Initiation of Dialysis

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ABSTRACT

The decision to initiate dialysis in a patient with progressive renal disease often depends on the physician's assessment of the patient's subjective symptoms of uremia. There is an increasing need to identify objective criteria for such a decision. Recent evidence suggests that malnutrition at the initiation of dialysis is a strong predictor of subsequent increased relative risk of death on dialysis. In this context, the role of prescribed protein restriction as well as the influence of the progression of renal disease on spontaneous dietary protein intake is examined. It is proposed that the indices of malnutrition such as progressive weight loss, serum albumin levels below 4.0 g/dL, serum transferrin levels below 200 mg/dL, and spontaneous dietary protein intake (using 24-hr urinary nitrogen measurement) below 0.8 to 0.7 g/kg per day be considered as objective criteria for the initiation of dialysis. Studies that have examined the role of "early" versus "late" dialysis have consistently shown a better outcome in the patients starting dialysis early. Other studies also suggest that early referral to nephrologists results in improved morbidity and mortality as well as hospitalization costs. An adequate vascular access, as well as social and psychological preparation of the patient, is an important early step in the process.

Key Words: Chronic renal failure, dietary protein intake, malnutrition, serum albumin, insulin-like growth factor 1

The decision to initiate dialysis in patients with chronic renal failure is one that involves the consideration of several subjective and a few objective parameters by physician and patient. These subjective parameters are often influenced to a great extent by the patient's perception of his or her quality of life and anxiety about starting a new technologically complex therapy. Because these social and psychological considerations play an important role in the decision to initiate dialysis or undergo transplantation, the discussion of this topic generally involves opinions as much as scientific data. In addition, over the past few years, a number of studies have sought to determine methods to slow the progression of renal failure and delay the onset of terminal renal failure, thus avoiding the need for dialysis (vide infra). These efforts have been promulgated in the interest of saving money, both for patients and society at large, and to prevent the patient from being exposed to the "unpleasant experience" of dialysis; these studies, as well as the availability of recombinant human erythropoietin, have had an effect on the indications and rationale for starting dialysis.

Clearly, the goal of any therapy, including dialysis, must be improvement of the patient's well-being and quality of life. However, the application of therapy must be at a time when the real risks of delaying the therapy outweigh the perceived benefits of withholding it. In this context, it is perhaps useful to recall the general consensus that exists about the timing of living related transplantation. For such patients, it is generally the custom to perform transplantation at a time when the patient has considerable residual renal function and is in a state of relative well-being. The rationale for encouraging patients not to endure prolonged conservative treatment of renal insufficiency is the resumption of near-normal renal function with successful transplantation. Perhaps such a concept is not sufficiently different that it might not also be an acceptable approach for the initiation of hemodialysis or peritoneal dialysis (PD).

In this discussion, we will limit our consideration to patients with chronic, progressive renal failure and, to the extent possible, will emphasize the medical aspects of the decisions to initiate therapy. In particular, we will emphasize the adverse effects of malnutrition at the start of dialysis and the importance of monitoring nutritional parameters as a guide in the decision to initiate dialysis. The influence of economic factors or the availability of dialysis facilities on the optimal time for dialysis initiation is beyond the scope of this review and will not be discussed.

ESTABLISHED INDICATIONS

The indications for the initiation of dialysis discussed below have been accepted since the mid-1960s, before the recent emphasis on prolonging conservative therapy. The decision to initiate dialysis in patients with progressive renal failure can be considered under two criteria (Table 1). "Absolute indica-
TABLE 1. Traditional indicators for the initiation of dialysis

