: 1) the patients' well being, defined in terms of continuation of normal functions at home and work, 2) presence or degree of heart failure, based on subjective complaints, objective physical findings and the need for cardiac drugs, and 3) the presence and degree of anemia. These qualities were scored with 14 patients in Group A with a clinical score of 8 – 10, expressing a good QOL, 6 patients in Group B with a score of 5 – 6, and 15 patients in Group C whose score was 0 – 3, expressing a poor QOL. The mean RRF of Groups A, B, and C were 3.8 ml/min., 1.3 ml/min., and 0.59 ml/min. respectively. The differences between mean RRF of the three groups were highly significant ($p < 0.001$). Mean daily UV were 724 in Group A, 207 in Group B, and 52 in Group C. Regression analysis showed a significant correlation between the clinical scores and RRF ($r = 0.80$; $p < 0.005$) and between the clinical scores and the daily UV ($r = 0.78$; $p < 0.005$). There was also a good correlation between the RRF and the UV of each patient ($r = 0.84$; $p < 0.005$).

3.7 Summary

This literature supports the use of UV as a useful measure of RRF among ESRD patients. Urine volume is readily available, inexpensive and an easy

measurement of RRF. Despite the imprecision of this measure, the advantage of potentially developing hypotheses regarding factors predictive of RRF from a large data set were felt to outweigh the limitations of using this measure as an outcome variable.

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Ann Intern Med 130(6):461-470, 1999

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CHAPTER 4: METHODOLOGY

4.1 Introduction

This chapter expands upon the methodology used for the study, *Predictors of Loss of Residual Renal Function among New Dialysis Patients.* An abbreviated discussion of the methodology, the results and the discussion regarding this study are found in Chapter 5.

4.2 Patient Population

The USRDS Dialysis Morbidity and Mortality Study (DMMS) is an observational study in which demographic, co-morbidity, laboratory, treatment, socioeconomic, and insurance data were collected from a large random sample of dialysis patients in the United States, using the patients' dialysis records. The study included four phases ("waves") of data on a total of 24,000 dialysis patients over three years. Waves 1, 3, and 4 were historical prospective studies in which data was collected from patients receiving in-centre HD on December 31, 1993 and each included approximately 6000 patients. Wave 2 was unique in that it was a prospective study of a random sample of incident patients initiating dialysis in 1996 and included 4500 PD and HD patients. Wave 2 was the data set used for the study *Predictors of Loss of Residual Renal Function Among New Dialysis Patients.*

Each wave included a data collection instrument for collecting core data. This provided a consistent, fundamental data set that was shared among the different

waves. Questions included information relating to adequacy of dialysis, dialyzer membrane, and dialysis reuse. The core data is being used to develop a co-morbidity infrastructure that will be useful for investigation of other important research questions. In addition, both Waves 1 and 2 included a non-core component designed to address additional research questions that required a smaller sample size. In Wave 2 additional data was collected on PD prescription and delivery, RRF, and medications. Wave 2 was also unique in that an extensive patient questionnaire was administered at baseline with questions pertaining to QOL, pre-ESRD care, modality choice, transportation, and rehabilitation.

4.3 Patient Selection

Wave 2 of DMMS is a prospective study of incident HD and PD patients (Medicare and non-Medicare) who initiated ESRD therapy in 1996. For the purposes of this study, the definition of an incident patient is one who is receiving regular in-centre HD or any type of PD treatment for ESRD at least once weekly for the first time. This does not include patients receiving intermittent dialysis treatment for fluid overload or heart failure. Modality type was identified on day 60 of the ESRD. Patients treated with PD or HD on this date (day 60) were eligible. The modality assignment for patients on HD, but who were training for PD, on day 60 was deferred 10 days. Patients were excluded if they were on another form of RRT (example: home hemodialysis), if they had a previous

transplant, or if they were less than 18 years of age. The study start date was considered the date that the modality type was defined (about day 60 of ESRD).

The dialysis units included in Wave 2 are a random selection of 25 % of the dialysis units in the United States listed in the Master List of Medicare-approved dialysis facilities as of December 31, 1993, and all new dialysis units opening after January 1, 1994. The master list exists as part of the annual Medicare survey of dialysis facilities. The number of participating dialysis units was 799. Patients initiating ESRD therapy in 1996, in the selected dialysis units, and who met the inclusion/exclusion criteria were eligible for sampling. To obtain comparable numbers of PD and HD patients within the sample, PD patients were over-sampled by a factor of 5. All eligible incident PD patients were included, whereas only 20% of all corresponding HD patients were included, selecting only those with social security numbers ending with 2 or 9.

The selection of dialysis units occurred at the USRDS Coordinating Centre. Data collection materials were distributed to the ESRD networks, which in turn distributed materials to the 799 participating facilities. Patient selection and enrollment occurred at the dialysis units according to instructions provided by the USRDS Coordinating Centre. Patient enrollment commenced in March 1996.

4.4 Data Collection

Patient specific data were collected at the time of enrollment (study start), and after 8 to 18 months of follow up. Data collected at the time of enrollment included the following:

1) Medical questionnaire: This questionnaire includes the core data common to all DMMS Waves, in addition to some of the non-core items and was completed by personnel at each dialysis unit by patient medical record abstraction. Personnel also obtained information directly from the patient. Patient-specific data pertaining to demographics, prior medical history, laboratory results, RRF, psychosocial history, dialysis prescription, dialysis delivery, vascular access, and medications were collected using this questionnaire. This questionnaire can be found in Appendix 3A.
2) Patient Questionnaire: All HD and PD patients enrolled in Wave 2 were asked to complete a patient questionnaire. The patient questionnaire collected data pertaining to the QOL using the Kidney Disease Quality of Life Short Form (KDQOL SF), a kidney-specific QOL questionnaire. It also collected data regarding medical care prior to chronic dialysis, choice of modality, transportation, employment, and rehabilitation.

Follow up questionnaires were administered 8 to 18 months after enrollment and included the following information:

1) Medical Update Questionnaire: This form was completed for all patients enrolled. Data regarding patient status, dose of dialysis, RRF, and for HD patients, vascular access was collected. (Appendix 3B)

2) Patient Questionnaire: All patients who completed a patient questionnaire at baseline were requested to complete a follow up questionnaire that included the KDQOL, SF-36, as well as questions pertaining to modality choice, compliance, employment, and rehabilitation.

Each participating dialysis unit completed a facility questionnaire (one time only). Data pertaining to dialyzer reuse, water treatment, URR, or Kt/V calculation, or other practice patterns were collected using this instrument.

A pre-test of the baseline medical and patient questionnaires were conducted in the fall of 1995. Four ESRD networks volunteered to participate in the pre-test and recruited a total of 24 dialysis units for participation. The pre-test focused on the selection enrollment of patients and on the overall feasibility of collecting both the medical and patient questionnaires, interruption, time required, etc. The USRDS Coordinating Centre developed the data collection instruments.

4.5 Outcome Measurements

The data collected at the start of dialysis (day 60), and at follow up (mean 12 months) was used to look at predictors of loss of RRF in patients initiating

dialysis. The outcome (dependent) variable, loss of RRF, was defined as estimated UV < 200ml/24 hours at the time of follow-up (8 - 18 months initiation of dialysis). The reason for using UV as a measurement of RRF is described in Chapter 2.

There are 2 issues involving measurement of RRF to be discussed. The first issue involves the measurement of baseline RRF at the start of dialysis. As the level of RRF at the start of ESRD varies for each patient and was expected to be associated with subsequent loss of RRF, it was important to adjust for such baseline differences. Ideally an estimated GFR, using an average of the creatinine and urea clearance from a 24-hour urine collection, at study start on every patient would be preferred. In this study, data necessary to calculate this estimated GFR was requested at or near day 60 of ESRD on a voluntary basis. It was available for only 10 HD patients and 428 PD patients. The average estimated GFR was 3.4 ml/min. among the HD-treated patients, and 4.9 ml/min. among the PD-treated patients. Given the low rate of reporting, particularly among the HD-treated patients, these numbers were unlikely to be representative of the population. We did have the baseline information necessary to calculate an estimated GFR or CrCl using the equations in the literature, including the Cockcroft Gault, the MDRD, and the Walser equation [1,2,3]. The Cockcroft Gault equation [1] estimated CrCl to be 10.3 ml/min, the MDRD equation [2] estimated GFR to be 7.5 ml/min., and the Walser equation [3] estimated GFR to be 6.08 ml/min. It was felt that the MDRD equation, corrected

for body surface area, was the best measure of estimated GFR at ESRD onset [2]. The MDRD formula includes serum creatinine (taken prior to initiation of dialysis), age, gender, race, serum BUN and albumin. This formula was developed and validated from data on 1628 patients with decreased GFR (average ^{125} I-iothalamate clearance = 39.9ml/min/1.73m^2) in the MDRD study [4]. This formula, however, has not been validated in patients at the start of ESRD. The Walser equation was not used because negative values of GFR were obtained at the lower end of CrCl values. The Cockcroft Gault equation was an estimate of CrCl rather than GFR and was developed on a population with a higher level of renal function. Baseline data on urine volume was not collected. As this was a study of incident dialysis patients with chronic renal failure, it was assumed that most patients would have some baseline RRF.

The second point relates to the measurement of RRF at follow-up. Follow-up data collection was completed 8 – 18 months after the initial data collection. Data necessary to calculate the estimated GFR (average of creatinine and urea clearance) from a 24-hour urine collection was available for only 11 HD patients and 369 PD patients so that once again this measure of RRF could not be used. Data on UV at follow-up was available and was reported as a dichotomous variable, < or > 200 ml/24 hours. For patients with estimated UV > 200 ml/24 hours, timed urine collection data (UV, creatinine and urea concentration) were collected on a voluntary basis at the dialysis facilities' discretion. Patients with an estimated UV of < 200 ml/24 hours were considered to have lost their RRF and

no further timed urines were collected. Among patients in the data set for whom an estimated GFR could be calculated, using the average of creatinine and urea clearance, the correlation coefficient for association between UV and the average of the creatinine and urea clearance was $r = 0.57$; ($p<0.01$) at baseline and $r = 0.49$; ($p < 0.01$) at follow up, further supporting the role of UV as an estimate of GFR.

Patients self-reported UV and the available data was examined to check the reliability of this information. Two questions were asked regarding UV. The first question asked if the approximate UV was > or < 200 ml/day. The second question asked for actual UV on the patients with values > 200 ml/day. For the purposes of analysis, patients were classified as having > 200 ml/day if either of these two questions categorized them as having > 200 ml/day. Both pieces of information were available on 557 patients. There were only 33 with discrepant information from the two questions. Only four patients reporting UV > 200ml/24hours had < 200 ml on timed urine collections. In patients reporting UV < 200 ml/day, 29 had > 200 ml on timed urine collections. These data are suspect in that patients with < 200 ml/day were not to have a complete collection obtained. However, overall it suggests that agreement between the two questions is high and the question distinguished between those with > 200ml/24 hours and those with < 200ml/24 hours.

4.6 ANALYTICAL METHODS

4.6.1 Data Screening

The data collected for the Wave 2 database were reviewed prior to analysis. Univariate procedures were run on each variable to define the mean and standard deviation as well as the quintiles and the extreme values. A range of values was established for laboratory parameters, and out-of-range values were identified. It was agreed that these values should be excluded from the analyses because the values were implausible and likely due to data input errors. Missing values for numerical variables were set to the mean for the overall group with the exception of estimated GFR at ESRD onset, which was set to the mean by race and gender [5]. For co-morbid conditions, missing values were considered to indicate absence of the condition.

4.6.2 Selection of Variables

A literature review was done to identify known predictors of RRF loss among the ESRD and CRF population. The DMMS Wave 2 database was reviewed to see if the data were available. The selection of the variables and the use of explanatory analyses are discussed below.

Thirty-three baseline variables were included in the model, for evaluation of possible independent predictors of RRF loss as shown in Table 2. These included age, gender, race, etiology of ESRD, diabetes, HTN, GN, other, data on

pre-ESRD care including late referral to a Nephrologist (defined as < 4 months prior to ESRD), and dietary consult pre-ESRD, a number of baseline co-morbid conditions, laboratory values at study start including serum albumin, calcium, phosphate, total cholesterol, hematocrit, body mass index (BMI), baseline mean arterial pressure (two-thirds of DBP, plus one-third of SBP), calculated from the average of three blood pressure readings taken post-dialysis at study start, dialysis modality (PD or HD), and a number of medications in use at the time of study start, including ACE inhibitors, calcium channel blockers, diuretics, erythropoietin, HMG Co A reductase inhibitors, non-steroidal anti-inflammatory agents (NSAIDS), and vitamin D.

