When to Initiate Maintenance Dialysis and How Much is Enough

by

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Brief Description of Interests:

I am interested in mechanisms, consequences and therapy of progressive renal diseases including hypertensive nephrosclerosis, diabetes mellitus and chronic glomerulonephritis. In addition, I am interested in the indications, benefits, risks and long-term outcome of dialysis and transplant therapy in end-stage renal disease populations. My research interests are along these lines and consist of studies of mechanisms of disease, clinical trials, outcomes and technology transfer.

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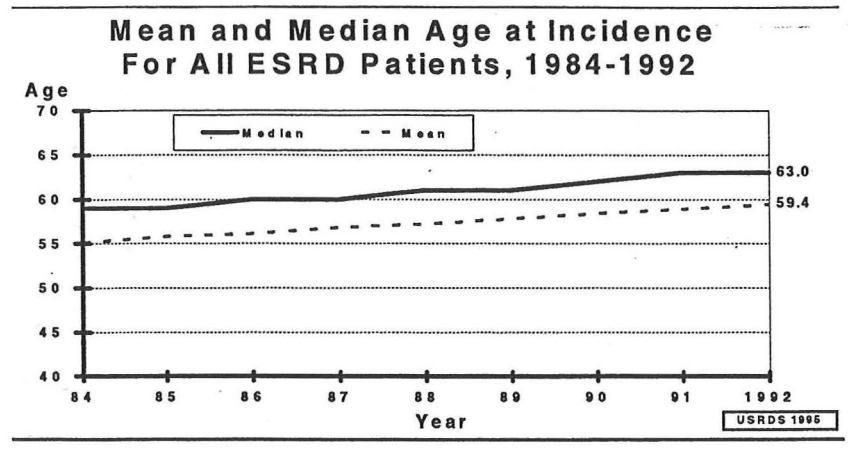
RENAL FAILURE: A SERIOUS DISEASE WITH A HIGH MORTALITY RATE

Epidemiology of ESRD in the United States

Renal failure is a relatively uncommon disease in a general medicine practice. In fact, End-Stage Renal Disease (ESRD) occurs in about 1/1300 population in the United States. However, the annual incidence rate of ESRD has been increasing at a rate of about 8% per year with diabetes and hypertension, accounting for about 60% of all new cases of ESRD, leading the way. The most striking increase in incidence of ESRD has been in older individuals, in fact the 65-74 age category is the fastest growing ESRD population in the Nation. Thus the mean age of the entire population has been increasing over the past decade (Figure 1).

Figure 1

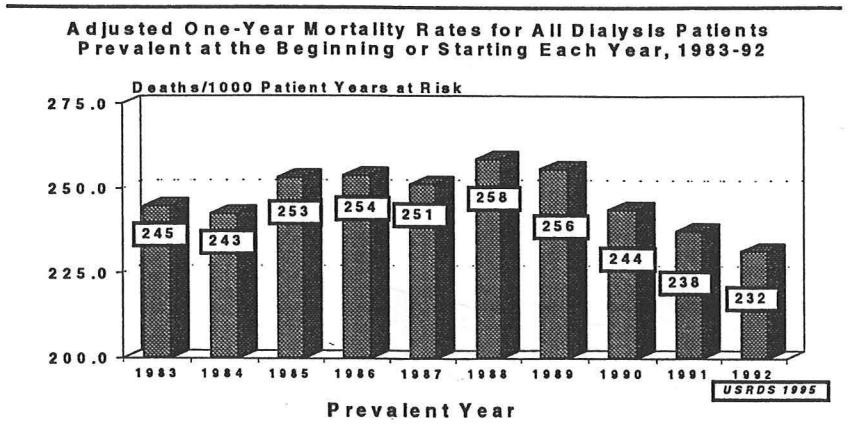


USRDS 1995 Annual Report

The prevalence of ESRD in 1992 in the U.S. was 206,000 patients according to the most up-to-date information from the United States Renal Data Systems (USRDS). Furthermore, the prevalent population is increasing in size because of three factors: 1) heightened awareness of ESRD; 2) an

aging population and 3) gradually declining annual mortality rate of the ESRD population (Figure 2).

Figure 2



Mortality rate (deaths/1000 patient years at risk) for all prevalent dialysis patients whose first treatment was after 1/1/1993. Patients prevalent at the beginning of each year, 1983-92. Rates are adjusted for age, race (black, white), sex and diagnosis (diabetic or nondiabetic). Source: Special Analysis.

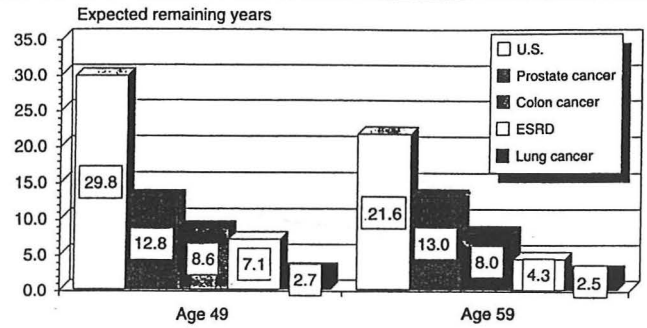
High Mortality Rate in ESRD

Despite the trend in decreasing mortality, the annual adjusted death rate in the United States ESRD population is about 20%, a level nearly double that for other Western industrialized nations. Thus the life expectancy of a 49 year old ESRD patient is 7.9 years, well below the normal U.S. population

and well below the life expectancy for prostate or colon cancer (Figure 3). The major causes of death are cardiac disease including cardiac arrest, acute MI and congestive heart failure, and infections. Underlying these conditions, one frequently finds evidence of malnutrition.

Figure 3

LIFE EXPECTANCY AT AGE 49 AND 59 YEARS FOR PATIENTS WITH ESRD, THE GENERAL POPULATION, AND PATIENTS WITH OTHER CHRONIC CONDITIONS.



Port, F.K.Kid Int., 46:17288-1737,1994.

What Can Be Done to Lower ESRD Mortality?: Importance of Nutritional Status

Two key strategies for lowering ESRD mortality are: 1) to prevent ESRD from occurring in the first place and 2) prevent and treat known risk factors for death in ESRD. The major risk factors for ESRD-related mortality include age, race, gender, diabetes and malnutrition. Clearly, among these factors only diabetes and malnutrition are treatable. Recent studies indicate that malnutrition in dialyzed patients is a strong predictor of mortality from all causes. As a result major efforts are now underway to identify and treat causes of malnutrition with the hope of reducing dialysis mortality. This Grand Rounds will intensely focus on malnutrition in renal failure in relation to two important questions in clinical nephrology: 1) when to initiate dialysis? and 2) how much is enough? These questions are at the core of a National debate. When to initiate dialysis is a particularly important issue for internists. Interestingly, the timing of initiation of dialysis becomes a double-edged sword for the patient: On the one hand dietary restriction of protein and energy intake whether therapeutic or spontaneous may slow deterioration of renal function and postpone dialysis, but on the other hand it may foment malnutrition posing a serious death risk. If the latter is

true, the does earlier dialysis lower morbid and mortal complications of ESRD? These questions will be addressed in detail at several levels. However, before discussing dialysis issues, it is worth pointing out recent progress in reducing the risk of developing ESRD.

PROGRESS IN THE PREVENTION OF ESRD

Several effective strategies for reducing the risk of developing ESRD in a variety of renal diseases including phramacologic intervention for strict blood pressure control, angiotensin converting enzyme inhibitors, fish oil (Table 1) and dietary protein restriction (Table 2). The mechanisms of these treatments are incompletely understood, but altered renal hemodynamics, a major factor in antihypertensive treatment, ACE inhibitors and dietary protein restriction plays an important role. The best example of a therapeutic benefit of pharmacologic intervention so far is the use of captopril in type I diabetes in which reduced the risk of ESRD/death by 50%

Table 1. RENAL FAILURE: SELECTED STUDIES INDICATING BENEFICIAL EFFECT OF PHARMACOLOGIC INTERVENTION*

Author	Year	Renal Disease	N	Treatment	Outcome
Lewis et al	1993	Type I DM	409	Captopril	↓ Doubling Scr, ESRD
Donadio, et al	1994	IgA Nephropathy,	106	Fish Oil	"
Toto, et al	1995	Hypertension	87	Strict BP control	↓ Slope of GFR
Maschio, et al	1996	Non-diabetic	583	Benazepril	↓ Doubling Scr

*Scr = serum creatinine, Mixed = hypertension, glomerulonephritis,

Table 2. RENAL FAILURE: SELECTED STUDIES INDICATING BENEFICIAL EFFECT OF DIETARY PROTEIN*

Author	Year	Renal Disease	N	Protein Intake	Outcome
Maschio et al	1982	Mixed	75	0.6 g/kg/d	↓ Slope of 1/Scr
Alvestrand et al	1983	Mixed	20	16-20 g/day	↓ Slope of 1/Scr

Ihle et al	1989	Non-diabetic	64	0.4 g/kg/d	↓ Slope of GFR
Zeller et al	1991	Type I DM	35	0.6 g/kg/d	↓ Slope of GFR
Klahr et al	1994	Non-diabetic	840	0.3-0.6 g/kg/d	↓ Slope of GFR

* Abbreviations same as table 1.

These therapies represent important advances and are now in practice but will take time to impact on the rising incidence of ESRD. It is noteworthy, that none of these studies have investigated the type II diabetes population which comprises 60% of cases of ESRD due to diabetes! However, in most cases, they slow but do stop progression of renal failure, thus ESRD may still be the end result for most patients even though the time to dialysis/transplantation is prolonged. To better understand when it is time to abandon conservative/therapeutic interventions designed to delay dialysis, we will now examine the relationships between the progressing renal failure, the development of the uremic malnutrition, and its attendant complications.

BUN AND CREATININE: MEASURING RENAL FUNCTION AND NUTRITIONAL STATUS IN RENAL DISEASE AND THEIR RELATION TO UREMIA

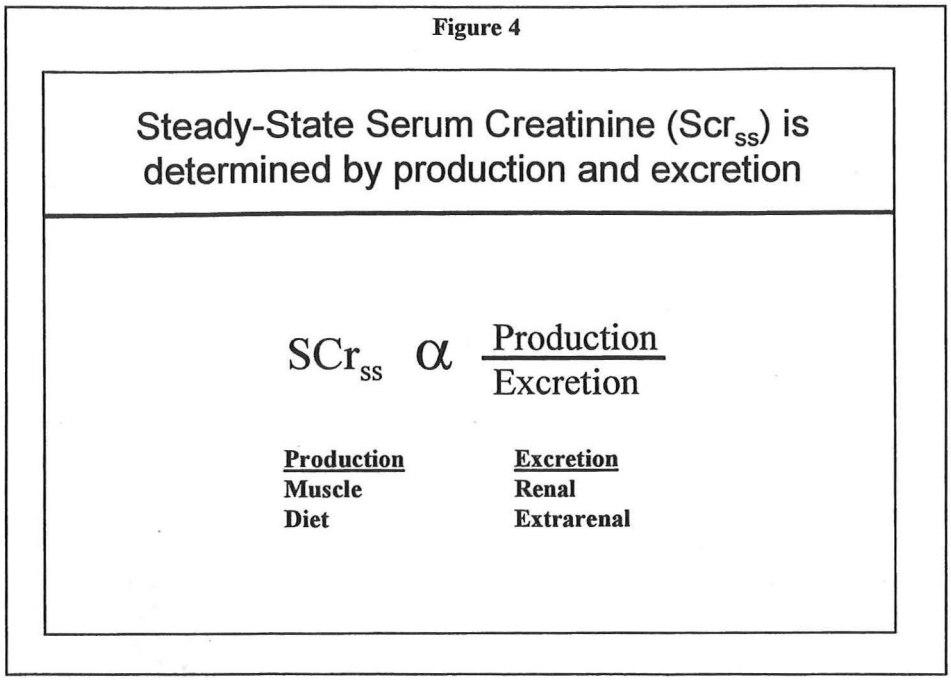
Glomerular filtration rate is widely regarded as a global assessment of renal function. Most clinicians use BUN and serum creatinine as markers of renal function because they estimate the level of GFR, are widely available and easily reproducible. Unfortunately, they are only crude estimates and do not tell the whole story, not only with respect to renal function but also with regard to the presence of important uremic manifestations. When interpreting BUN, serum creatinine, urea clearance and creatinine clearance as estimates of renal function, one must consider the contribution of urea and creatinine production to the steady-state BUN or serum creatinine values. The following review is a guide to the use of these parameters as well as the renal clearance of creatinine and urea as alternative markers of GFR and uremic signs.