<table>
<thead>
<tr>
<th>Absolute Indicators</th>
<th>Relative Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericarditis</td>
<td>Anorexia progressing to nausea and vomiting</td>
</tr>
<tr>
<td>Fluid overload and pulmonary edema unresponsive to simple measures</td>
<td>(characteristically early in the morning)</td>
</tr>
<tr>
<td>Hypertension poorly responsive to treatment</td>
<td>Profound fatigue and weakness</td>
</tr>
<tr>
<td>Advanced uremic encephalopathy and/or neuropathy</td>
<td>Decreased attentiveness, memory, and cognitive tasking</td>
</tr>
<tr>
<td>Clinically significant bleeding diathesis</td>
<td>Persistent and severe pruritus</td>
</tr>
<tr>
<td>Persistent severe nausea and vomiting</td>
<td>Depression and poor interpersonal relationships</td>
</tr>
</tbody>
</table>

tions" include the development of life-threatening or irreversible events (1). Most nephrologists would agree that the time course to these life-threatening events is not predictable, and to delay the initiation of dialysis until such indications are present places the patient at unnecessary risk of mortality and leads to morbidity with prolonged hospitalization (2,3).

The more commonly accepted criteria, so-called "relative" indications, reflect a general but fairly severe decline in the quality of life of the patient (4). A study by Porush and Faubert of the signs and symptoms of 118 patients starting dialysis has shown that 61% of the patients had anorexia and weight loss, 58% had generalized weakness, 49% had encephalopathy, and 41% had nausea and vomiting (5).

It should also be noted that the development and expression of these "relative" signs and symptoms in patients with slowly progressive renal disease is variable and may be accepted by the patient and family and not brought to the attention of the physician. Patients with slowly progressive renal failure often adjust their ability to perform tasks and downgrade their sense of well-being and habits as renal failure progresses. Further, some of the medications required by patients with chronic renal failure (CRF) may have side effects that mimic uremic symptoms. Conversely, the partial correction of anemia by treatment with erythropoietin may improve the patient's central nervous system and cardiovascular symptoms and sense of well-being without affecting the extent of uremia (6).

Finally, in many, there may be no "major" event that precipitates the need for the initiation of dialysis. Thus, it may be useful to identify other markers of uremia that are less subjective and/or equivocal, to avoid jeopardizing the health of the patient. Indeed, an important concept in these discussions is that the initiation of dialysis or transplantation should occur in an effort to improve the quality of life and rehabilitate the patient to full potential, not just to prolong a less than optimal survival. It is our view, based on a critical review of available data, that the signs and symptoms of malnutrition should be considered as objective criteria for the initiation of dialysis and are important early indicators.

DETERMINATION OF RENAL FUNCTION IN CRF PATIENTS

Many nephrologists consider specific target values of renal function as indicators for the initiation of dialysis. These target values may consist of a particular value of serum creatinine (SCr) or its reciprocal, blood urea nitrogen (BUN), or urinary creatinine clearance. The Health Care Financing Administration (HCFA) has recently mandated a set of renal failure criteria (Form 2728) on which reimbursement by Medicare for dialysis or transplantation will be based. It is therefore important to review the appropriateness of using these measurements in the context of starting ESRD therapy for progressive renal failure.

A recent review highlighted the problems inherent in the measurement of SCr, BUN, and creatinine clearance, particularly in patients with reduced renal function (7). Differences in the extent of tubular secretion, extrarenal elimination, and rate of generation of creatinine and urea, as well as composition of the diet (8), make an assessment of true renal function by such measurements in patients with chronic renal disease unreliable. More important, creatinine is appropriately recognized not simply as a measure of renal function but also as a measure of somatic mass (9); thus, a low serum creatinine may reflect a loss of muscle mass due to a reduction in physical activity or dietary intake as much as improvement of renal function (10). Similarly, the maintenance of a particular value of SCr may reflect a loss of muscle mass rather than a delay in the progression of renal failure (11,12).

Variations in the extent of creatinine homeostasis are seen not only between different individuals, but in the same individuals as a function of the progression of renal failure. GFR determined by $^{125}$Iiothalamate may vary greatly at the same level of SCr (13). Other studies using inulin clearance demonstrated markedly low GFR in the face of normal or near-normal SCr (7,14). Finally, it has been shown that with depressed renal function, creatinine clearance overestimates true GFR by as much as 100% (13).
not as exclusive criteria for the decision to initiate dialysis.