As the level of RRF at the start of ESRD varies for each patient and was expected to be associated with subsequent loss of RRF, we adjusted for baseline differences using the MDRD formula, as discussed above.

Analyses were adjusted for time from study start to follow-up as it also varied for each patient and was expected to be associated with loss of RRF.

Table 2: List of covariates and baseline descriptive statistics for total study population, HD only and PD only reported as mean (SD) or percent

Variable	**Total N=1843**	**HD N=811**	**PD N=1032**
Demographics			
Mean age, (years)	57.8 (15.0)	60.9 (14.7)	55.5 (14.6)
Race, % white	62.6	56.7	68.6
Gender, % female	47.2	48.8	47.5
Cause of ESRD (% of total population)			
Diabetes	44.5	46.7	43.6
Hypertension	25.0	27.6	22.9
Glomerulonephritis	9.1	6.8	10.9
Other causes	21.0	18.1	22.6
Co-morbid conditions (% yes)			
Diabetes (history of and/or nephropathy)	51.4	54.6	49.0
Coronary artery disease (history of) [a]	39.0	41.6	33.3
Peripheral vascular disease (history of) [b]	20.4	23.1	18.2
Congestive heart failure (history of)	32.7	39.2	27.6
Left ventricular hypertrophy (history of)	18.7	21.9	16.2
Laboratory Values, means (SD) (at day 60)			
Albumin g/dl	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
Calcium mg/dl	8.7 (1.0)	8.7 (1.0)	8.7 (1.1)
Phosphate mg/dl	5.5 (1.8)	5.5 (1.9)	5.5 (1.7)
Hematocrit %	30.8(6.1)	29.8 (5.7)	31.6 (6.4)
Total Cholesterol mg/dl	197.1 (51.6)	181.0 (47.9)	208.4 (63.24)
Estimated GFR at ESRD onset (ml/min)	7.4 (2.7)	7.33 (2.8)	7.5 (2.7)
Body Mass Index	26.2 (6.0)	26.2 (6.4)	26.2 (5.7)
Mean Arterial Pressure (mmHg)	100.6 (12.8)	98.4 (13.2)	102.2 (12.4)
Late referral (< 4months pre ESRD) (% of total)	56.1	59.8	52.7

Dietary Consult pre ESRD (% of total)	37.8	36.3	39.0
Months from onset ESRD to follow-up RRF	12 (1.8)	12.2 (1.8)	11.9 (1.7)
Dialysis modality			
Peritoneal Dialysis (% of all dialysis)	56.0		
Continuous Ambulatory Peritoneal Dialysis (% of all PD patients)			70.0
Dialyzer membrane, (% biocompatible) [c]		81.7	
Medications at baseline (day 60) (% of total population)			
Any antihypertensive	79.3	77.1	81.7
Angiotensin converting enzyme inhibitors	27.3	26.98	29.7
Calcium channel blockers	56.5	56.2	58.3
Diuretics	22.1	18.5	24.2
EPO	78.8	85.2	73.8
Vitamin D analogues	37.2	41.4	33.9
HMG CoA reductase inhibitors	12.8	9.1	15.7
NSAIDS	1.8	1.7	1.9

[a] Includes a history of coronary heart disease or coronary artery disease, coronary artery bypass surgery, angioplasty, or abnormal angiogram.

[b] Includes histories of peripheral vascular disease, amputation, absent pulses or claudication.

[c] Includes substituted cellulose and synthetic membranes

4.6.3 Multiple Logistic Regression Analysis

Multiple logistic regression analysis can be used for several purposes [5]:

- **To verify the association between a single explanatory variable and the response variable when controlling for one or more other explanatory variables.** If the explanatory variable continues to be highly associated with the response variable when included in the model with other explanatory variables, it is likely to be an important independent predictor of the response variable. If its association is strengthened or weakened as a result of its relationship with another variable or variables, these relationships can be investigated

- **To reduce a large number of variables to a "best" subset of variables of manageable size.** Large clinical registries or administrative databases may contain data for hundreds of explanatory variables. Instead of testing the association between each explanatory variable and the response variable separately, variable–selection techniques can be used to reduce the number of variables included in the final regression model by identifying those that meet specified statistical thresholds. Clinicians, however, must still identify that the clinically important variables are included in the model.

- **To quantify the risk associated with individual explanatory variables.** In the study of risk factors, it is sometimes useful to determine the change in risk associated with an incremental change in an explanatory variable, such as

the change in risk of stroke for every 20-mmHg decrease in systolic blood pressure. In this application, the regression coefficients are converted to odds ratios.

The "model building" of regression analysis is a process of selecting the best combination of explanatory variables to predict the response variable. One of the first steps in building a regression model is to identify the explanatory variables that are significantly related to the response variable. Several dozens of variables may be considered one at a time in this process of univariate analysis. Those values identified as significant by the univariate analysis are considered for inclusion in the model [5].

A logistic regression model, adjusted only for estimated baseline GFR and time to follow-up, was performed for each covariate to determine if any of these covariates were associated with loss of RRF ("adjusted" univariate analyses). Variables whose coefficients were significant at 0.05 (i.e. $p \leq 0.05$) were included in the multivariate analysis to determine if these baseline variables were related to loss of RRF. Similar analyses were performed looking at predictors of RRF loss in HD and PD populations separately. In the HD only analysis, the effect of membrane type (modified cellulose and synthetic membranes compared to unmodified cellulose membranes) was also evaluated. In the analysis limited to PD, the effect of type of PD (APD or CAPD) was evaluated. The results of these analyses are listed in Table 3. After those specific analyses, other explanatory

analyses were performed in an attempt to better understand the association of certain predictor variables with loss of RRF. The analyses are outlined in the methodology section in Chapter 5.

Table 3: Adjusted odds ratio for RRF loss

	Overall	N=1843			PD only	N=1032	HD only	N=811
	"Adjusted" Univariate[1]		*Multivariate*[2]					
Variable (reference)	AOR	P value	AOR	P value	AOR	P value	AOR	P value
Adjusting Variables								
Time to Follow-up (per month)	1.10	0.0005	1.06	0.03	1.11	0.01	1.02	0.86
Estimated GFR at ESRD onset (ml/min)	0.97	0.07	0.97	0.09	0.94	0.04	0.99	0.74
Demographics								
Age (per 10 years)	1.02	0.0001	1.01	0.18	1.01	0.24	1.00	0.60
Female (vs Male)	1.42	0.0006	1.45	<0.001	1.42	0.02	1.38	0.06
Nonwhite race (vs White)	1.72	0.0001	1.57	<0.001	1.94	<0.001	1.08	0.66
Cause of ESRD								
Glomerulonephritis (ref)	1.00	(ref)	1.00		1.00		1.00	
Diabetes	1.76	0.002	0.68	0.14	0.59	0.13	0.81	0.61
Hypertension	1.61	0.01	1.17	0.43	1.47	0.14	1.02	0.94
Other causes	1.26	0.24	1.05	0.82	1.35	0.25	0.78	0.47
Pre-ESRD Care								
Late Referral (<4 mo pre ESRD)	1.23	0.04	.99	.99	1.04	0.85	0.93	0.72
Dietary Consult	0.90	0.33	-	-	-	-	-	-
Co-morbid factors								
Diabetes	1.59	0.0001	1.82	0.006	2.17	0.01	1.66	0.10
Coronary Artery Disease	1.40	0.002	1.13	0.33	1.25	0.19	0.98	0.89
Cerebrovascular Disease	1.17	0.31	-	-	-	-	-	-
Congestive Heart Failure	1.60	0.0001	1.32	0.03	1.5	0.02	1.16	0.45
Peripheral vascular Disease	1.28	0.06	-	-	-	-	-	-
Left Ventricular Hypertrophy	1.57	0.0006	1.27	0.08	1.30	0.17	1.26	0.26
MAP (per 10 mmHg)	0.993	0.003	1.03	0.49	1.04	0.41	0.87	0.04
Body Mass Index (per kg/m^2)	0.99	0.49	-	-	-	-	-	-
Laboratory Values								
Serum albumin (per gm/dl)	0.88	0.18	-	-	-	-	-	-
Blood hematocrit (per %)	0.98	0.04	.99	0.68	0.99	0.94	1.01	0.53
Serum Calcium (per mg/dl)	0.90	0.02	0.81	0.05	0.99	0.94	0.79	0.006

Phosphate (per mg/dl)	1.05	0.07	-	-	-	-	-	-
Total Cholesterol (per 10 mg/dl)	0.99	0.03	1.00	0.93	1.01	0.47	1.01	0.42
Treatment parameters								
PD (vs HD)	0.28	0.0001	0.35	0.001	NA	NA	NA	NA
Pre/post dialysis delta MAP (HD)	1.04	0.0001	1.00	0.33	NA	NA	0.99	0.87
ACE inhibitor (vs no)	0.74	0.01	0.68	<0.001	0.70	0.02	0.71	0.06
Calcium Channel Blocker (vs no)	0.77	0.01	0.77	0.01	0.71	0.02	0.81	0.21
Diuretics (vs no)	0.90	0.41	-	-	-	-	-	-
EPO (vs no)	1.29	0.05	1.12	0.37	1.15	0.39	0.69	0.12
HMG CoA Reductase II (vs no)	0.60	0.001	0.81	0.17	0.95	0.78	0.56	0.03
NSAIDS (vs no)	0.72	0.43	-	-	-	-	-	-
Vitamin D (vs no)	1.02	0.89	-	-	-	-	-	-
Included in PD only analysis								
APD (vs CAPD)					0.96	0.96	NA	NA
Included in HD only analysis								
Biocompatible Membrane (vs Cellulose)					NA	NA	0.84	0.42

- not included in the analysis

NA not applicable to the analysis

[1] adjusted for time to follow-up and estimated GFR at ESRD onset only

[2] adjusted for all covariates significant in univariate analysis

4.7 References

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CHAPTER 5: PREDICTORS OF LOSS OF RESIDUAL RENAL FUNCTION AMONG NEW DIALYSIS PATIENTS

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5.1 Introduction

In recent years, there has been a greater focus on residual renal function (RRF) of patients on chronic dialysis therapy. Although RRF is often used to indicate remaining glomerular filtration rate (GFR), it also reflects remaining endocrine functions such as erythropoietin production [1], calcium, phosphorus and vitamin D homeostasis [2, 3], volume control, and removal of "middle molecules" or low molecular weight proteins [4, 5]. Residual renal function is clinically important as it can account for major differences in dialysis requirements since it contributes to measures of adequacy, both Kt/V urea and creatinine clearance (CrCl) [6-7]. Residual renal function has also been shown to be associated with mortality. Analysis of the CANUSA study [8] has shown that every 0.5ml/min higher GFR was associated with a 9% lower risk of death (RR= 0.91) [9]. It has been shown that clinically important and statistically significant decreases in nutritional parameters occur with RRF loss [8]. Furthermore, it has also been demonstrated that small increments in RRF may account for major differences in quality of life [10, 11]. It is therefore vitally important to determine and understand the predictors of loss of residual renal function in the dialysis patient.

The importance of identifying factors that protect and preserve RRF has been recognized among patients with chronic renal failure, pre-end stage renal disease (ESRD). Control of blood pressure, ACE inhibition, decreasing proteinuria, dietary modification, avoidance of nephrotoxins, and glucose control have all been considered as integral parts of the pre ESRD nephrology care [12]. However few studies have comprehensively evaluated whether these or other factors are important in preserving RRF after initiation of dialysis. Also on a clinical level, evaluating and monitoring factors that preserve RRF in patients who have just started on dialysis has not received the same level of care as among the chronic renal failure population.

Several authors have observed that preservation of RRF is prolonged with peritoneal dialysis (PD) compared to hemodialysis (HD) [13-15]. Others have noted a more rapid decline in RRF among patients on automated PD compared to continuous ambulatory PD (CAPD) [16]. For HD patients, there has been debate in the literature as to whether the type of dialyzer membrane has an effect on RRF. Some have suggested that biocompatible membranes preserve RRF for a longer time period, [17-19]. Cause of ESRD, level of blood pressure and various medications have all been implicated as having an effect on RRF [12, 20, 21]. However, these studies have methodological limitations including small sample size with inadequate statistical power, retrospective design and lack of inclusion of all known predictor variables and other modifying factors.