Markers of Renal Function and Nutritional Status: Creatinine and Urea

Creatinine Metabolism: Production

Serum creatinine in the steady-state (SCr_{ss}) is determined by production and excretion (Figure 4). As

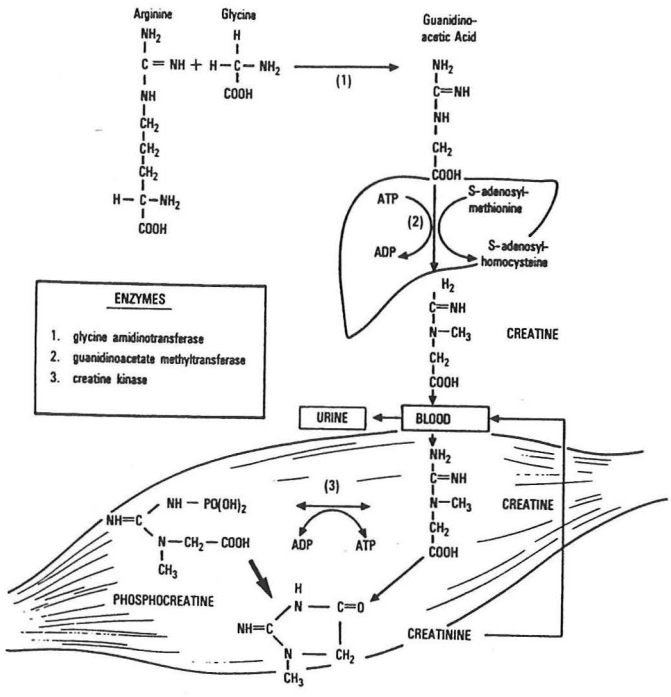
Figure 4



shown below in Figure 5, muscle is the principle site of creatinine production by nonenzymatic degradation of creatine and creatine phosphate. Other factors, especially dietary intake of creatine in the form of cooked meat, also contribute importantly to creatinine production (Table 3). This point is illustrated in Figure 6 in which the acute effect of dietary intake of meat versus plant protein on serum creatinine concentration. In normal subjects the entire body creatinine load is excreted by the kidney. Therefore:

Daily urinary excretion rate of creatinine = daily production rate of creatinine.

Figure 5 Principle Pathways in Creatine Metabolism



Heymsfield et al *Am. J. Nutr.* 37:478-494, 1983

So, one can obtain an accurate estimate of creatinine production from the urine creatinine excretion rate. Both body muscle mass and dietary intake influence this value. Therefore, creatinine serves as a combined marker of dietary protein intake and somatic protein content, i.e. muscle mass. A diet low in meat products sharply reduces creatinine intake and hence reduces urinary excretion of creatinine (Figure 7). Patients with progressive renal disease placed on low protein diets exhibit this effect as well. Loss of muscle mass will do the same. Therefore, as muscle mass decreases with aging or the development of uremia or both, creatinine production and hence excretion decrease accordingly. At the bedside, a malnourished uremic patient with low creatinine production may actually lower their serum creatinine concentration with or without altering renal function.

Creatinine Metabolism: Excretion

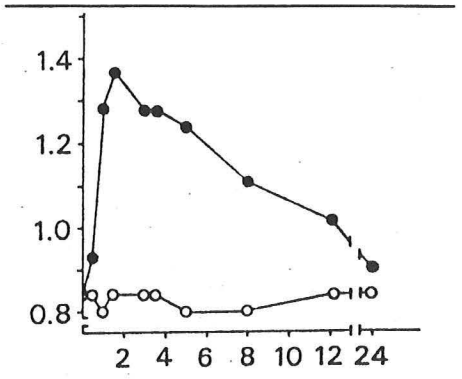
Creatinine is normally excreted by both glomerular filtration (90-95%) and tubular secretion (5-10%). Therefore, in normal individuals, urinary creatinine is the sum of filtered and secreted creatinine. Renal clearance of creatinine excretion varies directly with creatinine production rate, serum creatinine concentration and glomerular filtration rate. As kidney failure develops, tubular creatinine secretion can increase markedly, up to 50%! As a result renal creatinine clearance becomes an inaccurate estimate of true GFR. Thus, individuals with larger muscle mass and or high cooked meat diets have higher urinary creatinine excretion rates and conversely, those with lower muscle mass or on low cooked meat diets (e.g. vegetarian) have lower urinary creatinine excretion rates.

Table 3. Factors that influence daily urinary creatinine production/excretion other than changes in muscle mass.

Condition	Magnitude of effect
Normal daily variation	±4 to 8%
Very strenuous exercise	+5 to 10%
Emotional stress	±5 to 10%
Diet: switching from meat diet to creatine-free diet or vice versa	±10 to 30%
Menstrual cycle: minimum during menstrual flow, maximum second half of cycle	+10 to 15%
Renal disease: serum creatinine	
>2 mg/dl <6 mg/dl	*
≥6 mg/dl	↓†
Severe infection, high fever, trauma	+20 to 100%†

* Magnitude unknown.
† Magnitude and duration variable.

Figure 6



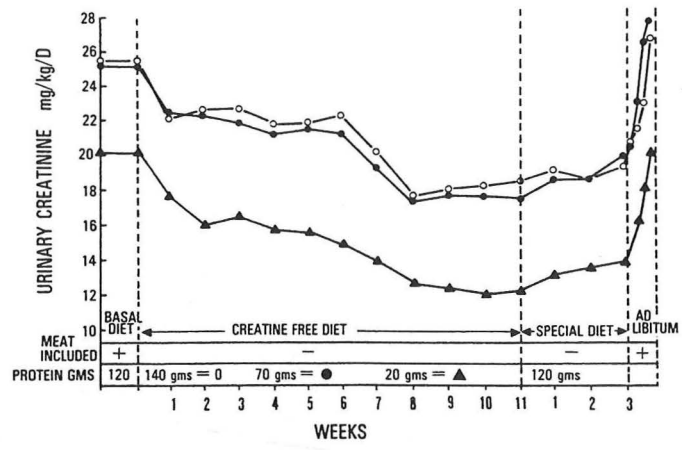
Mayersohn, M. J. Clin. Pharm.15: 227-230, 1983.

Effects of Production and Excretion on Steady-State Serum Creatinine

Table 4 illustrates the effects of changes in production in relation to excretion of creatinine on steady-state serum creatinine. Although many combinations of production and excretion may be considered, there are two key points to be made. First, changes in

either production or excretion alone can change steady-state serum creatinine. Second, if parallel decreases or increases in production and excretion occur, the serum creatinine may not change. It is this second combination that should be recalled when evaluating patients at risk for progressive renal failure and uremia, because it may indicate the combination of malnutrition and progressing renal failure.

Figure 7 Influence of Dietary Protein and Creatine on Urinary Creatinine Excretion.



Heymsfeld et al *Am. J. Nutr.* 37:478-494, 1983

Effects of Renal Failure on Creatinine Metabolism

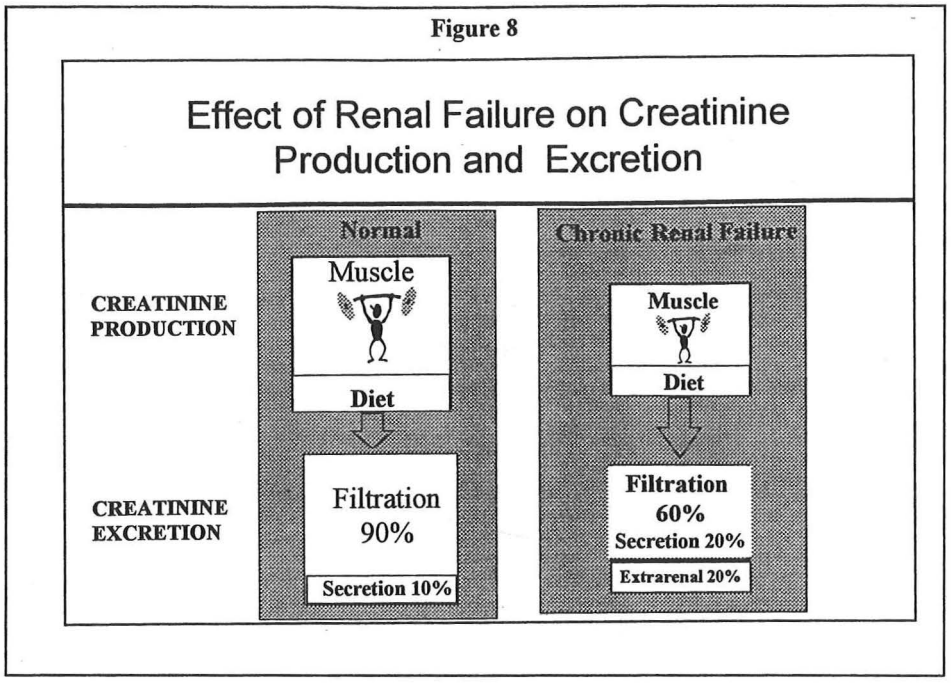
Table 4.

Stable Scr_{ss} (⇔) despite progressive renal failure: Importance of Creatinine Production

Steady-State Scr	Production	Excretion
↑	↑	↓
↓	↓	↑
⇔	↓	↓
⇔	↑	↑

Figure 8 illustrates the effects of renal failure on creatinine metabolism. Two important features of clinical relevance should be noted. First, as renal failure progresses, creatinine production rate falls because of loss of muscle mass and decreased protein intake. Second, the intrinsic handling of creatinine by the kidney is markedly altered. Thus, tubular creatinine secretion increases substantially, ranging from 20-50%. In addition, extrarenal creatinine metabolism by intestinal bacteria becomes evident to a variable extent.

Figure 8

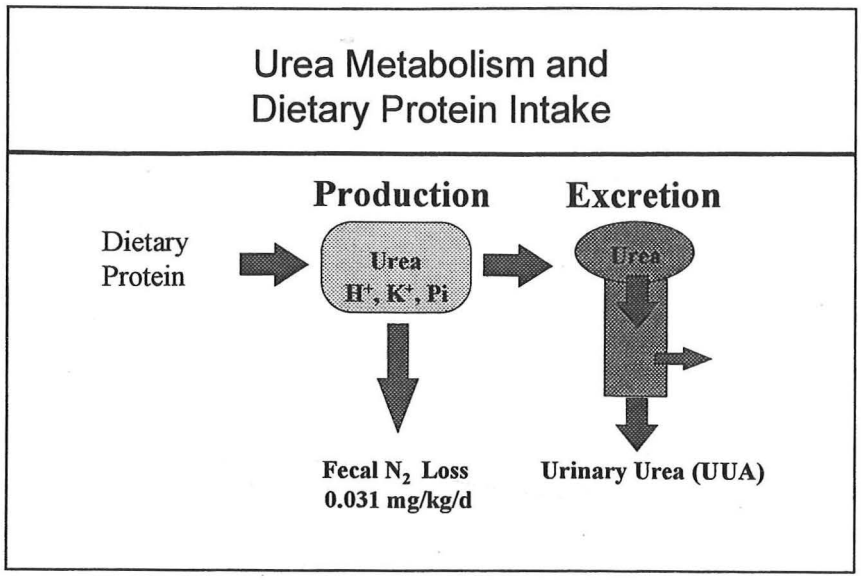


Urea Metabolism: Production

Metabolism of dietary protein produces urea, hydrogen ion (H^+), potassium (K^+) and phosphate (Pi^-), all requiring renal excretion. As shown in Figure 9, urea is primarily synthesized in the liver, so dietary protein intake, absorption of amino acids and hepatic urea cycle are the key determinants of urea production rate. Minimal amounts of urea may be synthesized from gut bacteria. As noted in the Figure protein breakdown liberates urea, hydrogen ion (H^+), potassium (K^+) and phosphate (Pi^-), hence their production varies directly with protein intake. Therefore, in uremia, higher protein intake is associated with greater degrees of azotemia, acidosis, hyperkalemia and hyperphosphatemia.