RENEAL FUNCTION AT INITIATION OF DIALYSIS

With these concepts in mind, is there a target GFR at which patients should be considered for the initiation of dialysis? Studies in the past measured renal function at initiation, relying on \( S_{\text{Cr}} \) concentration or creatinine clearance. When symptomatic uremia was used as a criterion for the institution of dialysis in 108 patients monitored in our clinic, time from \( S_{\text{Cr}} \) of 9.5 to 10.0 mg/dL to dialysis was 10 ± 1.2 months (16). Other studies have shown similar levels of renal function (as determined by creatinine) before the initiation of dialysis. In a study based on HCFA Form 2728, Wish and colleagues found that, in more than 1,700 patients, the mean creatinine at the initiation of dialysis was 9.1 ± 4.5 mg/dL (median, 8.2 mg/dL), but in diabetics, the mean was 8.1 mg/dL and the median was 7.8 mg/dL (17). Jungers et al. indicated that, independent of the degree of protein restriction, the average creatinine level at the initiation of dialysis was approximately 10 mg/dL (18), although in a more recent study from the same group, a slightly lower value of \( S_{\text{Cr}} \) at the initiation of dialysis was found (3). Those authors also found a more rapid rate of progression than our study: the interval between an \( S_{\text{Cr}} \) of approximately 5.6 mg/dL to dialysis was 15.4 ± 0.8 months and only 6.3 ± 0.4 months for patients once they reached a creatinine of approximately 8 mg/dL (18).

No studies have looked at the true GFR as measured by iothalamate clearance, inulin clearance, or other isotopic measures at the time of the initiation of dialysis, although ongoing studies as part of the Modification of Diet in Renal Disease (MDRD) study may perhaps answer this question in the future. Indeed, it is not clear that any particular level of creatinine or BUN is an appropriate marker for the initiation of dialysis. Measurements of averaged urea and creatinine clearance or of a more accurate determination of GFR that do not rely solely on creatinine would obviate the problem of reduced muscle mass and other variations affecting serum levels. As noted earlier, measurements of renal function by any means, should be considered only as supportive evidence and used in conjunction with the overall assessment of the patient and, in particular, clinical signs and symptoms indicating the onset of malnutrition.

EQUIVALENCE BETWEEN DIALYSIS AND RESIDUAL RENAL FUNCTION

It is instructive to consider the equivalence of dialytic clearance and residual renal function as a guide to the initiation of dialysis; in other words, how much of an equivalent amount of excretory function of the kidney does hemodialysis replace? Assuming a urea clearance of 200 mL/min, the weekly urea clearance, based on 3.5 h of dialysis, three times per week, is 126 L (19); averaged on a continuous basis, this is equiva lent to a clearance of urea of 12.5 mL/min. Similar considerations for creatinine (assuming a dialytic clearance of 170 mL/min) show that dialysis with the above regimen represents an average of 10.6 mL/min of creatinine clearance. The availability of high-flux dialyzers with higher urea and creatinine clearances and with membrane pore sizes that allow for the clearance of middle molecules may provide higher values for the "equivalent" urea and creatinine residual renal function and a closer approximation of native renal function. Clearly, the continuous function of the native kidneys and their multiple other functions in contrast to the discontinuous nature of intermittent hemodialysis make such an analysis a very simplified comparison (20); nevertheless, the model allows a frame of reference for the consideration of the initiation of dialysis.

ROLE OF PROTEIN RESTRICTION IN THE PROGRESSION OF RENAL DISEASE AND NUTRITIONAL STATUS OF PATIENTS

Numerous clinical studies have been published that demonstrate that dietary protein restriction slows the progression of renal disease (10,21-26). However, most of these studies relied on changes in \( S_{\text{Cr}} \) (or its reciprocal) or creatinine clearance to determine change in renal function. In addition, these studies were composed of small numbers of patients, lacked controls, and varied in their conclusions as to the effectiveness of protein restriction and when it should be used. Thus, the results of such studies should be interpreted with caution.