Since our knowledge of the factors that preserve RRF in ESRD is limited, we undertook a study to determine the predictors of RRF loss in a national sample of incident patients initiating ESRD treatment with dialysis. We used a large patient population, controlled for baseline variables and included major potential predictors. An epidemiological study of this type can help generate hypotheses regarding modifiable factors associated with loss of RRF, and these factors can subsequently be tested in interventional studies or confirmed in other epidemiological studies.

5.2 METHODS

5.2.1 Data Source

The Dialysis Morbidity and Mortality Study (DMMS) is a USRDS special study, including over 20,000 randomly selected dialysis patients. The study includes 4 "waves" of data collection over 3 years. A standard core of data was collected for all patients included in the DMMS study, to address research questions that require a larger sample size. The data used in these analyses were from the USRDS DMMS Wave 2. Wave 2 was a prospective study of incident hemodialysis and peritoneal dialysis patients (Medicare and non-Medicare) who initiated ESRD in 1996 and early 1997. Peritoneal dialysis patients were oversampled by a factor of 5 to result in comparable numbers of PD and HD patients. Wave 2 focused on PD prescription and delivery, PD and HD selection and outcomes, residual renal function, quality of life, pre ESRD care, and

medication use. The dialysis units included in Wave 2 were a random selection of 25% of the dialysis units in the U.S. listed on the Master List of Dialysis Facilities as of December 31, 1993 with addition of all new dialysis units opened during 1994. Modality type was identified on day 60 of ESRD. Patients treated with PD or HD on this date (day 60) were eligible. The modality assignment for patients who were on hemodialysis but who were training for PD on day 60 was deferred for 10 days. The study start date was considered the date that the modality type was identified (about day 60 of ESRD).

Patient-specific data were collected at the time of enrolment (study start) and was completed on over 4000 patients in Wave 2. Data were collected by means of a medical questionnaire, completed by dialysis facility personnel as well as a questionnaire completed by the patient. Questionnaires included patient-specific data such as demographics, prior medical history, laboratory results, dialysis prescription and dialysis delivery, data on vascular access, RRF, medications, pre-ESRD care and quality of life.

Follow-up data collection was completed 8 - 18 months after the initial data collection. The follow-up patient questionnaire included information on change in health status or treatment modality and questions related to vascular access. Data on estimated urine volume was collected and was reported as a dichotomous variable, less than or greater than 200ml/24 hours. For patients with estimated urine volume greater than 200ml/24 hours, timed urine collection

data (urine volume, creatinine and urea concentration) were collected on a voluntary basis (at the dialysis facilities' discretion). Patients with estimated urine output of less than 200ml/24 hours were considered to have lost their RRF and no further timed urines were collected. Personnel at each dialysis unit completed the follow-up questionnaire by medical abstraction. Personnel were also instructed to obtain information directly from the patient. Copies of the questionnaires used for the DMMS Wave 2 are found in Appendices 3A and 3B.

5.2.2 Analytical methods

Patients from USRDS DMMS Wave 2 study were included in these current analyses if they had a follow-up form completed and if, at the time of follow-up, they were known to be alive, on PD or HD and dialyzing in the same facility as at baseline. Patients were excluded if at the time of follow-up data collection, they had died (N=495), had return of renal function (N=41), had transferred to an alternate dialysis facility (N=234), had received a transplant (N=169), were age < 18 or of unknown age (N=60), or if vital status was unknown (N=80). Patients with implausible or inaccurate critical data were also excluded (N=426).

We operationally defined our outcome (dependent) variable, loss of RRF, as estimated urine output < 200ml/24 hours at the time of follow-up (8 - 18 months initiation of dialysis). The published association between urine volume and renal clearance supports this definition [4, 22].

We selected 33 baseline variables for evaluation as possible independent predictors of RRF loss as shown in Table 2. These included age, gender, race, etiology of ESRD (diabetes, HT, GN, other), data on pre-ESRD care including late referral to a nephrologist (defined as less than 4 months prior to ESRD) and dietary consult pre-ESRD, a number of baseline comorbid conditions, laboratory values at study start including serum albumin, calcium, phosphate, total cholesterol, hematocrit, body mass index (BMI), baseline mean arterial pressure *(2/3DBP + 1/3 SBP)* calculated from the average of 3 blood pressure readings taken post dialysis at study start, dialysis modality (PD or HD), and a number of medications in use at the time of study start including ACE inhibitors, calcium channel blockers, diuretics, erythropoietin, HMG Co A reductase inhibitors, non-steroidal anti-inflammatory agents (NSAIDS) and vitamin D. As the level of RRF at the start of ESRD varies for each patient and was expected to be associated with subsequent loss of RRF, it was important to adjust for such baseline differences. Baseline data on urine volume were not collected. It was assumed that most patients would have some baseline RRF, as this was a study of incident dialysis patients with chronic renal failure. However, data necessary to calculate an estimated glomerular filtration rate (GFR) at ESRD onset were available and the analyses were therefore adjusted for this. Baseline GFR, corrected for body surface area, was estimated using the MDRD formula, which includes serum creatinine (taken prior to initiation of dialysis), age, gender, race, serum BUN and albumin [23]. This formula was developed and validated from data on 1628 patients with decreased GFR (average ^{125} I-iothalamate clearance

= 39.9ml/min/1.73m^2) in the MDRD study. This formula, however, has not been validated in patients with ESRD on dialysis. Analyses were adjusted for time from study start to follow-up as it also varied for each patient and was expected to be associated with loss of RRF.

Missing values for numerical variables were set to the mean for the overall group with the exception of estimated GFR at ESRD onset, which was set to the mean by race and gender. We adjusted for these two factors because GFR is known to differ for these factors. For comorbid conditions, missing values were considered to indicate absence of the condition.

A logistic regression model, adjusted only for estimated baseline GFR and time to follow-up, was performed for each covariate to determine if any of these covariates were associated with loss of RRF ("adjusted" univariate analyses). Variables with "adjusted" univariate associations at $p \leq 0.05$ significance level were included in the multivariate analysis to determine if these baseline variables were independently predictive of loss of RRF. Additional analyses were performed looking at predictors of RRF loss in HD and PD populations separately. In the HD only analysis, the effect of membrane type (modified cellulose and synthetic membranes compared to unmodified cellulose membranes) was also evaluated. In the analysis limited to PD, the effect of type of PD (APD or CAPD) was evaluated. Additional analyses, including other

explanatory variables, were performed as appropriate in an attempt to better understand the association of certain predictor variables with loss of RRF.

5.3 Results

There were 2211 patients eligible for the study. Data on the outcome variable, urine volume was reported on 83% of patients at the time of follow-up leaving 1843 patients for analysis in this study. Comparison of the baseline characteristics of the patients with and without urine volumes showed a statistically significant difference in the proportion of patients on PD, patients with late referral to dialysis and patients receiving EPO. Comparison of the groups with and without urine volumes recorded at follow-up revealed significant associations for two factors. Female patients (AOR=1.37; p=0.01) and patients treated with PD (AOR=2.13; $p<0.001$) were more likely to have data on urine volume reported on the follow-up forms. Comparison of the baseline characteristics of the patients with and without urine volumes showed a statistically significant difference in the proportion of patients on PD, patients with late referral to dialysis, and patients receiving EPO.

The mean age of the patients was 57.8 years. Sixty three percent of patients were white, 47% were female, 51.4% reported a history of diabetes, and 44.5% reported diabetic nephropathy as the cause of ESRD. The average time from onset of ESRD to follow-up was 12 months. The mean GFR at ESRD onset was 7.46ml/min as estimated by the MDRD formula [23]. The average post dialysis

systolic blood pressure was 143 mmHg and the average diastolic BP was 78.9 mmHg for a mean arterial pressure (MAP) of 100 mmHg. By study design 56% of the patients in the study sample were on PD and of those 70% were using CAPD and the remainder were using a cycler (APD). Among hemodialysis patients 81.7% were using synthetic and semi-synthetic ("biocompatible") membranes and the remainder were using unmodified cellulose membranes. The frequency of co-morbid conditions and mean values for laboratory data at study start are shown in Table 1.

The "adjusted" univariate odds ratio (AOR) for each covariate tested, adjusted only for estimated GFR at ESRD onset and time to follow-up, is shown in the first column of table 3. Using only the variables that were significant at $p \leq 0.05$ in the "adjusted" univariate analysis, several covariates continued to be significantly associated with a loss of RRF in the multivariate model including female gender (AOR = 1.45; $p < 0.001$), non-white race (AOR = 1.57; $P<0.001$), prior history of DM (AOR = 1.82; $p=0.006$), and prior history of CHF (AOR = 1.32; $p=0.03$). As expected, the risk of loss of RRF was increased for longer time to follow-up (AOR = 1.06 per month; $p=0.03$). Higher levels of estimated GFR at ESRD onset was of borderline significance in predicting a lower risk of RRF loss (AOR=0.97 per ml/min, $p=0.07$). Patients treated with PD had a 65% lower risk of RRF loss than those treated with HD (AOR = 0.35; $p<0.001$). Patients with a higher serum calcium had a lower risk of RRF loss (AOR =0.81per mg/dl; $p=0.05$). Interestingly, treatment with an ACE inhibitor (AOR 0.68;$p<0.001$) and treatment

with a calcium channel blocker (AOR =0.77; p=0.01) were independently associated with decreased risk of RRF loss in this analysis which was controlled for baseline blood pressure. This relationship was present in patients with diabetes-related ESRD and as well as in patients with ESRD from all other causes. When all 33 variables were added to the model without consideration of the results from the univariate analysis the significant predictors of RRF were the same.

Age, cause of ESRD, comorbid factors other than history of diabetes and CHF, late referral, post dialysis MAP, and baseline BMI, serum albumin, hematocrit, phosphate, total cholesterol, and baseline use of diuretics, EPO, HMG CoA reductase inhibitors, vitamin D preparations or NSAIDS were not associated with RRF loss in the multivariate analysis.

At follow-up 38% PD patients and 69% of HD patients had loss of RRF defined as urine volume< 200ml/24 hours. We divided the follow-up time into three equal intervals and at each time interval HD patients were 3 times more likely to have lost RRF as PD patients.

In a separate analysis of PD patients only (N=1032), factors that were significantly associated with loss of RRF included female gender (AOR=1.42; p=0.02), non-white race (AOR=1.94; p<0.001), time to follow-up (AOR=1.11 per month; p=0.01), a history of DM (AOR=2.16; p=0.01), and a history of congestive

heart failure (AOR=1.50; p=0.02). Treatment with an ACE inhibitor (AOR=0.69; p=0.02) or a calcium channel blocker (AOR=0.88; p=0.006) remained independently associated with lower risk of RRF loss. A higher baseline GFR was associated with a lower risk of RRF loss (AOR=0.94; p=0.04). Among PD patients there was no significant difference in RRF loss between APD and CAPD (AOR=0.96; p=0.96).

In a separate, similar analysis of hemodialysis patients only (N=811), factors that were significantly associated with a lower risk of RRF included higher post dialysis MAP calculated at study start (day 60) (AOR=0.87 per 10 mmHg; p=0.04), higher pre-dialysis serum calcium (AOR=0.79 per mg/dl; p=0.01) and treatment with an HMG Co-A reductase inhibitor (AOR=0.56; p=0.03). The effects of gender, race and a prior history of CHF or diabetes were no longer statistically significant but the adjusted odds ratios were in the same direction as for the main and PD only models. Treatment with ACE inhibitors (AOR=0.71; p=0.06) and calcium channel blockers (AOR=0.69; p=0.12) were no longer significantly associated with a decreased risk of RRF loss but the AOR remained of the same magnitude as in the main and PD models. There was no significant difference in RRF loss between biocompatible versus cellulose dialyzer membranes (AOR=0.84 biocompatible; p=0.42) however the numbers were small for use of unmodified cellulose dialyzers (19%). Use of hi–flux synthetic dialyzer membranes vs all other dialyzer membranes was also not significantly associated with RRF loss.