Urea Metabolism: Excretion

Figure 9



Urea is excreted by glomerular filtration. However, in contrast to creatinine, urea is reabsorbed in both the proximal and distal nephron. Since virtually all urea is excreted into the urine and fecal nitrogen is stable, urinary urea excretion can be used to estimate protein metabolism.

Urea Metabolism as an Estimate of Dietary Protein Intake

In the steady-state protein intake equals protein catabolic rate which in turn can be quantified from the equation as follows:

Dietary Protein Intake (DPI) = 6.25 (UUA) + 0.031 x Wt in Kg + 24-hr urinary protein

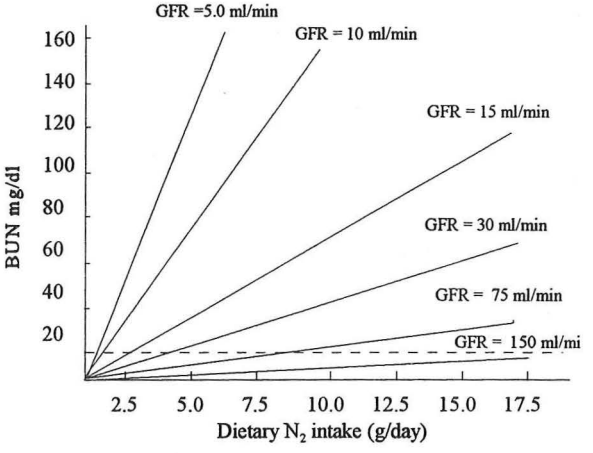
In this equation, UUA = urinary urea appearance (in g/day), the second term takes into account nitrogen lost in the feces (g/day) last term accounts for urinary protein losses (g/day) due to renal

disease. Measuring urea and protein in a 24-hour urine collection allows one to quantify the daily urea excretion rate, also known as the urinary urea appearance rate as well as the total amount of protein excreted by the kidney. These values are plugged in the equation and dietary protein intake (DPI) is estimated. This estimate of DPI becomes an important component for assessing nutritional status of patients with renal disease.

Effects of Renal Failure on Urea Metabolism

The relationship between dietary protein intake, using N2 as a surrogate, steady-state BUN and glomerular filtration rate are illustrated in Figure 10. There are 3 important points in the Figure 10: 1) At a normal GFR, BUN remains remarkably stable and well below 20 mg/dl. 2) As GFR declines BUN is higher at any given protein intake; 3) BUN is relatively low in the setting of severe uremia with low protein intake. Now consider a patient with a GFR < 10 ml/min who is anorectic, nauseated and vomiting from uremia and therefore has a low protein intake may have a BUN of only 20-30 mg/dl. In this case the clinician may be misled by the relatively low BUN and concluded that the patient has only mild renal insufficiency.

Figure 10 Relationship Between BUN and Dietary Protein Intake (Dietary $N_{2)}$ in progressive renal failure. Note that at very low GFR and protein intake BUN elevation is modest

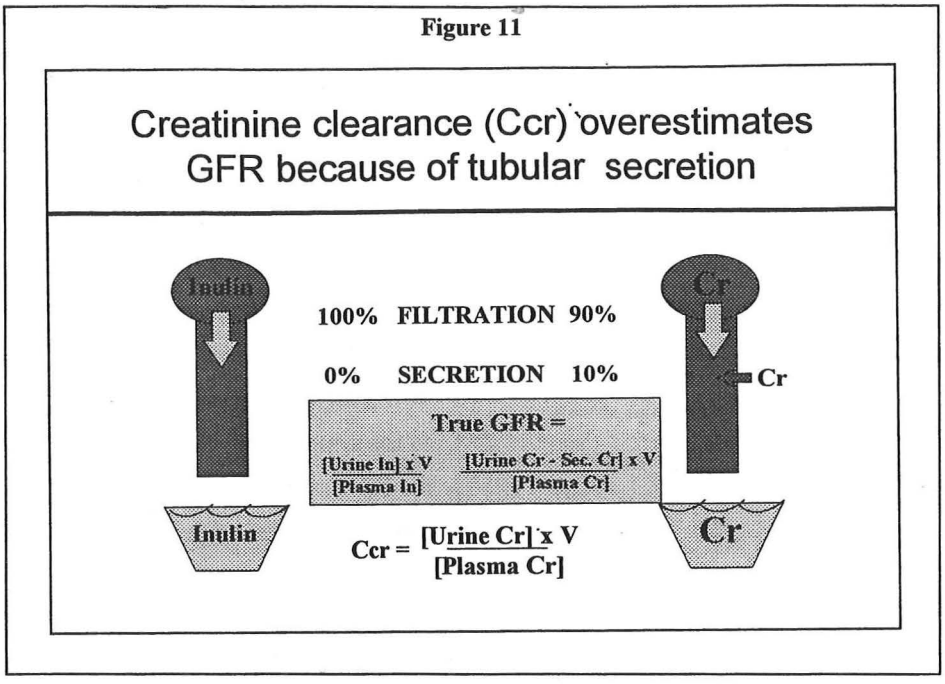


Creatinine and Urea as Filtration Markers

Renal clearance of inulin is still considered the gold standard for estimating

GFR. As shown in Figure 11, because creatinine is filtered and secreted it overestimates true GFR by an amount proportional to tubular creatinine secretion, about 5-10% even in normal individuals. In renal failure tubular creatinine secretion increases above 5-10%; therefore, creatinine clearance further overestimates true GFR by as much as 50%. The variability in muscle mass, protein intake and tubular secretion lead to marked discrepancies between true GFR and creatinine clearance particularly at very low levels of GFR. Thus, as shown in Figure 12, creatinine clearance can over-, under- or accurately estimate GFR, unfortunately it often yields false estimates of progression of chronic renal failure. In contrast to creatinine, urea clearance actually underestimates true GFR because urea is reabsorbed in the nephron.

Figure 11

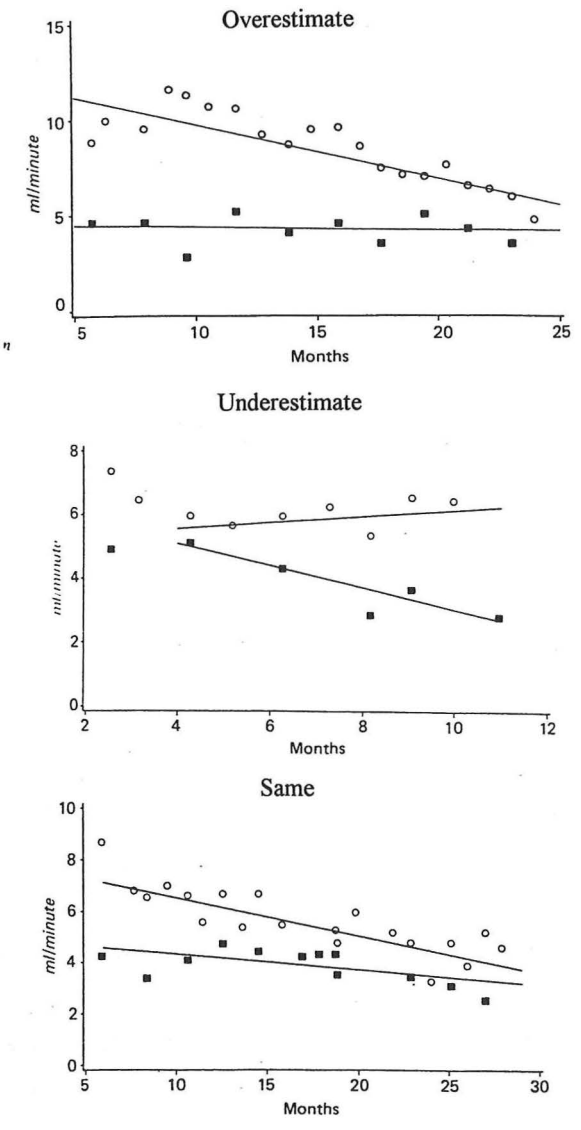


How Should GFR be Estimated in Patients with Renal Failure?

The most accurate way to measure GFR in chronic renal failure (CRF) would be to use inulin, or an equivalent filtration marker such as iothalamate, EDTA or DTPA. Unfortunately, these tests are not

easy to perform, they are expensive, inconvenient for the patient and not widely available. In contrast, serum creatinine and BUN are readily available and easy to perform; however, they are poor estimates of renal function because their plasma levels are heavily influenced by factors that alter production rate. As already discussed, changes in dietary intake and/or body muscle mass lead to changes in creatinine and urea production rates limiting their use as accurate measures of GFR. Further problems are encountered because the clearance of these markers is not an accurate way to estimate GFR. This is particularly true of creatinine because its secretion rate can increase markedly and to an unpredictable level in CRF so it progressively overestimates true GFR as renal function declines. Moreover, because decreasing muscle mass and increasing extrarenal creatinine

Figure 12 Creatinine Clearance often yields false estimates of true GFR

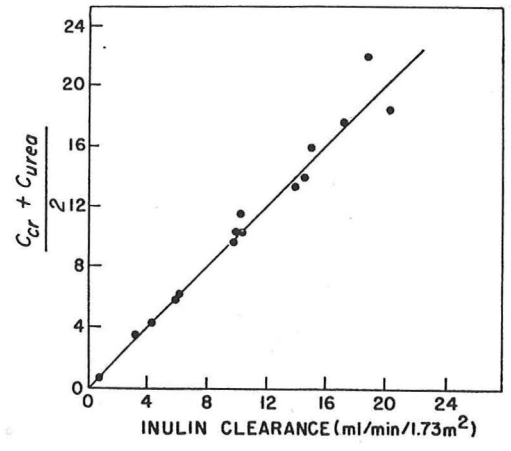


Walser *Kid. Int.* 34:412-418, 1988

clearance both reduce urinary creatinine excretion, the interpretation of creatinine clearance is confounded. How then should one estimate renal function in renal failure? Despite this seemingly complex and confusing alterations in transport of urea and creatinine, they actually help us estimate GFR quite accurately in the later stages of renal failure. As shown in Figure 13, in advanced uremia the average of creatinine and urea clearances correlates almost perfectly with inulin clearance. This has been shown to be a reliable way to estimate GFR and is superior to either creatinine or urea clearance. To perform this test one needs to calculate the clearances of both substances. This is done by performing a timed urine collection while the patient is ingesting their usual diet, measuring blood and urine urea and creatinine, calculating the clearances and averaging the two values.