Recently, results of the full MDRD study were published (27). This prospective controlled study of 840 renal failure patients with different levels of renal impairment studied the effect of both protein restriction and blood pressure control. The study concluded that in humans there was a small but not statistically significant benefit in the progression of renal disease from dietary protein restriction with a follow-up of 2.2 yr. Debate continues over the results of this study because of the early "physiologic" decrease in GFR and the length of follow-up.

Regardless of the effect of dietary protein intake on renal failure progression in humans, it is mandatory for the practicing nephrologist to assure that dietary protein restriction does not lead to malnutrition, because the occurrence of malnutrition in dialysis patients has been demonstrated to be a powerful and independent predictor of mortality (11,28-31). During the course of the MDRD Feasibility Study (similar to the full MDRD study but smaller in scope, without blood pressure randomization, and carried out for only 1 yr), despite intensive dietary attention and despite the fact that albumin concentrations remained "within normal limits," there were indications of early signs of malnutrition in the group of low dietary protein patients in that they appeared to have lost muscle mass, as shown by a further loss of daily
urine creatinine (32). Serum cholesterol and transferrin, as well as anthropometric measurements, decreased significantly. These decrements correlated directly with the individual reported mean energy intake. In all dietary protein groups, the estimated actual energy intake was significantly lower than the prescribed intake, and those with the lowest GFR tended to have lower energy intakes (32).

The nutritional outcomes of patients on the full-scale MDRD clinical trial have not been published except in abstract form (33). A recent abstract indicated that patients in both Study A (moderate renal failure) and Study B (advanced renal failure) who were on low protein intake had decreased energy intake, decreased serum transferrin, decreased urine creatinine excretion, decreased body weight, decreased arm muscle area, and decreased percentage of body fat (34). Although these changes were stated to be minor and not to show important deterioration in nutritional status, they were all statistically significant.

It should be pointed out also that such results were obtained only with intensive dietary counseling. In another abstract from the MDRD study, the time required to carry out a successful and complex behavioral intervention by dietitians in the first 4 months of the study was estimated to be 204 ± 73 min/visit in the very low-protein group, 186 ± 69 min/visit for instruction in the low-protein-diet group, and 171 ± 68 min/visit in the usual protein intake group (35). Estimations of nurse and physician time were not provided. Thus, an enormous effort is required to provide proper dietary monitoring and education in patients who are to undergo protein restriction to protect against the development of malnutrition.

**EFFECT OF PROGRESSION OF RENAL DISEASE ON SPONTANEOUS PROTEIN INTAKE**

An important issue concerning protein restriction and its effect on the progression of renal disease is the "reverse of the coin" question, i.e., the effect of the progression of renal disease on spontaneous dietary intake. Although anorexia has been recognized as one of the hallmarks of advanced uremia, the level of renal failure at which it occurs and the extent of anorexia have not been adequately documented (36,37).

Results of the MDRD Feasibility Study contain important information on this issue (32). It should be noted that patients with preexisting evidence of malnutrition, proteinuria ≥10 g/day, insulin-dependent diabetes, or heart or liver failure were excluded from this and the subsequent full studies. In this selection of "healthy" CRF patients, positive correlations were found at baseline between the true GFR (determined by [125I]iodotyramine) and actual and reported protein and calorie intake, albumin concentration, body weight, transferrin, and urine creatinine-to-height ratio. Thus, at entry into the study, i.e., before assignment to different dietary groups, the lower the GFR, the worse the biochemical markers of malnutrition. In all dietary groups, the estimated actual energy intake was significantly (20%) lower than the prescribed intake.

In an abstract presenting the results of the full MDRD study, Kopple and coworkers reported on the nutritional status of 1,687 patients evaluated during the initial baseline visit of the study (33). They again found that lower GFR was significantly associated with reduced protein intake. Decreased GFR was also significantly associated with reductions in caloric intake, body weight and muscle area, percent body fat, urine creatinine, (S_{AB}), and serum transferrin. They concluded that the preliminary signs of protein and calorie malnutrition began rather early in the course of chronic progressive renal failure and became more evident when the GFR was less than 10 mL/min. Thus, a decrease in dietary protein and energy intake was an early index of uremia and reasonably should be a marker for the consideration of dialysis.