Female gender predicted increased risk of RRF loss in the main model and the PD only model independent of differences in BMI, MAP, or albumin. In order to further explore this relationship between female gender and RRF loss we controlled for use of estrogen and for HDL cholesterol. Adjusting for use of estrogen did not change the relationship (AOR=1.67; $p<0.001$). We had data on HDL cholesterol on 280 patients. When controlling for HDL cholesterol the gender relationship was of similar magnitude but not significant, likely reflecting the decrease in power due to the small sample size (AOR=1.74; p=0.09). To determine if the relationship varied by menopause status we stratified the female population by two age categories, less than 50 years old or greater than or equal to 50 years old. The relationship was similar for the two age categories: age < 50 years (AOR=1.46; p=0.03) and age ≥50 (AOR=1.45; p=0.003).

Non-white race was found to be associated with loss of RRF in the overall and PD only models. To further understand this relationship blacks (27.3%) and other non-white race (Asians, North American Indians and others) (9.6 %) were analyzed as two separate groups in the main multivariate model. Both blacks (AOR=1.83; p=0.001) and other non-white race (AOR=1.53; p=0.04) were more likely to have RRF loss. We were unable to determine the specific relationship of Asian or North American Indian race and loss of RRF due to the limited number of patients in these race categories. Since one may speculate that non-whites may have greater risk of loss of RRF due to poorer pre-ESRD care, we further

explored the role of late referral to a nephrologist (< 4 months pre ESRD) and the occurrence of a dietary consult pre-ESRD. Controlling for these interventions did not alter the relationships.

Higher serum calcium was predictive of less RRF loss. Although there was a trend to greater loss of RRF with higher serum phosphate in the univariate analysis (RR=1.05; p=0.07), it was not an independent predictor when included in an additional multivariate model. To further understand the relationship of calcium and phosphate and RRF loss we also explored the role of the calcium phosphate product, PTH levels, use of phosphate binders and vitamin D use in univariate and multivariate models. These covariates were not significant predictors of RRF loss and their addition to the multivariate model did not change the previously identified relationships with RRF.

To further clarify the role of blood pressure we used post dialysis MAP and the pre to post dialysis change in MAP both as univariate predictors and in the full model. Neither was significantly predictive of RRF loss. As there is debate in the literature as to which BP measurement to use, we also analyzed post dialysis SBP and DBP and the relationship with RRF did not change. In order to examine RRF loss and different levels of MAP as a categorical variable compared to a continuous variable, we divided the MAP into quintiles using the middle range as the reference group. At no level did mean arterial pressure predict RRF loss and there was no suggestion of a J-shaped relationship.

5.4 Discussion

Accurate measurement and monitoring of RRF in ESRD patients remains a challenge as we approach the twenty-first century. Glomerular filtration rate (GFR) measured by isotope clearance is considered to be the standard measure of renal function. Other tests, such as serum creatinine, creatinine clearance ($CrCl_t$), urea clearance (C_{urea}), an average of the $CrCl_t$ and the C_{urea}, and urine volume (UV) have been used to assess RRF in chronic renal failure [24]. An average of the CrCl and the C_{urea} is commonly recommended in ESRD [25, 26].

In the DMMS Wave 2, timed urine collection was requested both at baseline and followup, if patients had an estimated urine out-put >200 ml (or approximately one cup) per day. The estimated GFR was then calculated using the average of the creatinine and urea clearance. Unfortunately data necessary for this calculation was available for less than 5% of HD patients and 30% of PD patients at baseline and fewer patients at follow-up. These data are unlikely to be representative of RRF in the ESRD population given the low rate of reporting and therefore could not be used for our measure of RRF loss.

We therefore defined loss of RRF as estimated urine volume < 200ml/24 hours. In spite of its shortcomings UV has been correlated to GFR in previous studies. Milutinovic et al compared urine volume to inulin clearance in 38 patients on HD with GFR <5ml/minute [4]. Using Milutinovic's data we calculated a correlation

coefficient for urine volume and inulin clearance and found an r-value of 0.71 (p=0.001). This compares to a correlation coefficient of 0.94 for correlating inulin clearance to the average of creatinine and urea clearance from the same data set. Van Olden also showed that urinary volume, in the interdialytic interval, is directly related to changes in GFR [22].

Among patients in our dataset for whom an estimated GFR could be calculated using the average of the creatinine and urea clearance, the correlation coefficient for the association between urine volume and the average of the creatinine and urea clearance was r=0.57 at baseline and r=0.49 at follow-up.

These analyses and prior data support the use of urine volume as a useful measure of RRF. Despite the imprecision of this measure the advantage of potentially developing hypotheses regarding factors predictive of RRF loss from a large data set were felt to outweigh the limitations of using this measure as the outcome variable. It is interesting to note that patients were more likely to have the outcome variable, urine volume, reported if they were on PD or if they were female. It has been recognized that RRF is important in PD due to its contribution to small solute clearance and more attention may be paid to monitoring RRF in this population. The reason for the gender difference is not clear. Comparison of the baseline characteristics of the patients with and without urine volumes showed more patients on PD in the group reporting urine volumes again explained by the contribution of RRF to dialysis dose. A greater proportion

of patients was classified as late referrals and were treated with EPO in the group not reporting urine volumes. This is due to higher proportion of HD patients in this group. Late referrals are usually started on HD and more HD patients receive EPO.

Follow-up data forms were completed after a mean of 12 months from the initiation of dialysis, with a range of 8 - 18 months. Several papers on the progression of chronic renal disease have reported the decline in renal function is either linear or exponential [12, 27]. Thus it was assumed that longer follow-up and lower levels of renal function at start of ESRD would be associated with a greater likelihood of loss of RRF. It was therefore necessary to control for these factors when evaluating the effect of other potential predictors. Duration of time on dialysis was indeed a significant predictor of RRF loss in the overall population and among the PD population but interestingly, not among the HD population. Among the PD patients, there was an increasing risk of loss of RRF over time suggesting time on dialysis to be an important variable. Likewise, higher estimated GFR at ESRD initiation was associated with lower risk of loss of RRF at follow-up among PD treated patients but not among HD treated patients.

Increasing age was not associated with RRF loss. This is consistent with data from the MDRD study [12] where age was not an independent predictor of progression of renal disease among patients with CRF. Female gender independently predicted RRF loss in the overall analysis and in the analysis

limited to PD patients. This gender effect could not be explained by differences in BMI, MAP, albumin, estrogen use, or menopausal status as the effect remained despite controlling for these variables. As mentioned, females were more likely to have data on urine volume reported on the follow-up form. It is unclear how this may have influenced our results. This gender effect is contradictory to previous studies that showed a slower rate of progression of RRF in females with CRF [28-31]. Data from the MDRD study indicated a slower mean GFR decline in women compared to men with chronic renal failure. However gender differences were reduced and no longer significant after controlling for baseline proteinuria, MAP and HDL cholesterol [12].

Non-white race was associated with RRF loss in the overall analysis, however this effect was found to be limited to PD patients only. This was true of both blacks and the category "other non-white race". These relationships were independent of cause of ESRD, MAP at dialysis initiation and also could not be explained by reported differences in pre-ESRD care. Blacks are known to have a faster rate of progression of renal failure in the CRF population [12, 32]. This analysis suggests that, at least among PD treated patients, this race effect may persist after ESRD initiation.

The presence of diabetes predicted RRF loss particularly in the PD population. Diabetic patients with hypertension and proteinuria have been shown to have an increased rate of loss of renal function in the CRF population. A history of

congestive heart failure also was predictive of RRF loss, likely due to decreased blood flow to the compromised kidney.

Higher serum calcium was significantly associated with a lower risk of RRF loss in the total analysis and in the HD population. The magnitude of risk was less and was not significant among the PD population. The mean serum calcium was not different between the two populations. Although these relationships did not change with adjustment of several other related covariates, this observation would be consistent with the hypothesis that increased calcium and frequently concurrent lower phosphate levels may contribute to less RRF loss. This may provide further support for the necessity of good phosphate control in the ESRD population.

The present study confirms earlier observations that patients receiving treatment with PD had a reduced risk of RRF loss when compared to HD treated patients [13-15]. In this study we controlled for possible risk co-factors of age, gender, co-morbid conditions, hypertension, medications, and level of estimated GFR at the start of ESRD and still found a significant difference in RRF loss between the HD and PD populations. It has been hypothesized that inflammatory mediators generated by the extracorporeal circulation, rapid intravascular contraction inherent in HD, lower preglomerular arterial pressure and lower protein intake among PD patients may explain these findings. Patients treated with PD were

significantly more likely to have urine volume reported on the follow-up forms. It is unclear how this may have influenced the results.

Several comparative studies of PD and HD mortality have shown that the relative mortality risk favors PD to the greatest degree early after ESRD start and the relative mortality risk increases for PD with time on dialysis (33-36). One reason that PD may offer this early advantage may be the greater preservation of RRF.

Higher post dialysis mean arterial pressure at baseline significantly correlated with a lower risk of RRF loss in the HD only population but was an insignificant predictor in the total and PD only analysis. We speculated that this relationship was likely driven by an increased risk of RRF loss associated with low blood pressure, resulting from post dialysis intravascular volume depletion due to excessive fluid removal. However, the relationship did not change adjusting for intradialytic weight loss. Accurate data on volume status which would allow further exploration of this hypothesis were not available in this epidemiologic study. Several studies have observed a relationship of higher mortality with low pre-dialysis blood pressure [38-40]. A similar phenomenon may exist for RRF.

Several interesting results of our study were related to medication use. We observed an independent lowering of risk of RRF loss among ESRD patients being treated with ACE inhibitors and/or calcium channel blockers. The effect of ACE inhibition and calcium channel blockers, which was adjusted for MAP, was

significant in the total and PD only analyses but was not significant in the HD population although the magnitude and direction of risk were in general similar to the main model. 3-hydroxyl-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors were significantly predictive of a reduction in RRF loss in the HD only analysis.

Among patients with chronic renal failure there is considerable evidence that ACE inhibitors [41,42] and perhaps calcium channel blockers (43,44) preserve renal function, independent of blood pressure. The data from this study would suggest that the benefit of slowing progression of RRF loss might be a continuum even when on dialysis. This association was present in ESRD due to diabetes as well as ESRD due to other causes.

Baseline treatment with HMG CoA reductase inhibitors was associated with a 44% lower risk of loss of RRF among HD patients. Treatment with a HMG CoA reductase inhibitor may also have some renoprotective effects, independent of its lipid lowering effect, by directly inhibiting mesangial cell proliferation and production of monocyte chemoattractants [45]. The question of whether lipids or lipid lowering agents have an effect on RRF loss is important and deserves further exploration.

It has been suggested that exposure to automated PD (use of a cycler) hastens RRF loss when compared to CAPD [16]. It is hypothesized that the acute

changes in volume status and osmotic load induced at each nightly peritoneal dialysis session could potentially accelerate deterioration of residual renal function. However in our study we did not observe a significant difference in loss of RRF by PD modality type. This area deserves further research, as automated PD is becoming a more utilized form of therapy.

Previous studies have shown that use of cellulose dialyzer membranes among HD patients hastens RRF loss [17-19] due to blood and cellulose dialysis membrane interactions which may induce potentially nephrotoxic inflammatory mediators [37]. We did not observe a significant difference in loss of RRF when we compared cellulose membranes to those generally more biocompatible membranes. However, the proportion of patients using cellulose membranes was small (19%) and our sample size may have been too small to detect a difference. Comparing PD patients to HD patients using biocompatible membranes revealed that PD patients were still significantly less likely to lose RRF than were HD patients.

Four hundred and ninety-five patients died prior to follow-up. We were unable to associate mortality with loss of RRF due to lack of data on RRF at the time of death.

Preservation of RRF is an important goal. In addition to identifying demographic groups at risk, this study has identified several potentially modifiable factors

(calcium, MAP) and therapies (dialysis modality, ACE inhibitors, calcium channel blockers, and HMG CoA reductase inhibitors,) that were associated with decreased loss of RRF in a national random sample of patients initiating dialysis in the United States. There appear to be substantial differences in both the actual loss of RRF and the contributing risk factors between PD and HD patients. These analyses are limited by the use of estimated UV < 200 ml/24 hours as a measure of loss of RRF. However several of the significant associations with RRF loss have generated testable hypotheses regarding potential therapies, which may preserve RRF among ESRD patients. Additional prospective studies, ideally clinical trials, are necessary to determine if these possible interventions are efficacious.