Figure 13

MEAN OF UREA PLUS CREATININE CLEARANCES vs. SIMULTANEOUS INULIN CLEARANCES



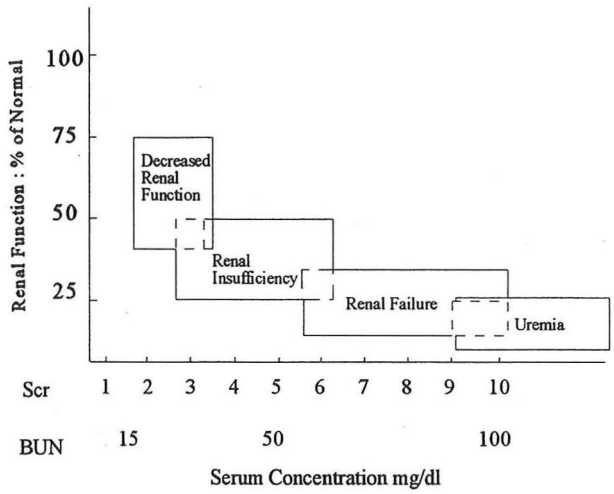
Lubowitz,H. et.al., JAMA, 199: 252-256,1967.

In summary, steady-state concentrations of serum creatinine and BUN are determined by production and renal excretion. They are not only markers of renal function but also dietary protein intake and in the case of creatinine, body muscle mass. Hence, both BUN and creatinine are markers of nutritional status because they reflect dietary protein intake and somatic muscle mass. Neither urea clearance nor creatinine clearance are accurate markers of GFR because of the complicated way in which they are handled by the kidney in contrast to inulin or iothalamate. However, the average of the urea clearance and creatinine clearance is a reasonably accurate way to estimate GFR for patients with advancing renal failure and developing uremic syndrome.

UREMIA, MALNUTRITION AND WHEN TO INITIATE DIALYSIS

Progressive Renal Failure and the Uremic Syndrome

Figure 14 The Stages of Renal Failure



Progressive renal failure leads to uremia. The "stages" of renal failure as depicted in Figure 14, uremia develops within the far end of the spectrum of progressive renal failure. In reality, there is no clear delineation between stages and (most forms of) progressive renal failure is a continuous spectrum. It is important to note that the development of uremia which literally means "urine in the blood", develops over a broad range near the far end of the spectrum to signify that the detection of uremia varies from individual to individual.

What is the Uremic Syndrome?

The uremic syndrome is a constellation of signs and symptoms resulting from both renal and

widespread organ dysfunction that accompanies renal failure. A complete description of each component is beyond the scope of this discussion. It should be noted that because these symptoms may develop at different levels in different individuals, no particular BUN or serum creatinine signals when these manifestations will begin. Generally speaking, most patients will exhibit some uremic signs and symptoms when true GFR is < 20 ml/min, but the range is as low as 10 ml/min and may be as high as 50 ml/min.

Eliciting History in Patients with Renal Failure

Moreover, because chronic renal failure progresses over a long period of time patients usually modify their behavior inadvertently or unconsciously and may not remember how or if their habits change. The uremic syndrome develops insidiously in chronic renal failure and for this reason repeated careful history taking over the course of progression of renal disease is an important factor in dialysis decision making. Interviewing a family member who knows the patients' behavior and habits well is often very revealing. It is not unusual to find discrepancies between the patient and the family member. This results from the fact that tissues compensate for changes induced by the uremic milieu and the patient accommodates to the new internal environment. Indications for initiation of dialysis are found in most renal textbooks, but general medicine textbooks either do not mention the subject or do so in passing. Table 5 lists the absolute and relative indications for dialysis.

Table 5. INDICATIONS FOR INITIATION OF MAINTENANCE DIALYSIS

Absolute	Relative
Pericarditis	CNS or GI symptoms
Pulmonary Edema	Fatigue and weakness
Poorly Controlled Hypertension	Weight Loss
Hyperkalemia	Severe Pruritus
Metabolic Acidosis	Malnutrition
Anorexia, Nausea and Vomiting	

The following is a discussion of the signs and symptoms that are useful in helping determine when to initiate dialysis when absolute indications are not present or not detected. Most patients exhibit several symptoms simultaneously, so the indication for dialysis is based on many not one sign or symptom.

Signs and Symptoms of the Uremic Syndrome

Central Nervous System. The most common CNS manifestation in early uremia is reversal of the normal biologic clock for sleep. Typically patients complain that they cannot get to sleep, toss and turn for several hours, finally falling asleep only to reawaken within 1-2 hours and again have difficulty returning to sleep. Most patients will admit to some degree of sleep disturbance when they develop uremia.

Gastrointestinal. This is extremely important because anorexia is an important factor that contributes to malnutrition in chronic renal failure and dialysis (Table 6). A detailed inquiry into the patients diet and eating habits indicates that the patient eats poorly, e.g. one meal a day or two to three small and inadequate meals. As a result, weight loss is common. Malnutrition is the net result.

Table 6

CAUSES OF ANOREXIA IN MAINTENANCE DIALYSIS PATIENTS
Uremic toxicity (underdialysis)
Unpalatable or inadequate diets
Gastropathy (diabetic patients)
Inflammation, infection, sepsis
Medications
Psychosocial and socioeconomic factors
Effects of the hemodialysis procedure

Bergstrom,J.et. al.,Nutrition and the Kidney,2nd ed.,263-289,1993.

Hyperkalemia. Hyperkalemia in renal failure is caused by low GFR and impaired tubular K^+ secretion or both. It is heavily dependent on dietary intake. For this reason, it is a late sign in patients with a poor oral intake due to anorexia, nausea and vomiting.

Pruritus. Generalized pruritus is often accompanied by excoriations on the back, trunk and sometimes the extremities. This sign is usually evident of physical examination with careful inspection.

Fatigue and Dyspnea. Three important uremic complications contribute importantly to fatigue and dyspnea. It is often difficult to differentiate which factor or which combination of factors accounts for these symptoms in any given patient. Therefore, bedside judgement weighs heavily when assessing these symptoms. *Volume overload* caused by excessive salt retention from renal failure along with left ventricular hypertrophy with diastolic dysfunction cause pulmonary edema. *Anemia* becomes progressively worse with loss of renal mass. *Metabolic acidosis* causes increases work of breathing and hence also aggravates dyspnea.

Physical Examination. The key findings on physical examination in the uremic patient are as follows:

GENERAL: Chronically ill appearance, hyperpnea (metabolic acidosis) tachypnea (pulmonary edema) pallor (anemia), periorbital edema and hypertension (volume overload)

HEENT: Injected conjunctivae due to calcium phosphorus deposits

CARDIOPULMONARY: Evidence of volume overload including elevated jugular venous pressure, rales, S3 gallop, peripheral edema

CUTANEOUS: Sallow color and excoriations on the chest, torso, back and extremities

Laboratory Data. Hyponatremia, hyperkalemia, hypocalcemia, hyperphosphatemia, anion gap or hyperchloremic metabolic acidosis, anemia, hypoalbuminemia, hypotransferrinemia, hypotransthyretinemia (pre-albumin), hypertriglyceridemia, mild fasting hyperglycemia and of course BUN and serum creatinine.

A Special Note About Patients with Diabetes Mellitus and CRF

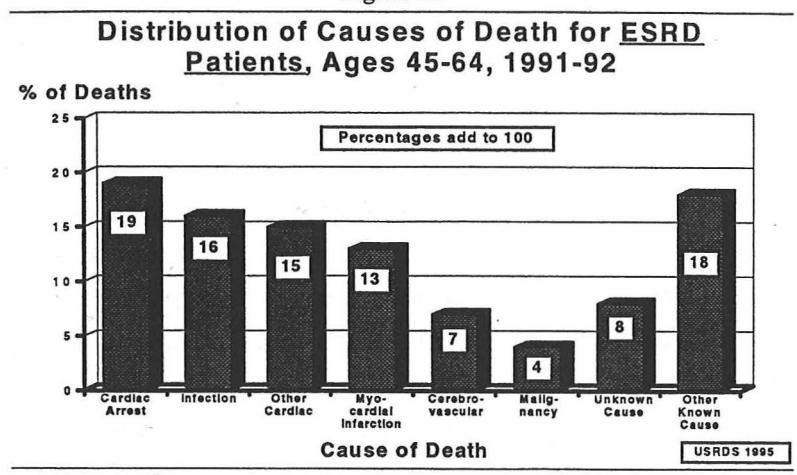
It is widely appreciated by clinicians that both type I and type II diabetics with progressing renal

disease develop uremic manifestations at higher GFR levels as compared to other populations. In practice diabetics receive closer and more frequent evaluation for uremic signs and symptoms when creatinine clearance is below 25-30 ml/min. This is true because diabetics, in as comparison to most other groups, have the worst cardiovascular risk profile and a the highest rates of vascular complications.

Major Risk Factors in Uremia

The major causes of death in dialysis patients are cardiac disease (including sudden death, CHF and MI) and infection (Figure 15). The uremic state predisposes patients to these complications for two main reasons: 1) Uremia has the worst cardiovascular risk profile 2) Uremia causes malnutrition.

Figure 15



The categories are collapsed from the Death Notification Form as per Table VI-1. Infection includes Septicemia, Other infection, and AIDS. Other known cause includes Hemorrhage, Cachexia, Hyperkalemia, and Other. Missing cause of death is excluded. Patients in Puerto Rico and the U.S. Territories are included. Medicare patients only. Source: Reference Table D. 31.

USRDS Annual Report 1995

Cardiovascular Risk Profile

The metabolic profile and cardiopulmonary complications of uremia together conspire to produce the most severe cardiovascular risk profile one can imagine. Insulin resistance, low HDL-cholesterol, hypertriglyceridemia, elevated Lp (a), hyperhomocysteinemia, hypertension, vascular calcification (due to Ca-P deposition) all contribute to accelerated atherosclerosis in dialysis patients. This leads to ischemic heart disease and myocardial infarction, left ventricular hypertrophy, stroke and peripheral vascular disease. Compounding the situation is the fact that volume overload and anemia can also induce left ventricular hypertrophy and result in congestive heart failure. Indeed anemia and LVH are known risk factors for death in chronically hemodialyzed patients.

Malnutrition

Malnutrition is a well recognized problem in chronic renal failure patients predialysis, on dialysis and even after renal transplantation. Protein-calorie malnutrition is known to adversely affect outcome in dialyzed patients and is highly associated with increased morbidity and mortality in ESRD populations. It begins prior to ESRD and persists after initiation of dialysis. Although there is debate as to whether malnutrition is due to other comorbid conditions, most authorities and recent clinical observations point to uremia per se as a cause of malnutrition. Therefore, malnutrition is considered an independent cause for morbidity and mortality in this population. It is beyond the scope of this Grand Rounds to review the causes and mechanisms, several excellent and recent reviews are included in the reference section. It is known that uremia has major effects on nutritional status. For example alterations in plasma amino acid patterns, lipid metabolism and carbohydrate metabolism (e.g. insulin resistance) are all well documented in uremia. Although non-dialyzed patients with progressive renal failure become malnourished, the problem may be even worse on dialysis. It is estimated that more than 40% of patients with CRF on dialysis are malnourished based on physical and biochemical measurements.

Assessing Nutritional Status in Renal Failure

Nutritional status in renal failure patients can be assessed in four ways: 1) Dietary Records and Urine Urea Appearance; 2) Anthropometric measurements; 3) Body Composition; and 4) Biochemical Measures

Dietary Records and Urine Urea Appearance

Measures of dietary intake by patient performed dietary recall provides insight and in some cases quantitative information on energy and protein intake. Measurement of urea appearance as described above can be used as a measure of dietary protein intake (DPI). Thus, assuming a steady-state one can calculate DPI from the equation : DPI = 6.25 (urea appearance rate in mg/min) + 0.031 g/kg (fecal N2 x BW in kg) + urine protein excretion rate (g/day).

Anthropometric measurements

Anthropometric measures can be used to estimated lean body mass and percent body fat. This is done by a nutritionist who performs a battery of measures including triceps skin-fold thickness, thigh skin-fold thickness, midarm muscle circumference, muscle strength, body mass index, and body weight.