In a previous study of patients with progressive azotemia, we reported decreased food intake even with no dietary instructions to restrict protein or calories (16,38). This decrease was thought to reflect a combination of anorexia and alteration in the smell and taste of foodstuffs. It was noted that the avoidance of food often applied to meat products, with patients "instinctively" avoiding these high-protein foods, even without dietary counseling. However, it was also noted that there was no decrease in the S_{AB} of such patients as they moved from mild to severe renal insufficiency, suggesting that visceral protein status was preserved (unlikely) or that low S_{AB} was a late indicator of malnutrition (16).

More recently, an analysis of protein intake by patients with progressive renal disease has been initiated in one of our clinics (39). Dietary interventions in these patients were minimal and consisted only in attempts to attenuate the hyperphosphatemia by limiting dairy products. Preliminary results indicate that many patients spontaneously restricted dietary protein with progression of renal disease, and in patients with creatinine clearance less than 10 mL/min, spontaneous dietary intake calculated from daily urine urea appearance (40) was as low as 0.6 g/kg per day. In these patients, other markers of nutrition, for example, transferrin, prealbumin, albumin, insulin-like growth factor-1 (IGF-1), and urinary creatinine excretion also correlated with renal function. Transferrin, IGF-1, and prealbumin may be even earlier markers of malnutrition (39,41,42).

Thus, we propose that a spontaneous decrease in dietary protein intake should be used as an early sign of malnutrition in patients with a GFR of 10 mL/min or less. Patients with a GFR of 10 mL/min or less should be advised for frequent follow-up to monitor nutritional status more intensely.

**EFFECT OF MALNUTRITION ON SUBSEQUENT ESRD OUTCOME**

A number of studies have documented the increased risk of mortality in hemodialysis patients who
A

Relative Mortality Risk (Cox): New Hemodialysis Patients, 1986-87

SERUM ALBUMIN CONCENTRATION AT TIME OF ESRD

n=3,399

Figure 1. (A) Relative risk of mortality in hemodialysis-dependent patients as a function of S_{.Ab} concentration at the initiation of ESRD. Data are based on cohorts in 1986 and 1987 (Courtesy of USRDS). (B) Relative risk of mortality in hemodialysis-dependent patients as a function of S_{.Cr} concentration at the initiation of ESRD. Data are based on cohorts in 1986 and 1987 (Courtesy of USRDS).

suffer from malnutrition (11,29,30,43,44). In an analysis of the risk of mortality in more than 13,000 patients on chronic maintenance hemodialysis, Lowrie and Lew showed that the risk of death increased exponentially as the concentration of S_{.Ab} decreased (11). When compared with a S_{.Ab} of more than 4.0 g/dL, S_{.Ab} values of 3.5 to 4.0 g/dL resulted in a twofold increase in the relative risk of death (11). This latter value of albumin is in the range of “normal” for many laboratories and in several prior studies. (Most of the data in these cited studies probably reflect the Bromocresol green methodology for the measurement of albumin; the Bromocresol purple methodology yields systematically slightly lower values, and such differences need to be kept in mind in the evaluation of albumin as an index of malnutrition [45].) Thus, malnutrition of hemodialysis patients is manifested by S_{.Ab} of less than 4.0 g/dL and is a harbinger of a significant risk factor for mortality (46). Likewise, low S_{.Cr} concentrations, which reflect muscle mass in the dialysis patient, were also associated with a higher risk of death (11). Moreover, it has recently been shown that the marked differences in mortality rates between diabetics and nondiabetics may be attenuated when differences in the values of S_{.Ab} and S_{.Cr} are accounted for in a logistic regression analysis, suggesting that malnutrition may be a factor in the well-known increased mortality of diabetic dialysis patients (43).