5.5 References

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CHAPTER 6: LIMITATIONS OF THE STUDY PREDICTORS OF LOSS OF RESIDUAL RENAL FUNCTION AMONG DIALYSIS PATIENTS

6.1 Data

The data for this study was collected prospectively however it was analyzed retrospectively. Facility personnel abstracted the core set of data questions for each patient from the dialysis record. The personnel were trained for data abstraction, however they were neither nurses nor physicians. Cause of ESRD and co-morbid conditions were defined by categories, however there was no system check in place to ensure it was coded correctly. Laboratory parameters were reviewed by the USRDS study center at the time of data entry to ensure they fell in a certain range but each value was not checked and it is possible that there my have been some clerical errors.

The hypothesis generation, baseline variables and end-point measurements were limited by the data available in the database. Parameters known to affect RRF in the chronic renal failure population were used to develop the model. Rate of peritonitis, use of certain medications including aminoglycosides and contrast agents are thought to be contributors to loss of RRF in the ESRD patient. Unfortunately, data were not available on several of these parameters and were not included in the analyses. The presence or absence of these parameters may have affected the overall results.

The limitations of the data regarding measurement of RRF have previously been discussed. There was no measurement of urine volume at the study start. An assumption was made that patients with CRF would have some RRF remaining at the start of dialysis. Similarly, the definition of the end point was limited by the available data. Urine volume, > or ≤ 200ml/24 hour was requested at follow-up. This was not reported on 1,843 patients. Patients in whom reporting was not done were more likely to be females or on peritoneal dialysis. This may have affected the analysis. Patients on PD are more likely to collect urine volume to determine the contribution of RRF to clearance. There was no explanation as to why females had more reporting of urine volume than had males.

Four hundred and ninety-five patients died during the year of follow-up. The role of RRF and mortality could not be explored, as there was no measure of RRF at the time of the death of these patients.

6.2 Analysis

In both the univariate and multivariate analysis, PD versus HD was the most significant predictor of loss of RRF (AOR = 0.36; $p < 0.001$). The significant variables from the adjusted univariate analysis were included in the multiple regression analysis. Separate univariate analyses on each of the separate populations (PD and HD) were not performed. It is possible that different variables could have been identified in the separate analyses for inclusion in the multivariate analyses.

A variable with a p value of ≤ 0.05 was considered to be significant in the adjusted univariate analysis and those variables were included in the multivariate analysis. This is a conservative estimate of significance and clinically significant variables may have been excluded from the model [1]. The p value was not adjusted for multiple testing.

Residuals are the difference between an observed value of the response variable and the value predicted by the model [2]. Residual plots show the deviation from the expected value for each x value in the model. The residuals were not plotted for this model.

An epidemiological study based on a large population database was undertaken to look at predictors of loss of RRF among patients on dialysis. Several modifiable parameters were associated with RRF loss. Additional prospective observational studies, ideally clinical trials, will be necessary to determine if these interventions are efficacious in preserving RRF and perhaps improving patient morbidity, mortality, and quality of life.

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CHAPTER 7: FUTURE DIRECTIONS

7.1 Introduction

Residual renal function contributes to dialysis dose, fluid and electrolyte balance, anemia control, calcium and phosphate balance, and clearance of small, middle and large molecular weight molecules. RRF is also likely an important contributor to patient morbidity, quality of life, and mortality. Potential therapies that may preserve RRF among ESRD patients have now been identified.

7.2 Measurement of Residual Renal Function

The lack of a suitable measure of residual GFR in ESRD has blurred the understanding of the remnant kidney function. Factors that preserve the RRF cannot be investigated until there is an accurate, precise, and practical measure of RRF. Inulin is considered to be the gold standard for GFR measurement, as discussed in Chapter 3. The GFR method used at London health Science Centre-Victoria Campus (LHSC-VC) is 99m Tc-DTPA. This measure of GFR has been compared to inulin in patients with chronic renal failure and in patients on dialysis [1, 2].

A study has been developed and implemented looking at the measurement of RRF among the local dialysis population at LHSC-VC. This study was submitted and approved by the Department of Medicine for research funding and has received University of Western Ontario Human Ethics approval. The study proposal is attached in Appendix 4 and the human ethics approval is attached in Appendix 5.

7.3 Progress to Date

The target enrolment is 60 patients and 20 patients have currently completed a DTPA GFR study and 24-hour urine collections. This study should confirm that 24-hour clearance of urea and creatinine is an accurate measure of RRF among patients on dialysis at LHSC.

7.4 Intervention Studies

The epidemiological study, Predictors of Loss of Residual Renal Function among New Dialysis Patients, identified that PD and use of ACE inhibitors had the greatest impact on preservation of RRF. PD patients maintained their RRF for a longer period of time than did HD patients and for this reason PD patients may be the better group to study. ACE inhibition had the largest effect on the RRF in this population and would be a reasonable therapeutic intervention to study.

The next step in the investigation of the factors that preserve RRF in the ESRD population would be a multi-center, double-blind, placebo-controlled study examining the effect of ACE inhibition therapy on preservation of RRF among the PD population. The issues in developing this proposal are discussed below.

7.4.1 Hypothesis

Primary: The use of ACE inhibitors in the PD population will slow the progression of RRF loss.

Secondary: The maintenance of RRF will improve technique survival and decrease patient morbidity and mortality.

7.4.2 Population

Only 32.4% of dialysis patients are on PD in Canada [3]. The study would, therefore, require multiple centers in order to recruit the necessary number of patients. Residual renal function declines with time so it would be best to study incident patients only. This would further limit the patient enrolment. If prevalent patients were included, adjustment for time on dialysis would have to be made and important events such as rate of peritonitis or use of aminoglycosides and contrast dye may not be documented.

7.4.3 Methodology

Baseline parameters thought to be important in RRF loss would need to be identified and measured at the start of the study. These would include co-morbid conditions such as diabetes, coronary artery disease and peripheral vascular disease. Ideally, baseline co-morbid scales would be recorded for each patient rather than the just the presence of the co-morbid condition.

The intervention would be the use of ACE inhibitors versus placebo. ACE inhibitors are known to have an effect on left ventricular function, blood pressure, and progression of chronic renal failure [4]. Blood pressure would have to be controlled

to a similar level in both groups. Left ventricular function would need to be measured by echocardiogram at the study start as a baseline variable. Patients with echocardiograms showing a left ventricular ejection fraction less than 30% may also need to be excluded as ACE inhibition would traditionally be offered to this group and some investigators may consider it unethical to randomize this patient population.

Twenty-seven percent of ESRD patients were on ACE inhibitors at the start of dialysis in 1996 in the USRD population. The indications for use of ACE inhibition in this group would need to be reviewed and it is likely that this population may need to be excluded from the study.

Patients on PD often require switching to HD due to technique failure. The technique survival at five years ranges from 55 to 72% [5]. The switch from PD to HD may influence the RRF loss. It may be best to analyze the data both as intention to treat and "as treated" which censors patients who switched dialysis type at the time of therapy change.

7.4.4 End Point

The loss of RRF in the PD population is a function of time. The issue would be whether to use a dichotomous end point, such as CrCl < 1.0 ml/min. at two years, or to do a rate of change of CrCl over time. Significant information is lost using the dichotomous variable, so rate of change in CrCl over time may be the more

suitable, although more time-consuming and expensive, endpoint. The use of rate of change of CrCl would record changes in the RRF associated with certain events. CrCl measurement, using an average of creatinine and urea clearance from a 24-hour urine, would be done every three months for two years.

Secondary end-points would be morbidity, as measured by rate of hospitalization, and mortality.

7.5 Summary

ACE inhibition has the potential to decrease RRF loss and therefore improve technique survival, patient morbidity, and patient mortality. Although the challenge of studying this effect may appear daunting at first glance, it is essential to explore interventions that will maintain native kidney function within the dialysis population. A commitment to understand, influence, and control the function of the remnant kidney represents an ambitious challenge and one that would have to be undertaken without guarantee of a positive outcome. However, the benefit of success would be substantial and appreciable, especially for the future acceptance of peritoneal dialysis.

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APPENDIX 1

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APPENDIX 2

EQUATIONS USED TO ESTIMATE GFR AND

1. **MDRD Equation:**

$$GFR \times 1.73\ m^2 = 170 \times [P_{cr}]^{-0.999} \times [Age]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [SUN]^{-0.170} \times [Alb]^{+0.318}$$

*SUN = serum urea nitrogen in mg/dl

2. **Walser Equation:**

Males, $GFR = 7.57\ [Cr]^{-1} - 0.103\ age + 0.096\ weight - 6.66$. Females, $GFR - 6.05\ [Cr]^{-1} - 0.08\ age + 0.08\ weight - 4.81$.

- weight in kilograms
- creatinine in μmol/L
- GFR was expressed as height[20].

3. **Cockcroft Gault Equation – Estimates of Creatinine Clearance (CrCl):**

$$CrCl\ ml/min = \frac{[140 - age] \times [weight\ in\ kg] \times 1.2}{Serum\ creatinine\ (\mu mol/L)}$$

- Deduct 15% for females

Patient Soc. Sec. #

Patient Medicare #

107

APPENDIX 3A

Confidential Report
Medical Questionnaire
(DMMS -Prospective)

First Dialysis Date (A6): mm dd yy

Study Start Date (A7): mm dd yy

Check box to left of item if unable to determine, and leave item (right) blank.

A. Patient and Facility Identification

1. Abstractor Initials:
2. Date Completed: mm dd yy
3. Ethnicity : 1 -Hispanic Origin 2 -Not of Hispanic Origin
4. Race: 1 - White 2 -Black 3 -Asian 4 -. Native American 5 -Other
5. Patient's Zip Code:
6. Date of first regular dialysis for chronic renal failure: (at least once weekly; regardless of setting). Please exclude intermittent dialysis treatments only for fluid overload or heart failure. mm dd yy
7. Study Start Date (Date #A6 plus 60 days): mm dd yy

Please copy these dates from A6 and A7 to the upper hand right corner of each page

8. Was date of earliest known dialysis -same as #A6? ... (i.e. were there no intermittent treatments prior to date at A6?) 1 - Yes 2 - No

➨ *(If item 8 is "no," give earliest date):* mm dd yy

9. Insurance (answer all that apply in both columns):

1 - Yes 2 - No	in the month before date A6	at or near date A7
a. Blue Cross/Blue Shield :		
b. Private (other than BC/BS):		
c. Medicare:		
If "no," is Medicare pending?		
If "yes," is Medicare secondary?		
d. Medicaid:		
e. VA:		
f. Other:		
g. None:		
h. Enrolled in an HMO?		

B. Patient History Within 10 Years Prior to Study Start Date (date A7)

1. Primary cause of ESRD:
   1 -Diabetes
   2 -Hypertension
   3 - Primary glomerulonephritis
   4 -Other
2. Regular cigarette smoking status:
   1 -Active (still smoking)
   2 - Former, stopped <1 year ago
   3 -Former, stopped >1 year ago
   4 -Smoker, current status unknown
   5 - Non Smoker

3. History of Coronary Heart Disease (CHD) or Coronary Artery Disease (CAD)

For a through g code 1 -Yes 2 -No 3 -Suspected

a. Prior diagnosis of CHD/CAD:
b. Angina:
c. Myocardial infarction (MI):
d. Bypass surgery (CABG):
e. Coronary angioplasty (PTCA):
f. Coronary angiography:
   Abnormal?
g. Cardiac arrest:

4. History of Cerebrovascular Disease:

For a & b code 1-Yes 2- No 3-Suspected CVA or TIA

a. Diagnosis of Cerebrovascular Accident (CVA, Stroke)

➨ *(If item 4a is "yes," skip to item 5.)*

b. Any Transient Ischemic Attacks (TIA)?

5. History of Peripheral Vascular Disease (PVD, PVOD):

For a through e code 1 - Yes 2 -No 3 -Suspected

a. Prior diagnosis of PVD:
b. Amputation due to PVD:
c. Limb amputation (other):
d. Absent foot pulses:
e. Claudication:

Date A6 : mm dd yy

Date A7: mm dd yy

Check box to left of item if unable to determine, and leave item (right) blank.