Body Composition

Lean body mass using MRI, dual X-ray absorptimetry (DEXA) and bioelectrical impedence can be performed accurately. These techniques are more expensive and time consuming but they accurately estimate tissue stores of protein and are now being used with increasing frequency in the research literature. DEXA measures both bone mineral content as well as muscle mass therefore, it can be used to calculate lean body mass. However, it does not separate extracellular from intracellular pools so in volume overloaded patients it may overestimate true intracellular lean mass. Bioimpedence allows separation of intra and extracellular water and may provide a more reliable estimate of lean body mass than DEXA. Further studies are investigating these techniques in uremic dialysis patients.

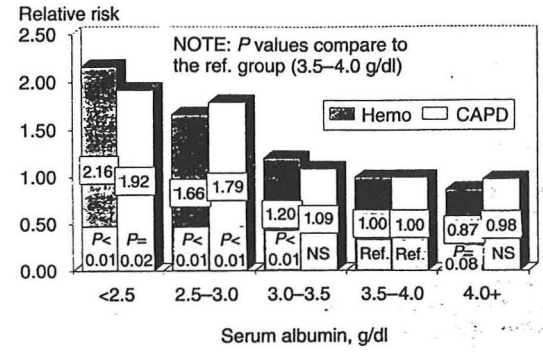
At the present time most physicians use diet recall, anthropometrics and biochemical measures.

Biochemical Measures

Serum Albumin. Serum albumin concentration is the most commonly used biochemical measure of nutritional status in renal failure. It is an estimate of visceral protein stores and is the strongest predictor of mortality in both chronic ambulatory peritoneal dialysis (CAPD) and hemodialysis patients (Figure 16). Thus hypoalbuminemia is an important risk factor for mortality in the dialysis population. The risk profile of dialysis patients now routinely includes ascertainment of this marker and therapeutic interventions are directed toward treating hypoalbuminemia. The causes, mechanisms and treatment of hypoalbuminemia are the subjects of intense investigation. The mechanisms of hypoalbuminemia in chronic renal failure are not completely understood, however, nutritional status is an important cause. For example, most patients with hypoalbuminemia have low dietary

Figure 16

CORRELATION OF MORTALITY RISK



Port, F.K.Kid Int., 46:17288-1737,1994.

Table 7

PROTEIN CATABOLIC FACTORS IN HEMODIALYSIS PATIENTS

General Effects
Physical inactivity
Heart failure
Low energy intake
Endocrine abnormalities
Corticosteroid therapy
Inflammation, infection, sepsis
Acidosis
Amino acid abnormalities

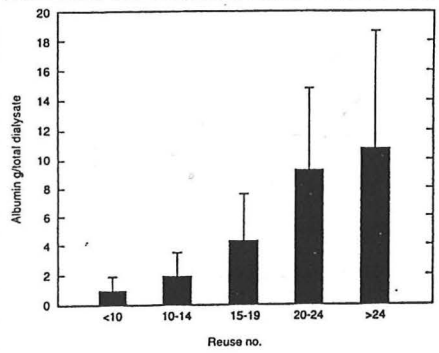
Bergstrom, J. et. al., Nutrition and the Kidney, 2nd ed.,263-289,1993.

protein intake rate and therefore have low albumin synthetic rates. Also, infection or other inflammatory states may suppress albumin synthesis. In fact, increased concentrations of cytokines including serum IL-I, IL-6 and TNF-α have been reported in dialysis patients and they suppress albumin synthesis and increase acute phase reactant synthesis as well. Hypoalbuminemia can also be caused by loss or increased protein catabolism (Table 7). For example, peritoneal dialysis causes loss of albumin into the dialysate and hemodialysis may cause both amino acid and albumin losses. Furthermore, the use of "high-flux" membranes which have larger pore membranes or reuse of the artificial kidney with bleach can lead to loss of albumin directly (Figure 17).

Figure 17

A

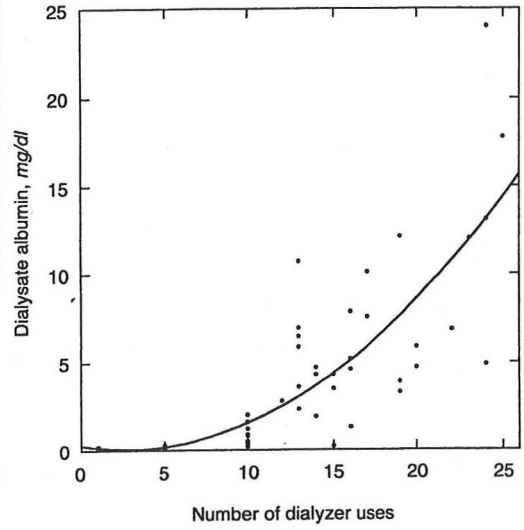
DIALYSATE ALBUMIN LOSSES PER DIALYSIS SESSION WITH INCREASING REUSE NUMBERS FOR HIGH FLUX PS MEMBRANES



Ikizler, T.A., Kid Int., 46: 830-837,1994.

B

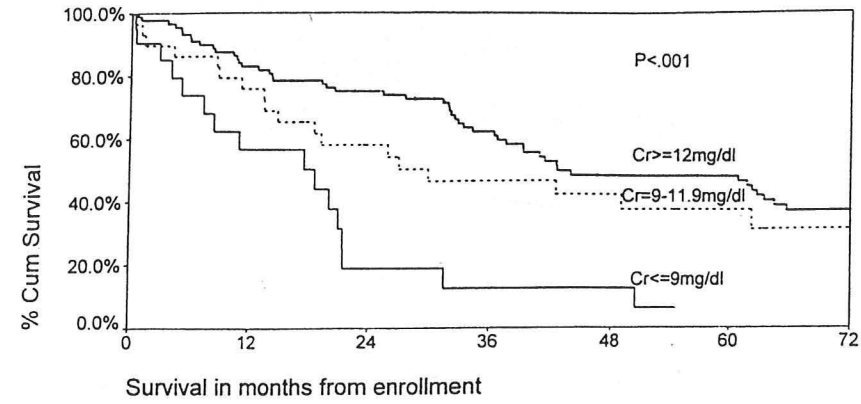
RELATION BETWEEN THE DIALYSATE ALBUMIN CONCENTRATION AND THE NUMBER OF BLEACH PROCESSED DIALYZER USES



Kaplan, A.A., KI, 47:573-578,1995.

Serum Creatinine. Serum creatinine in dialysis patients is also a predictor of poor outcome (Figure 18 a). As already reviewed above it is a marker of somatic protein stores. Although standards have not been set for a "normal" serum creatinine in a dialysis patient, mortality rates are higher in patients with serum creatinine concentration below 8.0 mg/dl at the time of initiation (Figure 18 b).

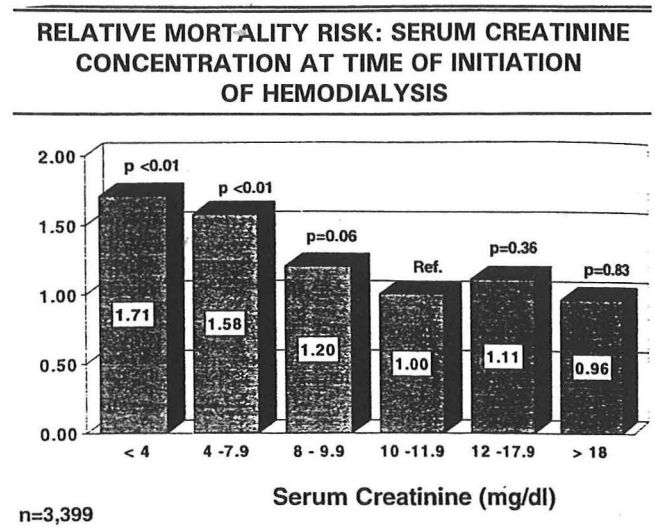
Figure 18 a



Avram, M.M., et.al., AJKD, 26:209-219,1995.

Other Biochemical Markers. Low levels of serum transferrin, transthyretin, cholesterol and urinary creatinine measurements have been shown to correlate directly with nutritional status. Patients with low levels of these parameters tend to show other signs of malnutrition as well including low protein intake, reduced midarm muscle circumference, etc. In addition, recent studies indicate that insulin-like growth factor-1 (IGF-1) levels are low in malnourished chronic renal failure patients. Table 8 summarizes commonly employed indices of malnutrition in dialyzed patients. The values in the table are based on estimates from the literature. In some cases precise values that increase risk for nutritional deficiency are not known (e.g. serum potassium).

Figure 18b



Hakim, R.M., Adv. in Nephrol.,295-309,1994.

Table 8: SOME INDICES OF MALNUTRITION IN HEMODIALYSIS PATIENTS

Serum Albumin < 4. G/dl
Serum Total Cholesterol < 150 mg/dl
Serum Transferrin < 150 mg/dl
Serum transthyretin (prealbumin) < 29 mg/dl
Low Predialysis Serum Potassium
Serum IGF-1 < 300 υg/L
Body Weight < 80% of ideal
Marked reduction in anthropometric measurements
Dietary Protein intake < 0.8 g/kg/d
Continuous decline in dry weight

Modified from Hakim and Levin. See text for details

Causes of Malnutrition

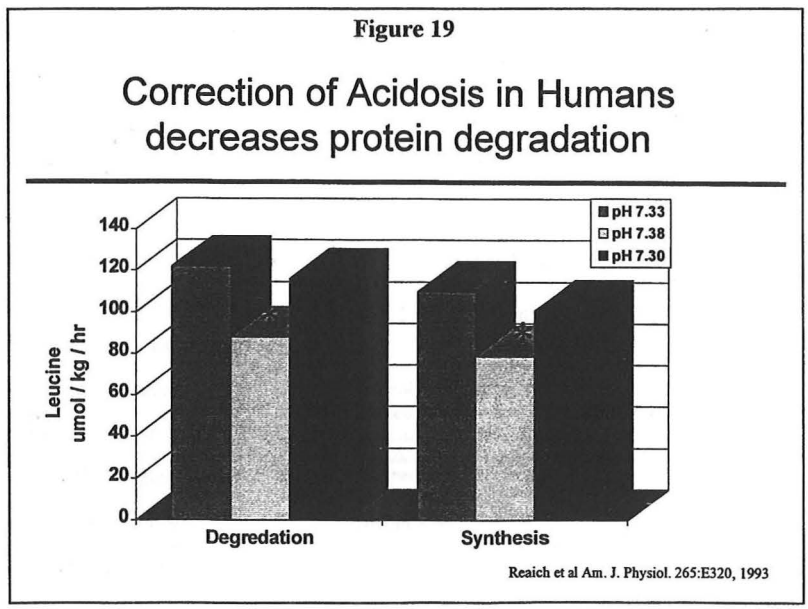
Dietary Intake

Anorexia is a major uremic complication that leads to both reduced energy and protein intake in dialysis patients. Uremic toxicity, unpalatable diet, dysgeusia, gastrointestinal illnesses, serious infections, medication side effects, psychosocial factors and effects of the dialysis procedures can all contribute to reduced intake. Patients on hemodialysis may experience cardiovascular instability, nausea and vomiting and postdialysis fatigue and patient on CAPD may "feel full" because of the peritoneal dialysate and thereby limit intake. Because of uremic toxicity caused by underdialysis, excessive retention of middle molecules, which suppress appetite, suppressant, may contribute to poor nutrition. The role of underdialysis is discussed in detail below.

Metabolic Acidosis

It is now well established that metabolic acidosis causes muscle catabolism. Animal and human studies support the view that correction of acidosis ameliorates its protein catabolic effects. Figure 19 illustrates the effects of correction of metabolic acidosis on

Figure 19



the rate of muscle protein degradation in peritoneal dialysis patients.

Serum IGF-1

Insulin like growth factor-1 is an anabolic hormone that is being evaluated in treatment of malnutrition in dialyzed patients. Not only is the serum concentration of this hormone low, but the tissue response is impaired in uremia.