Does the correlation of increased risk of death and low S_{.Ab} in the chronic maintenance dialysis patients apply to patients with chronic renal failure before dialysis? The United States Renal Data System (USRDS) analyzed subsequent mortality of patients presenting for dialysis with different levels of S_{.Ab} concentrations. In this study of approximately 3,500 patients, the risk of death was substantially higher for patients starting dialysis with an S_{.Ab} concentration lower than the “reference” population (S_{.Ab} between 3.6 and 4.0 g/dL). It should be appreciated also that patients with S_{.Ab} concentrations higher than 4.0 g/dL had a statistically significant lower risk of death than the reference population (4) (Figure 1a). Similar findings were demonstrated with S_{.Cr} (Figure 1b). It is important to note that low S_{.Ab} is an independent risk factor for mortality and not just a reflection of underlying comorbid conditions (47). The importance of S_{.Ab} at the initiation of dialysis is also underscored by unpublished data by Lowrie (E.G. Lowrie, personal communications) based on a large number of patients starting dialysis. As shown in Figure 2, life table analysis shows a marked decrease in survival in patients starting dialysis, with S_{.Ab} levels less than 4.0 g/dL, and is clearly worse the lower the initial S_{.Ab}. Finally, in an analysis of the risks of mortality in the first 90 days of dialysis, Khan et al. showed that patients dying in those first 90 days had a significantly lower albumin concentration than did those who survived (3.1 versus 3.7 g/dL), but both groups had similar levels of creatinine (48). Thus, an S_{.Ab} less than 4.0 g/dL is an important factor to consider in the

Survival Stratified By Albumin Concentration
3,487 Patients Beginning Dialysis in 1988

Figure 2. Life-table analysis of patients initiating hemodialysis with various levels of S_{.Ab} (in grams per deciliter). National Medical Care Inc. data (courtesy of Dr. E. Lowrie).
decision to initiate dialysis in CRF patients. Other measures of malnutrition should be considered as well as low \( S_{Ab} \). Weight loss, decreased transferrin, decreased cholesterol, and decreased muscle mass (as indicated by an \( S_{cr} \), inappropriately low for the level of renal function) may be helpful indicators of nutritional status. At present, there are no data to indicate whether a low \( S_{Ab} \) concentration, resulting primarily from nephrotic syndrome, has the same grave prognosis as in patients with low \( S_{Ab} \), but without nephrotic syndrome (49). It is not unreasonable to believe, however, that a low \( S_{Ab} \) from any cause would carry the same risk.

Although the majority of these studies cited above reflect the outcome of patients initiating hemodialysis, most studies of peritoneal dialysis patients also indicate a correlation of low \( S_{Ab} \) with increased morbidity and mortality (50,51). Indeed, because most patients starting peritoneal dialysis have a further decrease of \( S_{Ab} \) (because of peritoneal losses), the prognostic importance of \( S_{Ab} \) at the initiation of dialysis is probably more evident in this patient population.

**POTENTIAL EARLY MARKERS OF MALNUTRITION**

Because \( S_{Ab} \) concentration, even slightly less than 4.0 g/dL, has such an important effect on mortality risk, it is important to identify earlier markers of malnutrition in the CRF patients. The concentration of albumin is determined by several factors, including the rate of synthesis and catabolism (49,52). In addition, the distribution of albumin between extracellular and intravascular spaces may be variable depending on the cause of renal disease or the presence or absence of fluid overload. In malnourished patients, albumin appears to shift into the intravascular compartment. Finally, low \( S_{Ab} \) may reflect unrecognized inflammatory conditions independent of nutrition (53). Thus, despite its strong correlation with mortality, plasma albumin concentration may not reflect total albumin mass and is probably not an ideal early marker of malnutrition (54).

Several visceral proteins have a shorter half-life and may be earlier markers of malnutrition (55). Among these are transferrin (which has a half-life of 8 days instead of 20 days for albumin) and prealbumin, which has a half-life of 2 days (41). A recent study of prealbumin in patients on dialysis has shown it to correlate inversely with mortality in dialysis patients (56). However, data correlating the concentration of prealbumin with risk of mortality in the chronic renal failure patient before dialysis are not available and no firm conclusions about its utility can be made at present.