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6. **Hx of Heart Disease (other than CAD/CHD):**
   For all code: 1 - Yes 2 - No 3 - Suspected
   - ☐ a. Congestive heart failure: ☐
   - ☐ b. Pericarditis : ☐
   - ☐ c. Pulmonary edema: ☐

☐ 7. **Prior diagnosis of diabetes:** ☐
1 - Yes 2 - No 3 - Suspected

➨ *If item 7 is "no," skip to item 8.*

- ☐ a. Insulin therapy: ☐
  1 - Active 2 - Former 3 - Never
- ☐ b. Diabetes pills: ☐
  1 - Active 2 - Former 3 - Never

☐ 8. **History of Lung Disease:**
Chronic obstructive pulmonary disease (COPD) ☐
1 - Yes 2 - No 3 - Suspected

☐ 9. **Neoplasms (other than skin):** ☐
1 - Yes 2 - No 3 - Suspected

➨ *If item 9 is "no," skip to item 10.*

- ☐ a. Primary sites (up to 2) .. ☐☐ ☐☐

10 - Lung
11 - Stomach/Esophagus
12 - Breast
13 - Pancreas
14 - Prostate
15 - Liver
16 - Colon/Rectal
17 - Myeloma
18 - Lymphoma/Leukemia
19 - Brain
20 - Ovary/Uterus
21 - Melanoma of skin
22 - Bladder
23 - Oral/Larynx
24 - Kidney
25 - Other, Unknown

- ☐ b. Year of first dx: .... 19☐☐

☐ 10. **HIV Status:** ☐
1 - Positive 2 - Negative 3 - Unknown 4 - Can't disclose

☐ 11. **AIDS Diagnosis:** ☐
1 - Positive 2 - Negative 3 - Unknown 4 - Can't disclose

C: Information at Study Start Date (Date A7)

You may use information from the period between 30 days prior to date at A7 to 30 days after date at A7

1. **Height (at any time):** (REQUIRED)
   ☐ ft. ☐☐ in. ☐☐☐ OR cm.

If bilateral amputee give original height and check this box ☐

☐ 2. **Dry weight as ordered nearest study start date:**

wt: ☐☐☐ lbs. OR ☐☐☐.☐ kgs.

☐ 3. **Undernourished or cachectic (malnourished) at study start date (A7)** ☐
1 - Yes 2 - No 3 - Suspected

4. **Blood pressure and weight (most recent 3 readings before date (A7); please right justify entry):**

☐ a. Predialysis BP (sitting preferred) for HD (any readings for PD patients):

			weight (rounded)
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐

Required:
weight in pounds (lbs) ☐ or in kg. ☐ rounded (check one)

☐ b. Postdialysis BP (sitting preferred) for HD (skip for PD patients):
1 - Yes 2 - No

			weight (rounded)
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐
SBP ☐☐☐	/ DBP	☐☐☐	☐☐☐

HEMODIALYSIS (If used on date A7)

➨ *If patient is using peritoneal dialysis, skip to PD section*

5. **Hemodialysis prescription at date A7:**
   - ☐ a. Dialysate: ☐
     1 - Bicarbonate 2 - Acetate
   - ☐ b. Prescribed hours per treatment: ☐ hr. : ☐☐ min.
   - ☐ c. Prescribed # of dialysis sessions per week: ☐
   - ☐ d. Blood flow rate (BFR): ☐☐☐ ml/min

➨ *If BFR varies please enter the prescribed or the most common "high" rate.*

- ☐ e. Patient usually reusing dialyzer: ☐
  1 - Yes 2 - No
- ☐ f. If reuse does not occur, please indicate reason: ☐
  1 - Unit does not reuse 2 - Patient refuses
  3 - Hepatitis 4 - Other Medical
- ☐ g. Dialyzer type (see codes on back of page 5):

Only if you have entered code 9999, please specify below the manufacturer and dialyzer model: .... ☐☐☐☐

manufacturer _____

dialyzer model _____

_____

_____

*Patient Soc. Sec. # ☐☐☐-☐☐-☐☐☐☐

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Confidential Report
USRDS DMMS - Prospective

Date A6: ☐☐ ☐☐ ☐☐

Date A7: ☐☐ (mm) ☐☐ (dd) ☐☐ (yy)

Check box to left of item if unable to determine, and leave item (right) blank.

☐ h. Vascular access in use: ..... at date A6 ☐ at date A7 ☐
1 - AV Fistula
2 - PTFE graft e.g. Gortex, Impra, Teflon
3 - Bovine graft
4 - Permanent catheter e.g. Permcath (any site)
5 - Temporary internal jugular (IJ) catheter
6 - Temporary subclavian catheter
7 - Temporary femoral catheter
8 - Other

☐ i. Side of THIS access: ..... at date A6 ☐ at date A7 ☐
1 - Right 2 - Left

j. First permanent vascular access created or attempted on or before date A7:
☐ Type (use codes 1-4 from item 5h above):..... ☐
☐ Date of surgery: ☐☐ (mm) ☐☐ (dd) ☐☐ (yy)
☐ Date of first use of THIS access before A7: (leave blank if never used before date A7) ☐☐ (mm) ☐☐ (dd) ☐☐ (yy)
☐ Did this access require revision ☐ or did it fail ?... ☐
(Be sure to answer both boxes)
1 - No, not before date A7
2 - Yes, before date A6
3 - Yes, between date A6 and date A7

☐ Did this access fail to mature before date A7?..... ☐
1 - Yes 2 - No

☐ k. Temporary access in central vein anytime before date A7..... ☐
1 - Yes 2 - No

➡ *If item 5k is "no," skip to item 5l.*

☐ Any Subclavian (SC)..... ☐
☐ Any Internal jugular (IJ)..... ☐
1 - Right 2 - Left 3 - Right and Left 4 - Neither

☐ l. Number of HD treatments skipped by patient during 30 days prior to A7..... ☐☐
(do not include time in the hospital)

☐ m. Number of prescribed HD treatments shortened by more than 10 minutes by the patient during the 30 days prior to A7 ☐☐
(do not include skipped treatments):.....

☐ n. Did this patient have any peritoneal dialysis before date A7 (study start date)?..... ☐
1 - Yes 2 - No

➡ *If item 5n is "no," skip to item 8 (Psychosocial Evaluation)*

☐ o. Date of placement for PD catheter: ☐☐ (mm) ☐☐ (dd) ☐☐ (yy)

If patient is on hemodialysis on date A7, skip to page 4, Psychosocial Evaluation, item C8

PERITONEAL DIALYSIS (If used on date A7)

➡ *If patient did not receive PD, then skip to Psychosocial Evaluation.*

6. Peritoneal dialysis prescription at study start date (Date A7):
☐ a. Dialysis location:..... ☐
1 - Home 2 - Home Training 3 - In-center

☐ b. Type:..... ☐
1 - CAPD only 2 - Cycler(full when off cycler) 3 - Cycler (empty when off cycler) 4 - Combined

☐ c. Peritoneal Dialysis Prescription:

	Cycler	Manual
# of exchanges/ day	☐☐	☐
liters/exchange (most common)	☐.☐	☐.☐
total hours/day on cycler	☐☐	N/A
days/week	☐	☐
Total dialysate volume per 24 hrs	☐☐.☐	

☐ d. Type of PD catheter in use at date A7: ..... ☐
1 - single cuff 2 - double cuff 3 - no cuff

☐ e. Date of placement for THIS catheter: ☐☐ (mm) ☐☐ (dd) ☐☐ (yy)

☐ f. Was this the first peritoneal catheter for this patient?..... ☐
1 - Yes 2 - No

☐ g. Was this patient treated with hemodialysis before date A7 (study start date)?..... ☐
1 - Yes 2 - No

☐ h Did this patient have a permanent vascular access before date A7 (study start date)?..... ☐
1 - Yes 2 - No

➡ *If item 6h is "yes," go back to item 5j (go left) and complete 5j.*

7. Please give, on a voluntary basis, 24 hour dialysate urea N and creatinine in period of A6 to A7 + 30 days.

Total volume (drained) ..... ☐☐.☐

Dialysate Urea N - mg/dl ..... ☐☐☐.☐

Dialysate Creatinine - mg/dl ..... ☐☐.☐

BUN (same day) - mg/dl..... ☐☐☐.☐

Serum creatinine - mg/dl..... ☐☐.☐

Date A6: ☐☐ ☐☐ ☐☐

Date A7: ☐☐ ☐☐ ☐☐ (mm dd yy)

Check box to left of item if unable to determine, and leave item (right) blank.

PSYCHOSOCIAL EVALUATION

Complete this section for both PD and Hemo patients

➡ *Complete the following with information from the psychosocial evaluation most recent before the STUDY START DATE (or up to 30 days after A7). Use social worker's evaluation supplemented by the nurse's, and/or dietitian's records. You may want to consult with the social worker, dietitian, or ask the patient.*

☐ 8. Activities of daily living (currently or recently): 1 - Yes 2 - No

a. Able to eat independently :..... ☐

b. Able to transfer independently:..... ☐

c. Able to ambulate independently (includes ambulating with an assistance device)..... ☐

☐ 9. Marital status:..... ☐
1 - Single 2 - Married
3 - Widowed 4 - Divorced 5 - Separated

☐ 10. Living alone:..... ☐
1 - Yes 2 - No
3 - Nursing home, institution 4 - Homeless

☐ 11. Education:..... ☐
1 - Less than 12 Yrs. 2 - High School Grad
3 - Some College 4 - College Grad

☐ 12. Primary occupation before ESRD:..... ☐
1 - Clerical
2 - Professional
3 - Tradeperson
4 - Manual Labor
5 - Student
6 - Other
7 - Not Employed Outside of Home
8 - Homemaker
9 - Disabled

☐ 13. Employment Level:

☐ a Please indicate the one most appropriate employment category for the patient during the periods of time indicated. Please enter one number only in each box from the list below.

	24 mo. prior to ESRD - 6 mo. prior to ESRD	near date at A7
1 - Employed full time or full time student.....	☐	☐
2 - Employed part time or part time student		
3 - Homemaker		
4 - Retired		
5 - Never Employed		
6- Unemployed		
7 - Disabled		
8 - Other (specify)		

☐ b. If unemployed, is patient looking for employment:..... ☐
1 - Yes 2 - No

D: Laboratory Data

➡ *Complete with information closest to study start date (A7) from a period of up to3 months before study start date (A7) and one month after study start date (A7+ 30 days).*

☐ 1. Cardiomegaly by X-ray:..... ☐
1 - Yes 2 - No

2. Left ventricular hypertrophy:
1 - Yes 2 - No
☐ a. by EKG..... ☐
☐ b. by echocardiography..... ☐

☐ 3. Total serum calcium, predialysis:..... ☐☐.☐ mg/dl

☐ 4. Serum phosphate or phosphorus, predialysis:..... ☐☐.☐ mg/dl

☐ 5. Serum bicarbonate or CO_2, predialysis:..... ☐☐.☐ mEq/l

6. Hematocrit information (from the lab report)

☐ a. Hematocrit (If transfused, give value before blood transfusion):..... ☐☐.☐ %

☐ b. Hemoglobin (If transfused, give value before transfusion..... ☐☐.☐ g/dl

☐ c. Transfused in first 60 days of dialysis?..... ☐
1 - Yes 2 - No

➡ *If item 6c is "no," skip to item 7.*

☐ d. If transfused, number of transfusions in first 30 days of dialysis:..... ☐

7. Was the patient taking EPO (Erythropoietin)? .... ☐
1 - Yes 2 - No

☐ a. During first 60 days of dialysis (between A6 and A7):..... ☐

If yes: iv.=1, subcutaneous = 2 ..... ☐

☐ b. During last month before ESRD:..... ☐
(30 days prior to A6)

8. Serum Creatinine:

☐ a. Before first regular dialysis.. ..... ☐☐.☐ mg/dl
(on day of first regular dialysis or on the closest day prior to date A6)

☐ b. Nearest day 60 (A7):..... ☐☐.☐ mg/dl

9. BUN or urea values: Check here if urea:..... ☐

☐ a. Before first regular dialysis: ..... ☐☐☐ mg/dl
(on day of 1st regular dialysis or on the closest day prior to date A6)

Patient Name

Patient Soc. Sec. # ☐☐☐-☐☐-☐☐☐☐

DMMS ID#

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Confidential Report
USRDS DMMS - Prospective

Date A6: ☐☐ ☐☐ ☐☐

Date A7: ☐☐ ☐☐ ☐☐ (mm dd yy)

Check box to left of item if unable to determine, and leave item (right) blank.

☐ b. Nearest day 60 (measurements must be from same date):

Predialysis:..... ☐☐☐ mg/dl required

Postdialysis:..... ☐☐☐ mg/dl required

c. Weights pre and post dialysis (must be on same day as 9b):

weight in lb. ☐ or kg. ☐ rounded (check one)

☐ predialysis:..... ☐☐☐ required

☐ postdialysis:..... ☐☐☐ required

Dates for pre and post BUN values and pre and post weights MUST match.