How Does Malnutrition Increase Mortality in ESRD?

The specific mechanisms of how malnutrition in relation to increased mortality in ESRD patients is not known; however several theories have been suggested (Table 9). The major prevailing hypothesis is that malnutrition increases infection rate because of impaired host defense and wound healing. In addition, it has been speculated that because uremia is associated with impaired nitric oxide production this might increase the likelihood of a cardiovascular event. Finally, hypoalbuminemia per se may increase mortality risk by inducing overhydration, increasing drug toxicity (by decreased drug binding) and by allowing increased formation and action of free radicals.

Malnutrition and Initiation of Dialysis

An apparent paradox has arisen in the management of patients with chronic renal failure. On the one hand there is accumulating evidence that dietary protein restriction slows the progression of chronic renal failure to ESRD (previously reviewed). On the other hand reducing protein intake could lead to malnutrition, which may in turn reduce survival

Table 9

How Does Malnutrition Increase Mortality in ESRD?

- Increased incidence of Infection
- Increased Cardiovascular Disease
  - Decreased Nitric Oxide Production
    - ADMA accumulates in uremia and inhibits NO synthase
- Hypoalbuminemia
  - Overhydration
  - Reduced Therapeutic Drug Binding
  - Increase in free radicals

after dialysis is initiated. For example, as shown in Table 10 a restricted protein diet in patients with renal disease not only slowed the deterioration of renal function but also caused significant reductions in mid arm muscle circumference, triceps skin fold thickness, body weight and urine creatinine. Importantly, these aspects of nutrition were negatively affected despite no detectable change in serum albumin concentration. What is even more striking is the fact that when studied prospectively, patients with chronic renal failure apparently restrict their protein, and caloric intake spontaneously (Figure 20). Presumably, this could lead to malnutrition as suggested by the accompanying reduction in urinary creatinine excretion which reflects both diet and muscle mass.

Table 10

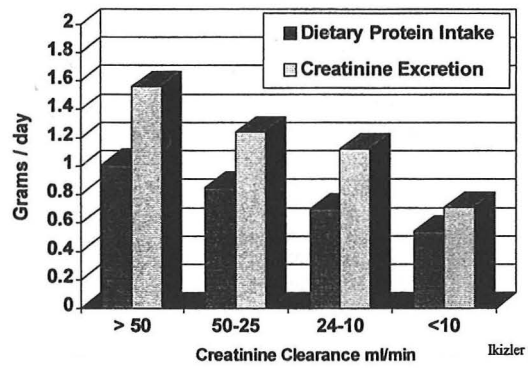
The Risks and Benefits of a Low Protein Diet

Parameter	Outcome
Decline in renal function	Slowed
Serum Albumin	No Change
Mid Arm Muscle Circumference*	- 1.7 cm
Triceps Skin Fold*	- 1.4 mm
Body Weight*	- 3.3 kg
Urine Creatinine*	- 21%

Lucas, P et al *Kid. Int.*29:995, 1986

Figure 20

Dietary Protein Intake and Creatinine Excretion Rate Decline with Advancing Renal Failure



Ikizler et al *Kid. Int.* 1996

Duality of Protein Restriction

Protein restriction may be a double-edged sword. The attributes of conservative (late dialysis) therapy, for example using dietary protein restriction, versus early dialysis are compared in Table 11. On the one hand restricting protein slows progression, and reduces uremic complications such as azotemia, hyperkalemia and hyperphosphatemia thereby reduces short-term complications of uremia. On the other hand it may induce malnutrition insidiously which in the long run may confer increased mortality risk Consequently, a debate has arisen with respect to when to initiate dialysis from the standpoint of long-term outcome. Although it is desirable to slow the rate of progression of renal

Table 11

The Razor's Edge : Conservative Therapy versus Dialysis Therapy

- **Conservative Measures**
  - Positive
    - Preserve renal function
    - Slow progression to ESRD
    - Prepare patient for eventual ESRD therapy
  - Negative
    - Malnutrition
    - Untreated Anemia
    - Worse outcome in future
- **Initiation of Dialysis**
  - Positive
    - Improve cardiovascular condition
    - Help correct anemia and volume overload
    - Improve nutrition
  - Negative
    - Access problems including infection
    - Hemodynamic instability on dialysis
    - Adverse reactions to extracorporeal circuit

failure, delay dialysis and thereby prevent dialysis complications, delaying dialysis in this setting may actually worsen long-term outcome. In other words, if a patient is started on dialysis later but becomes malnourished in the process is he/she being set up for increased mortality risk and shortened life on dialysis later on?

Conservative Therapy of Renal Failure

Many therapeutic components of conservative management of renal failure can be employed to postpone dialysis in patients with progressing renal disease or overt ESRD. In addition, patients themselves may attempt to bargain with their physician concerning the initiation for dialysis or refuse treatment until a major catastrophic complication (e.g. pulmonary edema, malignant hyperkalemia) necessitates emergency life-saving dialysis. Therapeutic interventions include dietary restrictions which are the cornerstone of conservative therapy. These include protein restriction for slowing progression and minimizing azotemia as well as potassium and phosphorus restriction to reduce hyperphosphatemia and control hyperparathyroidism. In addition, vitamin D and phosphate binders to control hyperparathyroidism and osteomalacia, sodium bicarbonate to ameliorate acidosis, and subcutaneous twice weekly erythropoietin therapy to ameliorate anemia and its consequences.

Early Versus Late Dialysis

There is little information on the effects of early versus late dialysis in the present environment of CAPD, more efficient dialysis membranes, etc. However, we know that late referral for dialysis causes increases morbidity (Table 12). Furthermore, actuarial survival is lower in patients started on dialysis with long-standing

Table 12

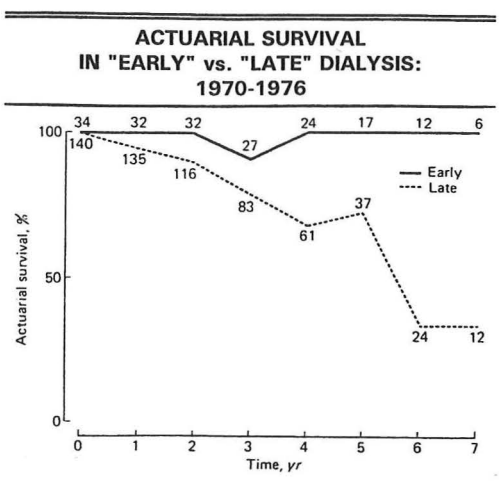
CAUSES OF HOSPITALIZATION IN REGULAR DIALYSIS (DAYS/YR/PATIENT)

	Early dialysis (31 patients)	Late dialysis (92 patients)
Infections	3.4 (66.7%)	5.5 (29.0%)
Vascular access	0.6 (12.9%)	4.4 (23.8%)
Cardiovascular problems	0.5 (9.7%)	4.0 (21.4%)
Gastrointestinal problems	0.2 (3.9%)	2.6 (13.6%)
Total	4.7 (93.2%)	16.5 (87.8%)

Bonomini, V., et. al, KI, 13 supl.,112-116, 1978.

versus short-duration uremia (Figure 21).

Figure 21



Bonomini, V., Kid.Inter., Vol 13, S8, S112-S116,1977.

Criteria Based on BUN and Serum Creatinine

Unfortunately, BUN and serum creatinine values are unreliable indicators of when to initiate maintenance dialysis (Table 13). Because of the heterogeneity in the patient population with regard to age, gender, body mass, dietary protein intake and underlying renal diseases it is not possible to choose a single value of either of these indices as a criterion for initiation of dialysis. This explains why studies evaluating these criteria indicate hypervariability of BUN and creatinine values incident with dialysis initiation. Moreover, careful studies of GFR at onset of dialysis have not been performed.

Table 13

BUN and Serum Creatinine Levels are Not Absolute Indicators for Dialysis Initiation

- No particular level of BUN or Scr has been shown to correlate with timing of onset of dialysis
- Serum creatinine at onset of dialysis varies from study to study
- BUN is unreliable because it indexes not only renal function but also protein intake

Who Is a Candidate for Dialysis Therapy?

First, it should be noted that not all patients with renal failure should be considered candidates for dialysis. It is proper to ask not only *when* to initiate dialysis but also *when not* to initiate dialysis. The discussion of this latter question is beyond the scope of this review.

However, within the context of our discussion it should be noted that the decision to initiate dialysis always involves the patient and or their family/loved ones. Any patient with advancing renal failure may be considered a candidate for dialysis; but not all patients or physicians may choose treatment with renal replacement therapy (RRT), i.e. dialysis and renal transplantation. Patients should be educated about the possibility of ESRD, its consequences and possible therapies at an early stage of renal failure if possible. For example, when the GFR is above 50 ml/min and signs and symptoms of uremia are completely absent or minimal/biochemical only. Since it is clear that our patient population is aging, age is not a useful criteria for determining candidacy. Therefore, the decision to proceed with dialysis is made on an individual basis in part based on need for therapy and in part based on the patient or family's wishes. The greater the level of understanding by the patient of the potential consequences and quality of life on dialysis versus the known risk of death without therapy, the better off the patient/family will be in the decision making process.

Recognizing that different renal diseases may progress at different rates and that some populations of patients tend to develop more severe manifestations of uremia, particularly diabetic subjects, rigid criteria for initiation of maintenance dialysis are not available. Patient selection for dialysis should be done carefully.

Absolute Indications

Individuals with absolute indications for dialysis as outlined (Table 8 above) including pericarditis, pulmonary edema and uncontrollable or poorly controlled hypertension, hyperkalemia, metabolic acidosis or severe anorexia, nausea and vomiting from uremia should be initiated on dialysis as soon as an access can be placed.

Relative Indications

For patients who are progressing to ESRD and have developed uremic symptomatology, initiation of dialysis when signs of malnutrition become manifest seems to be a rationale point in time to initiate

dialysis. This point may be reached when the GFR is 15-20 ml/min in some and 5-10 ml/min in other patients. Recently advocates of malnutrition is a major morbid and mortal complication of uremia have suggested that dialysis be initiated when signs of malnutrition become evident. This has not yet become the standard of practice and will be debated. However, it is reasonable to consider this possibility given the very high mortality rate of uremic dialyzed patients in our country. Despite all the limitations of the markers outlined in this Grand Rounds, HCFA funding for dialysis requires documentation of a creatinine clearance of ≤ 15 ml/min in diabetics and ≤ 10 in non-diabetics, or if the level is higher evidence of clear indications for initiation of dialysis. At the present time these indications do not specifically cite malnutrition per se. Therefore, there are economic implications and potential obstacles to such practice.

Table 14. RECOMMENDATIONS FOR INITIATION OF DIALYSIS BASED ON NUTRITION

1.	During protein restriction, symptoms and signs of malnutrition should be monitored carefully and dialysis should not be delayed at the expense of deteriorating nutritional status
2.	Definite or absolute signs or complications of the uremic syndrome should be anticipated and avoided.
3.	Dialysis should be initiated whenever indices of malnutrition develop. Early detection of malnutrition particularly in diabetics should warrant aggressive monitoring and earlier dialysis and aggressive feeding
4.	Preparations for dialysis should begin when the Ccr is ≤ 20 ml/min so that adequate time is available for placement of dialysis access and/or work up for renal transplantation
5.	Patient education concerning risks and benefits of dialysis including a visit to a dialysis unit, videotape lectures on dialysis techniques should be performed. A team approach including dialysis nurse, transplant coordinator, social worker, dietician and nephrologist should be used.

Adapted from Hakim and Lazarus *J. Am. Soc. Neph.* 6:1319-1328, 1995

Recognizing that at the present time it is difficult to establish precise criteria because the effects of

early versus late dialysis on outcome are not known in the current climate, recommendations may be given that seem reasonable. It should be noted however, that until a clinical study is performed to evaluate whether earlier dialysis clearly reduces morbidity, saves lives and/or saves money within the health care system, rigid objective criteria must still be sought for and established. On the basis that malnutrition is a complication that should be avoided at the expense of a regimen that is slowing deterioration of renal function Hakim and Lazarus have recently proposed recommendations for initiation of dialysis as outlined in Table 14.

HOW MUCH DIALYSIS IS ENOUGH?

What Can Dialysis Do for the Patient?

First, dialysis can be life-saving by reversing immediate life-threatening conditions such as pulmonary edema, hyperkalemia, metabolic acidosis, coma, etc. These immediate effects are not long-lasting; therefore dialysis must be continued on a routine basis which is generally three times per week for 3-4.5 hours per session. What one can expect when placing a patient on dialysis is that the patient will achieve restoration of normal fluid, acid-base and electrolyte balance, amelioration or complete correction of hypertension, improvements in energy level, exercise tolerance and anemia. However, maintenance dialysis week alone does not completely or continuously correct these abnormalities, so that dietary restrictions and administration of medications must continue. There are potential complications of dialysis that must be considered both during the decision to initiate dialysis as well as after initiation. Dialysis does not reverse completely the adverse metabolic effects of uremia including the accelerated atherosclerotic process. Adverse consequences of dialysis include hypotension during both hemodialysis and peritoneal dialysis, infections, effects of blood - dialyzer interactions in hemodialysis. Furthermore, , patients on dialysis have psychosocial problems part and parcel to their condition and the treatments including depression, feelings of dependence and attachment to medical devices. Finally, patients may be depressed for reasons common to patients with chronic diseases including the routines of dialysis such as travel to and from centers as well as the procedures and interactions with medical professionals on a regular and life-long basis. Despite

its shortcomings, dialysis does prolong life and affords the patient some rehabilitation in comparison to untreated ESRD which carries 100% mortality usually within the first 6-8 months after diagnosis. Whether continuing life-long dialysis truly improves and maintains an "adequate" quality of life for a patient depends on the point of reference. Objective criteria for measuring quality of life and the decision to discontinue dialysis are not part of this discussion.

How Much Renal Function Does Routine Dialysis Provide the Patient?

Routine hemodialysis is carried out three times per week for about 4 hours per treatment. But what does this provide in terms of replacement of renal function. First, it should be clear that artificial kidneys are only capable of solute dialysis and water removal. None of the metabolic or endocrine functions of the kidney are carried out during dialysis. For this reason urea, the currently used surrogate marker of uremia is the main measure of dialysis adequacy. On this basis one can calculate how much urea clearance dialysis provides as compared to a normal kidney. An example of what a modern high-efficiency dialyzer with a high blood flow rate can provide in comparison to normal:

Normal Kidney 80 ml/min

Dialyzer $\frac{\text{Urea Clearance 240 cc/min x 240 minutes per treatment x 3 treatments per week}}{\text{1440 min per day x 7 days per week}}$

$= 17\text{cc/min.}$

Similarly if one compares normal creatinine clearance to dialyzer creatinine clearance the findings are similar

Normal kidney Ccr 100 ml/min

Dialyzer $\frac{\text{Creatinine clearance 220 cc/min x 240 min per Rx. x 3 Rx. per week}}{\text{1440 min per day x 7 day per week}}$

= 16 cc/min

As patients on dialysis lose residual renal function over time the total clearance of uremic solutes declines. The decline in total clearance must be offset by additional dialysis or the patient will become more uremic from the relation noted earlier, i.e. Uremia is proportional to the ratio of the production of toxins/removal of toxins (analogous to BUN α production/removal). To quantify the amount of uremic surrogate solute - urea - removal the dialyzer clearance of urea has been related to the amount of total body urea. The following discussion describes in brief methods for quantifying urea removal as a measure of dialysis adequacy.

Measuring Dialysis Adequacy

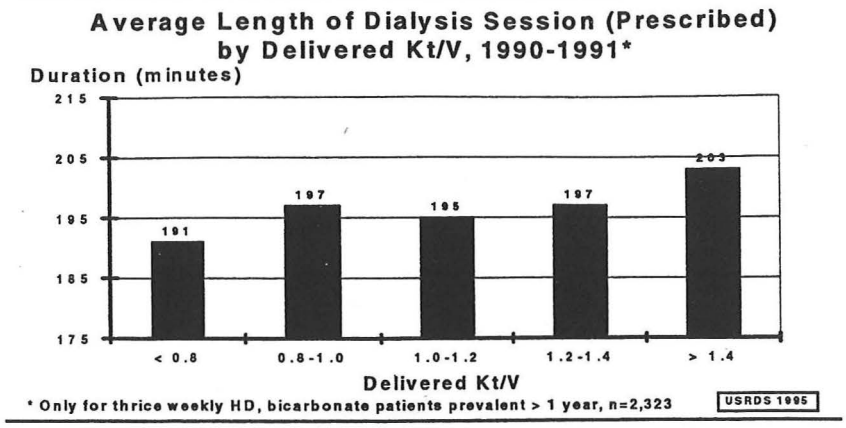
For purposes of this discussion I will concentrate on hemodialysis but the same general principles apply to peritoneal dialysis although methods of measuring adequacy are slightly different. Dialysis adequacy in the following discussion refers to removal of urea, the surrogate marker of uremia. Because there is no better marker available on a routine basis, urea remains the main measure for clinical assessment of dialysis adequacy. It should be noted that many other factors are routinely monitored and managed as part of the dialysis care of the patient including blood pressure, fluid and electrolyte balance, anemia, nutrition and dietary intake and dialysis access care,

Measuring the Amount of Dialysis

Currently the main method of estimating urea removal with each dialysis treatment is to compare the ratio of the amount of blood cleared of urea/urea distribution space. This term is computed from the dialyzer urea clearance (K) in liters per minute, the time (t) in minutes and the estimated urea distribution space (V) in liters. The expression for the amount of dialysis using these three variables is : Amount of dialysis = Kt/V. Kt/V is a dimensionless term (L/min*min/L) which is taken as an indication of urea removal and for purposes of the following discussion represents the main parameter for determining "How much is enough". In this formulation the time on dialysis is a critical variable. The average time on dialysis in relation to Kt/V for the U.S. population is shown in Figure 22. As

expected, average Kt/V increases with increasing time. There are many variables that can affect the measurement of Kt/V; however, these will not be considered in detail here. References on dialysis adequacy discuss the virtues and pitfalls of this measurement technique.

Figure 22



Average Length of Dialysis Session by delivered Kt/V, Center HD patients only, 1990-91. Medicare Patients only. From the USRDS Case Mix Adequacy Study.

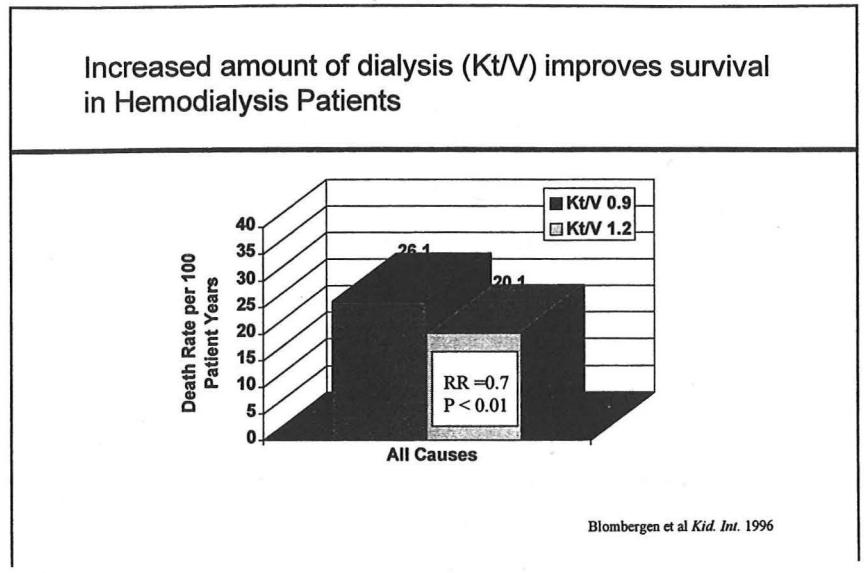
USRDS Annual Report 1995

Relationship Between Amount of Dialysis and Mortality

The increased rate of mortality in the U.S. ESRD population has been explained on the basis of inadequate dialysis. In general patients in other industrialized nations are dialyzed for longer periods yielding higher Kt/V ratios. An example of the impact of this comes from Tussin, France where patients are dialyzed 8 hours per session and the adjusted annual mortality rate is 6% compared with 20% in the U.S.

It seems reasonable to expect that greater amounts of dialysis (higher Kt/V) alone would improve survival on dialysis; however this has never been tested in a prospective study. The United States Renal Data Systems Database includes information related to dialysis adequacy on approximately 150,000 hemodialysis patients. Retrospective analyses of survival data stratified by Kt/V reveal that in fact higher amounts of dialysis are associated with higher survival rates (Figure 23). Reports from

Figure 23 a

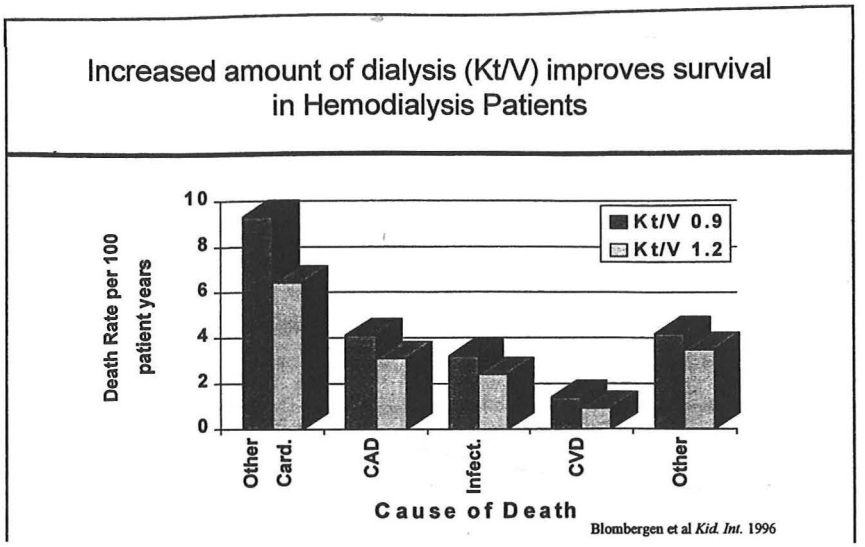


several centers in which dialysis time has been increased over a 3 year period indicated that survival rates improve with increased amounts of dialysis. Several reports involving smaller numbers of patients also indicate that higher amounts of dialysis are associated with better survival.