☐ 10. Predialysis or random Serum Albumin: ☐.☐ g/dl

Complete with information closest to study start date (A7) from a period of up to 3 months before study start date (A7) to 1 month after study start date (A7+30)

11. Lipids:

☐ a. Cholesterol Total:..... ☐☐☐ mg/dl

☐ b. HDL cholesterol:..... ☐☐☐ mg/dl

☐ c. LDL cholesterol:..... ☐☐☐ mg/dl

☐ d. Triglycerides:..... ☐☐☐☐ mg/dl

☐ 12. Serum Intact PTH:..... ☐☐☐☐ pg/ml

☐ 13. Serum Aluminum: ..... ☐☐☐☐ µg/l

(Random or if DFO, please use base line measurement)

14. Residual Renal Function

This section is important but is not an official requirement. Please give all available information and/or obtain the measurements within period of date A6 to date A7 + 30 days, (i.e.days 0 -90 days ESRD) on a voluntary basis if at all possible:

☐ a. Urine collection time:

start..... ☐☐ mm ☐☐ dd (Date) ☐☐:☐☐ hr min ☐ AM=1 PM=2 (Time)

end..... ☐☐ mm ☐☐ dd (Date) ☐☐:☐☐ hr min ☐ AM=1 PM=2 (Time)

Total hours of urine collection (Verification)..... ☐☐

☐ b. Lab Values

	Value	Units
Urine Volume	☐,☐☐☐	ml or cc
Urine Creatinine	☐,☐☐☐	indicate units ☐ mg/vol ☐ mg/24 hrs. ☐ mg/dl=mg%
Urine Urea Nitrogen	☐,☐☐☐	
Pre Creatinine*	☐☐.☐	mg/dl
Pre BUN*	☐☐☐	mg/dl
Post Creatinine*	☐☐.☐	mg/dl
Post BUN*	☐☐☐	mg/dl

* For the pre and post blood creatinine and BUN, please provide values taken ideally at the beginning (pre) and end (post) of URINE collection If this is not possible:

For hemo patients, enter values from measurements taken pre and post dialysis on a date as close as possible to the dates of urine collection.

For PD patients, enter blood creatinine and BUN values taken on a date as close as possible to the date of urine collection available.

15. Medications at time of A7, please copy the list of all medications as generic or trade name. (The dosage is not required)

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

16. Was patient receiving at time of A7 injectable vitamin D

(Calcijex) ..... ☐

1 - yes 2 - no

USRDS
DMMS Follow-Up Study
Medical Update Questionnaire

Patient Name_____

DMMS ID#_____

Date at Day 60 of ESRD (Date A.7)_____

Modality at Day 60 of ESRD (Date A.7)_____

Check box to left of item if unable to determine, and leave item (right) blank.

C. Vascular Access Status of Patient who was on Hemo on Day 60 of ESRD

Complete this section only if patient was on hemo at Day 60 of ESRD. We need to know the status of this patient's **FIRST PERMANENT VASCULAR ACCESS.** Please complete the following items with information from the patient's medical record. **Please complete this section even if the patient has died or changed modality.**

Codes to be used for type of vascular access
1-AV fistula
2-PTFE graft
3-Bovine graft
4-Permcath 5-Other

☐ 1. Has a permanent vascular access ever been created or attempted in this patient? ☐ 1-Yes 2-No

If NO, please do not complete the rest of this section on Vascular Access (Items 2-6)

☐ 2. This patient's Medical Questionnaire indicated that on or before _____(Date 60 of ESRD), the patient had the following type of first permanent access: _____

If this is incorrect, please provide the correct answer using codes 1-4 from above. ☐
(If C.2 is correct, please leave this box blank)

If C.2 above is blank, what was the first permanent vascular access created or attempted? ☐
(Use one of codes 1-5 from above.)

☐ What SIDE was this first permanent access placed on? ☐ 1-Right 2-Left

☐ 3. The patient's Medical Questionnaire indicated that the date of surgery for creation of first permanent vascular access was:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

If incorrect or blank, please provide the date of the surgery for creation of the first permanent vascular access:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

☐ 4. Was this first permanent access ever used for dialysis? ☐ 1-Yes 2-No

If YES, what was the first date that this permanent access was used for dialysis?

☐ Date: ☐☐ ☐☐ ☐☐
MM DD YY

If NO, did this first permanent access fail to mature adequately for dialysis? ☐ 1-Yes 2-No

☐ 5. Did this first permanent access fail after being used for dialysis? ☐
1-Yes 2-No 3-Unknown

If YES, please provide the date of first failure.

Date: ☐☐ ☐☐ ☐☐
MM DD YY

If NO or UNKNOWN, please provide the last known date the access was used for dialysis.

Date: ☐☐ ☐☐ ☐☐
MM DD YY

☐ 6. Were there any revisions or procedures made to this first permanent access? ☐
1-Yes 2-No 3-Unknown

If YES, please give the FIRST two dates and type of revisions (or procedures) that were made subsequent to the date provided in C.3. Please use the codes provided.

1-Thrombolysis
2-Balloon angioplasty with or without thrombolysis
3-Surgical repair or declotting
4-creation of a new AV fistula
5-creation of a new PTFE graft (e.g. Goretex)
6-creation of another permanent access (e.g. Permcath)
7-other

First Revision or Procedure:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

Type: ☐ (use codes 1-7 above)

Second Revision or Procedure: Was there a second revision or procedure within two weeks of the first one? If yes, please indicate the type using codes 1-7 from above and the date:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

Type: ☐ (use codes 1-7 above)

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

Abstractor's Initials ☐☐

Today's Date: ☐☐ ☐☐ ☐☐ (mm dd yy)

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USRDS

DMMS Follow-Up Study

Medical Update Questionnaire

Patient Name_____

DMMS ID#_____

Date at Day 60 of ESRD (Date A.7)_____

Modality at Day 60 of ESRD (Date A.7)_____
(If Hemo, please fill out section on Vascular Access on back of page)

Check box to left of item if unable to determine, and leave item (right) blank.

A. Patient Status Since Day 60 of ESRD (Date A.7)

☐ 1. We need to know the **first change in patient status** or modality since _____ (Day 60 of ESRD). The date of this **FIRST** change in patient status or modality since Day 60 of ESRD was:

Please enter date of **FIRST** change

Date: ☐☐ ☐☐ ☐☐ (MM DD YY)

(Please enter Today's Date if there was no change in the patient's status or modality. If unavailable, give month and year or year only.)

For the date you just entered, give the code for patient status:

Codes for Change in Status or Modality ☐

1=had no change in status or modality
2=changed to PD (for at least 2 weeks)
3=changed to hemodialysis (for at least 2 weeks)
4=changed to home hemodialysis (for at least 2 weeks)
5=had return of renal function
6=transferred to another facility
7=received a kidney transplant
8=died
9=was lost to follow-up
10=withdrew from dialysis

☐ 2. The patient's **current** status is (please enter code): ☐

1-alive 2-died 3-lost to follow-up

If the patient died, please enter the date of death. If the patient is living or lost to follow-up, please enter the date that the patient was last know to be alive.

Date: ☐☐ ☐☐ ☐☐ (MM DD YY)

B. BUN and Residual Renal Function

Complete this section only for patients from your unit who are currently on in-center hemodialysis or peritoneal dialysis. Use information as close as possible to today's date, that is not more than 60 days from today's date.

☐ 1. The patient's current modality of treatment is: ☐
1-hemo 2-PD (CAPD or CCPD)

☐ 2. The approximate urine output of the patient is currently: ☐
1 - greater than 200 ml/day
2 - less than 200 ml/day (200 ml is about 1 cup)

3. BUN and weight:

All values for a. and b. must be from same date

☐ a. Pre-dialysis BUN ☐☐☐ mg/dl
(most recent if PD)

Pre-dialysis Weight

☐☐☐ lbs *or* ☐☐☐.☐ kg

☐ b. Post-dialysis BUN ☐☐☐ mg/dl
(Hemo Patients Only)

Post-dialysis Weight

☐☐☐ lbs *or* ☐☐☐.☐ kg

Question #4 is Voluntary.

4. Residual Renal Function (Do not complete this item urine volume is less than 200 ml/day.)

☐ a. Urine collection time:

Start (Post dialysis for hemo patients)

☐☐ ☐☐ ☐☐ ☐☐:☐☐ AM=1 PM=2
mm dd yy hr min
Date Time

End (Usually next pre-dialysis treatment for hemo patients)

☐☐ ☐☐ ☐☐ ☐☐:☐☐ AM=1 PM=2
mm dd yy hr min
Date Time

Total hours of urine collection (Verification)..... ☐☐

☐ b. Lab Values

	Value	Units
Urine Volume	☐,☐☐☐	ml or cc
Urine Creatinine	☐,☐☐☐	check one ☐ mg/dl ☐
Urine Urea Nitrogen	☐,☐☐☐	☐ mg/24hrs. ☐ mg/dl=mg%
Start Serum Creatinine**	☐.☐	mg/dl
Start BUN**	☐☐☐	mg/dl
End Serum Creatinine**	☐☐.☐	mg/dl
End BUN**	☐☐☐	mg/dl

** For PD patients, enter only one set of serum creatinine and BUN values (START) taken on a date as close as possible to the date of urine collection. *Start* and *End* refer to the same point in time as in 4a above.

USRDS
DMMS Follow-Up Study
Medical Update Questionnaire

Patient Name_____

DMMS ID#_____

Date at Day 60 of ESRD (Date A.7)_____

Modality at Day 60 of ESRD (Date A.7)_____

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Check box to left of item if unable to determine, and leave item (right) blank.

C. Vascular Access Update (Patients who were on Hemo on Day 60 of ESRD)

Complete this section only if patient was on hemo at Day 60 of ESRD. We need to know the status of this patient's **FIRST PERMANENT VASCULAR ACCESS.** Please complete the following items with information from the patient's medical record. **Please complete this section even if the patient has died or changed modality.**

Codes to be used for type of vascular access
1-AV fistula
2-PTFE graft
3-Bovine graft
4-Permcath 5-Other

☐ 1. Has a permanent vascular access ever been created or attempted in this patient? ☐ 1-Yes 2-No

If NO, please do not complete the rest of this section on Vascular Access (Items 2-6)

☐ 2. This patient's Medical Questionnaire indicated that on or before _____(Date 60 of ESRD), the patient had the following type of first permanent access: _____.

If this is incorrect, please provide the correct answer using codes 1-4 from above. ☐
(If C.2 is correct, please leave this box blank)

If C.2 above is blank, what was the first permanent vascular access created or attempted? ☐
(Use one of codes 1-5 from above.)

☐ What SIDE was this first permanent access placed on? ☐ 1-Right 2-Left

☐ 3. The patient's Medical Questionnaire indicated that the date of surgery for creation of first permanent vascular access was:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

If incorrect or blank, please provide the date of the surgery for creation of the first permanent vascular access:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

☐ 4. Was this first permanent access ever used for dialysis? ☐ 1-Yes 2-No

If YES, what was the first date that this permanent access was used for dialysis?

☐ Date: ☐☐ ☐☐ ☐☐
MM DD YY

If NO, did this first permanent access fail to mature adequately for dialysis? ☐ 1-Yes 2-No

☐ 5. Did this first permanent access fail after being used for dialysis? ☐
1-Yes 2-No 3-Unknown

If YES, please provide the date of first failure.

Date: ☐☐ ☐☐ ☐☐
MM DD YY

If NO or UNKNOWN, please provide the last known date the access was used for dialysis.

Date: ☐☐ ☐☐ ☐☐
MM DD YY

☐ 6. Were there any revisions or procedures made to this first permanent access? ☐
1-Yes 2-No 3-Unknown

If YES, please give the FIRST two dates and type of revisions (or procedures) that were made subsequent to the date provided in C.3. Please use the codes provided.

1-Thrombolysis
2-Balloon angioplasty with or without thrombolysis
3-Surgical repair or declotting
4-creation of a new AV fistula
5-creation of a new PTFE graft (e.g. Goretex)
6-creation of another permanent access (e.g. Permcath)
7-other

First Revision or Procedure:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

Type: ☐ (use codes 1-7 above)

Second Revision or Procedure: Was there a second revision or procedure **within two weeks of the first one**? If yes, please indicate the type using codes 1-7 from above and the date:

Date: ☐☐ ☐☐ ☐☐
MM DD YY

Type: ☐ (use codes 1-7 above)

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE!

Abstractor's Initials ☐☐

Today's Date: ☐☐ ☐☐ ☐☐ (mm dd yy)

USRDS

DMMS Follow-Up Study

Medical Update Questionnaire

Patient Name_____

DMMS ID#_____

Date at Day 60 of ESRD (Date A.7)_____

Modality at Day 60 of ESRD (Date A.7)_____

(If Hemo, please fill out section on Vascular Access on back of page)

Check box to left of item if unable to determine, and leave item (right) blank.

A. Patient Status Since Day 60 of ESRD (Date A.7)

☐ **1. We need to know the first change in patient status or modality since _____ (Day 60 of ESRD). The date of this FIRST change in patient status or modality since Day 60 of ESRD was:**

Please enter date of **FIRST** change

Date: ☐☐ ☐☐ ☐☐ (MM DD YY)

(Please enter Today's Date if there was no change in the patient's status or modality. If unavailable, give month and year or year only.)

For the date you just entered, give the code for patient status:

Codes for Change in Status or Modality ☐

1=had no change in status or modality
2=changed to PD (for at least 2 weeks)
3=changed to hemodialysis (for at least 2 weeks)
4=changed to home hemodialysis (for at least 2 weeks)
5=had return of renal function
6=transferred to another facility
7=received a kidney transplant
8=died
9=was lost to follow-up
10=withdrew from dialysis

☐ 2. The patient's current status is (please enter code): ☐

1-alive 2-died 3-lost to follow-up

If the patient died, please enter the date of death. If the patient is living or lost to follow-up, please enter the date that the patient was last know to be alive.

Date: ☐☐ ☐☐ ☐☐ (MM DD YY)

B. BUN and Residual Renal Function

Complete this section only for patients from your unit who are currently on in-center hemodialysis or peritoneal dialysis. Use information as close as possible to today's date, that is not more than 60 days from today's date.

☐ 1. The patient's current modality of treatment is: ☐

1-hemo 2-PD (CAPD or CCPD)

☐ 2. The approximate urine output of the patient is currently: ☐

1 - greater than 200 ml/day
2 - less than 200 ml/day (200 ml is about 1 cup)

3. BUN and weight:

All values for a. and b. must be from same date

☐ a. Pre-dialysis BUN ☐☐☐ mg/dl
(most recent if PD)

Pre-dialysis Weight

☐☐☐ lbs *or* ☐☐☐.☐ kg

☐ b. Post-dialysis BUN ☐☐☐ mg/dl
(Hemo Patients Only)

Post-dialysis Weight

☐☐☐ lbs *or* ☐☐☐.☐ kg

Question #4 is Voluntary.

4. **Residual Renal Function (Do not complete this item if urine volume is less than 200 ml/day.)**

☐ a. Urine collection time:

Start (Post dialysis for hemo patients)

☐☐ ☐☐ ☐☐ ☐☐:☐☐ (mm dd yy hr min AM=1 PM=2)
Date Time

End (Usually next pre-dialysis treatment for hemo patients)

☐☐ ☐☐ ☐☐ ☐☐:☐☐ (mm dd yy hr min AM=1 PM=2)
Date Time

Total hours of urine collection (Verification)..... ☐☐

☐ b. Lab Values

	Value	Units
Urine Volume	☐,☐☐☐	ml or cc
Urine Creatinine	☐,☐☐☐	check one ☐ mg/dl ☐ mg/24hrs. ☐ mg/dl=mg%
Urine Urea Nitrogen	☐,☐☐☐	
Start Serum Creatinine**	☐☐.☐	mg/dl
Start BUN**	☐☐☐	mg/dl
End Serum Creatinine**	☐☐.☐	mg/dl
End BUN**	☐☐☐	mg/dl

** For PD patients, enter only one set of serum creatinine and BUN values (START) taken on a date as close as possible to the date of urine collection. *Start* and *End* refer to the same point in time as in 4a above.

APPENDIX 4

UWO-DOM Research Competition

1. Louise M. Moist

2. Measurement of renal function among patients on dialysis

3. Myura Muhunthan, Medical resident

4. SUMMARY of PROPOSAL

Residual glomerular filtration rate (GFR) is clinically important as it accounts for major differences in dialysis requirements and mortality among patients on dialysis. As a consequence, it is important to investigate methods for accurately measuring the small amount of residual GFR in patients receiving maintenance dialysis. The literature has small case series reviewing various tests used to measure residual GFR, but few compare measurements among patients on dialysis and none compare the measures available for use in our center. The aim of the proposed research is to establish the best method that can be used in clinical practice to measure residual GFR in dialysis patients. We propose to simultaneously measure residual GFR using 99m Tc-DTPA, clearance of urea and creatinine, the average of the urea and creatinine clearance, urine volume, and published equations used to predict GFR from various patient parameters. The correlation between 99m Tc-DTPA and each other test will be analyzed by linear regression. The results of this study will give the nephrologist a practical, reliable test to measure residual GFR in the dialysis population.

Budget Details:

Item	Responsible Person	Cost
Patient identification and entry	Medical resident	No cost
Data collection and entry	Medical resident	No cost
Statistical support Consultation and SAS time	Department of Epidemiology and Biostatistics	$1000.00
Supplies	Office supplies Publication Costs	$200.00 $200.00
GFR study	Nuclear Medicine Includes cost of materials and technician time only Professional fee waived for research purposes	$80.00/study x 80 patients $6,400.00
Travel	Presentation at American Society of Nephrology	$1,000.00
TOTAL:		$8,800.00

Dr. Myura Muhunthan will be doing a 2 month research elective in Nephrology to look at measurement of renal function among patients with chronic renal disease and among patients with end stage renal disease on dialysis. She will be responsible for enrolling patients; co-ordinating investigations and data entry so there will be no cost for this. Dr. Mattar is Chief of Nuclear Medicine and he will waive the professional cost of the GFR study and charge only for the direct costs.

Background

In recent years, there has been a greater focus on residual renal function of patients on chronic dialysis therapy. Although RRF is often used to indicate residual glomerular filtration rate (GFR), it also reflects remaining endocrine functions such as erythropoietin production, calcium, phosphorus and vitamin D homeostasis, volume control, and removal of "middle molecules" or low molecular weight proteins. Residual renal function is clinically important as it can account for major differences in dialysis requirements since it contributes to measures of adequacy, both Kt/V urea and creatinine clearance (1, 2). RRF has also been shown to be associated with mortality. Analysis of the CANUSA study (3) has shown that every 0.5ml/min higher GFR was associated with a 9% lower risk of death (RR=0.91) (4). It has been shown that clinically important and statistically significant decreases in nutritional parameters occur with RRF loss. Furthermore, it has also been demonstrated that small increments in RRF may account for major differences in quality of life.

The understanding of the importance of the residual renal function demands that we have an accurate and practical test to measure the residual renal function. The usefulness of a diagnostic test is based on its accuracy (compared to standard), precision (inversely related to the variability of measurements), and convenience. The GFR is believed to be the best overall index of renal function in health and disease since it is a direct measure of renal function, it declines before the onset of signs and symptoms of uremia, and it correlates with severity of structural changes in progressive renal disease. However, the GFR can be affected by volume status, nonsteroidal anti-inflammatory drugs, acute protein loading, level of arterial blood pressure and some anti-hypertensive agents (5).

Accurate measurement of GFR using Inulin is time consuming, expensive, and not practical for routine use. Estimates of GFR using formulas including patient and lab parameters such as the Cockcroft Gault (6), MDRD (7), and Wasler (8) formula can be imprecise and have not been validated in the end stage renal disease (ESRD) patient on dialysis.

Other markers, such as serum creatinine reciprocal of creatinine clearance, urea clearance, and the average of the creatinine and urea clearance have been used to assess the level of residual GFR. Indices of GFR, such as reciprocal of serum creatinine and creatinine clearance are of limited value in assessing renal function particularly in patients with advanced renal function (9).

Clearance of creatinine is another measure of residual GFR in the dialysis patient. Creatinine clearance is influenced by enhanced tubular secretion. As renal failure progresses and the total GFR declines, less creatinine is filtered and proportionately more of the urinary creatinine is derived from tubular secretion, leading to an over-estimate of GFR. In view of the limitations of creatinine

clearance as an index of GFR, the average of the creatinine clearance and urea clearance has been used as a better marker of GFR (10). The effect of the urea reabsorption is offset by the creatinine secretion, making the average of the urea clearance and the creatinine clearance a closer approximate of the GFR in patients with a GFR less that 15ml/min/1.73m^2.

Urine volume is variable in ESRD and is determined by the GFR and the rate of tubular reabsorption. In spite of its shortcomings, urine volume has been correlated to GFR in previous studies (4). Tzamaloukas demonstrated that urine volume was the primary determinant of urinary clearance among patients treated with continuous peritoneal dialysis. This finding supported previous findings that urine volume is a major contributor of Kt/V and total creatinine clearance.

The lack of a suitable measure of residual GFR in the dialysis population has blurred our understanding of the remnant kidney. We cannot look at factors which preserve the residual GFR until we have an accurate, precise and practical measure of residual renal function. If a test was identified that was accurate, precise and convenient, we would measure the residual GFR more frequently and get a better understanding of the remnant kidney and the factors that will preserve the valuable remaining GFR. Inulin is considered the gold standard in GFR measurement. At our center we use 99m Tc-DTPA as our GFR measurement. It has been correlated with Inulin in patients with chronic renal failure (11) and in patients on dialysis (4). 99m Tc-DTPA will be considered as the best available test or the gold standard in our study.

PART 2: MEASUREMENT OF RRF AMONG PATIENTS ON DIALYSIS

Objective: 1.To compare the available measures of residual GFR to the "gold standard" GFR measurement with 99m Tc-DTPA among patients on dialysis.

Hypothesis: 1.Measurement of the average creatinine and urea clearance will provide a simple accurate and inexpensive test of renal function among patients on dialysis.

2. Availability of a simple, inexpensive test to measure renal function will allow the nephrologist to prescribe adequate dialysis prescriptions and monitor factors, which influence the residual GFR.

Methods:

Population:
Patients receiving hemodialysis and peritoneal dialysis in units associated with London Health Science Centre and St. Joseph's Health Centre.

Inclusion Criteria:
1. Informed consent
2. Duration of dialysis from 1 month to 5 years
3. Age between 20-75.
4. Urine production of >100ml/24 hours.
5. Stable dialysis for the last 2 weeks

Exclusion Criteria:
1. Urine out-put < 100ml/24h
2. Unable to attend nuclear medicine study

Design:
Cross-sectional study of a hemodialysis and peritoneal dialysis population to compare measures of residual GFR.
Patient consent will be obtained by a senior medical resident. The nature of the study, accurate collection of urine and the nuclear medicine study will be explained to the patient. After patient consent the following measures of residual GFR will be performed.

1. 99mTc_DTPA GFR study (Protocol attached Appendix 2)
2. 24 hour urine collection with measurement
    1. urine volume
    2. 24 hour creatinine clearance
    3. 24 hour urea clearance
    4. average of 24 hour creatinine and urea clearance
3. Lab parameters measured to calculate GRR using MDRD, Cockcroft-Gault and Walser formula.

For hemodialysis patients all clearance measurements will be carried out during a 24-hour inter-dialytic period between two dialysis. The serum creatinine and urea will be a pre dialysis level. Patients on peritoneal dialysis will have urea and creatinine measured from a 24 hour urine collection as well as the urea and creatinine level in serum samples taken during the same 24 hours, or 12 hours before or after.

Analysis: The correlation between 99mTcDTPA and each test will be analyzed by the method of linear regression and a correlation coefficient calculated. The p values of the correlation coefficient will be calculated by Fisher transformation.

Anticipated Results:
Residual GFR is an important predictor of adequacy of dialysis and mortality within the dialysis population. Currently we do not know which test will reliably measures residual GFR in a practical, inexpensive manner. We anticipate that the average 24-hour creatinine and urea clearance will provide an accurate estimate of residual GFR both in the hemodialysis and peritoneal dialysis population. This measure will allow us to follow residual GFR more closely and follow parameters that will effect its preservation.

Problem:
1. Inaccurate collection of 24 hour urine. The medical resident will give careful verbal and written instructions to the patient to ensure accurate collection.

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