Relationship Between Amount of Dialysis and Nutrition

Steady-state BUN is determined not only by the amount of dialysis but also by the dietary protein

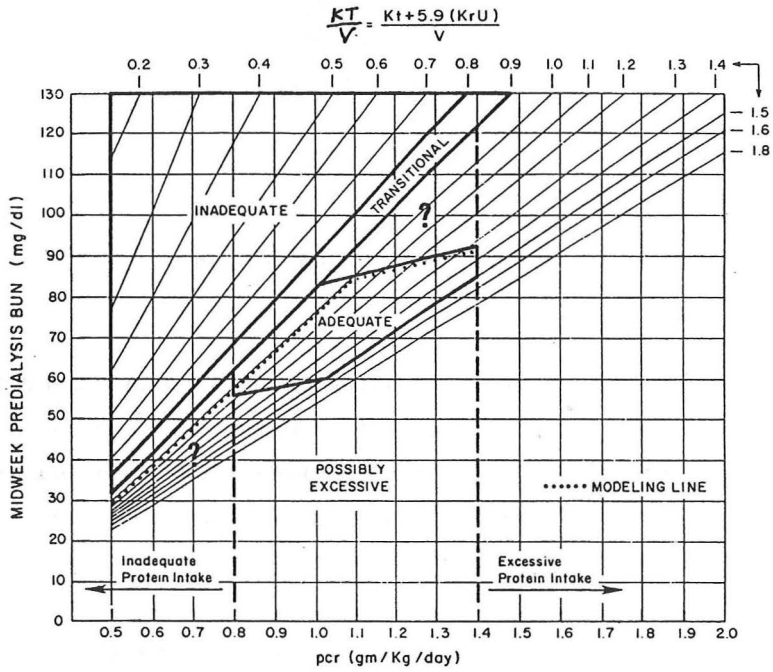
Figure 23 b



intake (Figure 24). As indicated in the Figure (analogous to Figure 10), for any given protein intake, the steady -state BUN is lower at higher delivered Kt/V values. Therefore, steady-state BUN in dialysis patients must be interpreted in this light. Since dialysis morbidity and mortality are impacted on by nutritional status, as expected patients with better nutrition and higher amounts of dialysis have lower mortality risk as indicated in Figure 25. In this Figure, Urea Reduction Ratio represents the amount of dialysis, and for the purpose of this discussion is equivalent to Kt/V, and values below 55% are associated with increased mortality. Albumin is the marker of nutrition and values below 4.0 g/dl are associated with increased risk of death in dialysis patients. The illustrates two important points: 1) Hypoalbuminemia is associated with an increased risk of death regardless of the amount of dialysis; 2) Lower amount of dialysis coupled with hypoalbuminemia increase risk of death for albumin levels below about 3.5 g/dl and URR below 55%. Thus both nutritional status and the amount of dialysis are important and interdependent. A major issue is whether one can distinguish whether lower amounts of dialysis cause malnutrition or vice versa. Why is this so? Review of Figure 24 indicates

that if one uses pre-dialysis BUN to determine dialysis adequacy one could conclude incorrectly that all patients with a BUN below 50 mg/dl are adequately dialyzed. This could lead to reduction in dialysis prescription in a patient who may not only be underdialyzed but also severely malnourished.

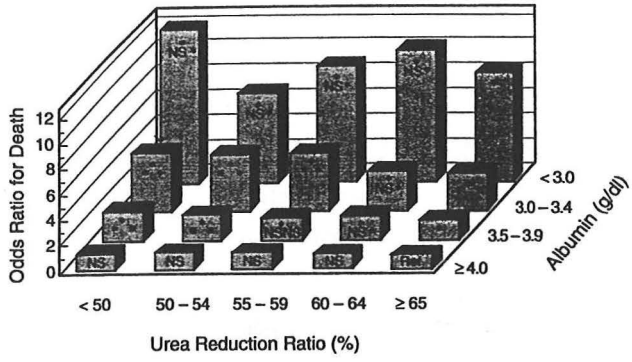
Figure 24. Relationship Between Amount of Dialysis (Kt/V), Dietary Protein Intake (pcr) and Midweek Predialysis BUN Concentration



Therapy assessment plot for thrice-weekly dialysis. (Reproduced by permission from Cogan and Garovoy: Introduction to Dialysis. New York, Churchill Livingstone Inc., 1985.)

Figure 25

ODD RATIOS FOR DEATH FOR A RANGE OF UREA REDUCTION RATIOS AND SERUM ALBUMIN CONCENTRATIONS IN 13,473 PATIENTS WITH ESRD TREATED WITH HEMODIALYSIS



Owen, W.F.et.al., NEJM. 329:1001-1006,1993.

Therefore a malnourished patient with a low BUN who is misdiagnosed as adequately dialyzed could actually receive even less dialysis, increase his/her risk for morbid and mortal complications and succumb to uremic complications. In fact, data from some studies suggest that this is the case. Thus in a study involving data on nearly 12,000 patients on dialysis, patients with lower average pre-dialysis BUN had a higher mortality rate than those with a higher BUN. Clearly, predialysis BUN is not a good marker for dialysis adequacy. On the other hand, if a patient is receiving a low dose of dialysis, and has little or no residual renal function, such a patient may indeed become malnourished as a result of insidious uncontrolled uremia.

Effects of Dialysis Membranes on Morbidity and Mortality

Biocompatibility

When blood comes in contact with synthetic dialysis membranes pro- inflammatory cytokine pathways become activated. In other words the patient is chronically inflamed during routine dialysis. Newer synthetic membranes, so-called biocompatible membranes, minimize but do not eliminate these effects

which include increased plasma levels of IL-1, IL-6, TNF a, upregulation of leukocyte adhesion molecules and complement system activation. Biocompatible membranes have been reported to reduce the incidence of infection, improve dialysis dyslipidemia, reduce the risk of anaphylactic and "first-use" reactions to the dialyzer and reduce dialysis-associated symptoms

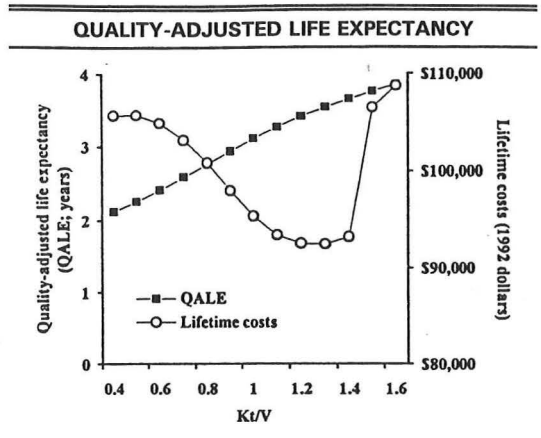
High-Flux

Many but not all of the newer membranes also have higher permeability for large molecules including proteins and have been dubbed "High-Flux" to indicate their high permeability. The increased permeability to large molecules is closely associated with high water permeability, thus these dialyzers are capable of very high rates of ultrafiltration as well. The beneficial effect of such membranes is removal of middle molecule uremic toxins and B_2 microglobulin which is known to cause a form of crippling amyloidosis in chronically dialyzed patients. On the other hand removal of albumin which has been observed after reuse of high-flux membranes is an untoward and unwanted side effect. Given the potential benefits of high-flux for removal of middle molecules balanced with the potential for loss of albumin or other essential human proteins, it is not known whether high-flux membranes improve dialysis mortality.

Based on these above observations, The HEMODIALYSIS study an NIH-sponsored multicenter clinical trial involving 15 centers and 1700 patients, has been initiated to address two key questions: 1) Does a mean delivered Kt/V of 1.60 as compared to 1.20 improve survival; 2) Does a high-flux versus a low-flux membrane improve survival in chronic hemodialysis patients. These questions have important implications for the care and cost of care for patients on chronic dialysis. The study is a 7 year trial with a 2 year recruitment and 5 year follow-up periods. The study will control for other co-morbid variables known to alter outcome including dietary intake, blood pressure, access problems and the impact of renal transplantation. The quality-adjusted life expectancy and the estimated lifetime cost of dialysis as functions of the amount of dialysis are shown in Figure 26. The Figure indicates that higher Kt/V values are cost-effective over the duration of dialysis up to values of 1.40-

1.50. Above this range, the cost-effectiveness is called into question. The HEMODIALYSIS study will also address the cost and cost-effectiveness prospectively.

Figure 26

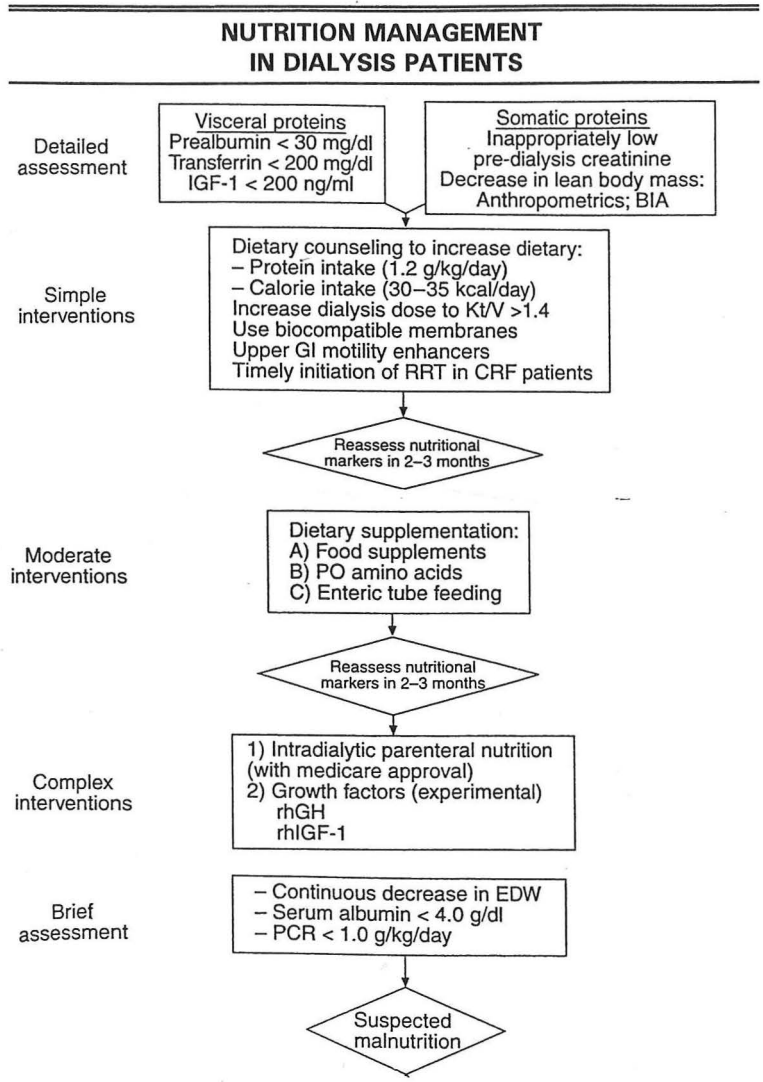


Hornberger, J.C., JASN, 4: 1021-1027,1993.

RECOMMENDATIONS FOR TREATMENT OF MALNUTRITION IN CHRONIC RENAL FAILURE

Identification of causes, mechanisms and treatment of malnutrition in chronic renal failure patients in pre-dialysis and dialysis phases are a high priority in renal research. In addition to dietary interventions use of recombinant growth factors including IGF-1 and human growth hormone are under investigation. IGF-1 has been shown to improve nutritional parameters in dialysis patients. However, it has not yet been shown to lower morbidity or mortality. Recently, Ikizler and Hakim have proposed a scheme for evaluation and management of malnutrition. This recently published scheme is now under serious investigation regarding impact on nutritional parameters and long-term outcome (Figure 27).

Figure 27



Ikizler,A. et.al., KI, 50: 343-357.1996.

. CONCLUSION

End-stage renal disease carries with it a high mortality rate. To reduce this rate improved methods of preventing progression of established disease and reducing the risks of death in patients already at ESRD are underway. The timing of initiation of maintenance hemodialysis is currently being revised and becoming more scientific based upon new information concerning the increased mortality risk observed in malnourished patients. Although many comorbid risk factors are responsible for death in ESRD patients, overwhelming evidence indicates that death risk from any cause is increased by malnutrition. Furthermore, underdialysis appears to be an additional and perhaps independent risk factor for death in ESRD patients. Identification of these two important and now measurable and determinable factors is leading to improvements in dialysis techniques, nutritional assessment and improved overall care of our patient population. With better recognition and understanding of these and other risk factors coupled with improvements in dialysis technology I am optimistic that the declining rates of dialysis mortality in the U.S. population will continue. Who knows, one day we can identify and treat renal disease at an earlier stage, we may eradicate ESRD altogether. I hope I am around to witness it.

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