Anthropometric measurements have often been used to estimate body composition and nutritional adequacy. The reproducibility of anthropometric measurements is poor and is dependent on the skill of the observer. There are, likewise, no studies that have correlated anthropometric measurements of predialysis patients with clinical outcome. Less well established, but potentially useful, are analyses of specific plasma or intracellular amino acid concentrations (57). However, the relative contributions of acidosis and malnutrition in these amino acid profiles require further definition.

In the MDRD study, urinary nitrogen appearance was a useful tool to measure protein intake in the evaluation of nutritional status (27,40). We also monitor the protein intake of our patients from 24-h urinary collection, according to the methodology described by Maroni et al. (40). As indicated earlier, studies in patients with CRF not on supervised protein restriction have demonstrated that protein intake decreases gradually as renal failure progresses (39). Spontaneous decreases in urea nitrogen appearance (reflecting decreased dietary protein intake) coupled with decreased creatinine appearance (reflecting decreased muscle mass) may well be easy and readily available indices of early malnutrition that should be sought. Finally, newer assessment tools such as bioelectrical impedance and dual energy x-ray absorptiometry may be useful to assess body composition and nutritional status in both dialysis patients and those patients approaching dialysis (58).

**OUTCOMES OF EARLY INITIATION OF DIALYSIS**

It is interesting that in the 30 yr since chronic hemodialysis has become available, there are more publications about criteria for stopping dialysis than for the initiation of dialysis. Most of the studies on the issue of the early initiation of dialysis have come from the work of Bonomini and colleagues (59–61). On the basis of the hypothesis that starting hemodialysis earlier would attenuate the potential for malnutrition and maintain renal and extrarenal hormone equilibrium, his group initiated patients on chronic dialysis when the creatinine clearance was between 15 and 20 ml/min. In such patients, they reported a 4-yr survival of 85%, at a time when the 4-yr survival in the United States was less than 50% (59). This study was criticized because of differences in the dose of dialysis as well as other factors between the United States and Italy. In a subsequent study, Bonomini and colleagues reported an 88% 10-yr survival in their patients beginning therapy at a creatinine clearance of more than 10 ml/min, compared with a 55% 10-yr survival for their patients when starting chronic dialysis at an average creatinine clearance of 4 ml/min (61). In addition, the former group had less than half the hospitalization days (5 days/yr per patient) than patients starting late (14 days/yr per patient). On the basis of reduced morbidity and improved rehabilitation, Bonomini and colleagues have shown that the early initiation of dialysis had economic advantages as well (59–61). Although critics have pointed out that there were differences in initial residual renal function and the extent of renal failure between both groups of patients, it is unlikely that a 35% difference in 10-yr survival would only reflect differences in "disease
progression equivalency point." Nevertheless, those studies do not comment on the nutritional parameters of both groups of patients with the initiation of dialysis.

In a recent publication, Tattersall et al. measured the residual renal function of 63 patients starting dialysis in terms of daily Kt/V for urea. Before the initiation of dialysis, the mean daily Kt/V was 0.15 ± 0.05, compared with 0.49 ± 0.08 in patients 6 months after the initiation of dialysis. Increased mortality and morbidity correlated with the initial Kt/V but not with the initial creatinine or BUN level (62).

A somewhat different approach to the evaluation of the earlier initiation of dialysis was provided in a study by Ratcliffe et al. (2). Those investigators compared two groups of patients—one group with a mean 4-yr follow-up by nephrologists before starting dialysis and another group referred much later and requiring the initiation of dialysis soon after referral. Of the patients referred late and starting dialysis with a residual renal function below 6 mL/min, 70% required prolonged hospitalization, during which their mortality was 13%. In contrast, in the group with longer follow-up by a nephrologist and starting dialysis with a creatinine clearance above 6 mL/min, only 9% required prolonged hospitalization and the mortality was 4%. Similar conclusions were made in a study by Jungers and colleagues (3). In the group of patients who were referred to nephrologists late in the course of their disease, fluid overload and severe hypertension were significantly higher and serum bicarbonate, calcium, hematocrit, and albumin were significantly lower than in patients referred early in the course of their renal disease. These and other factors led to a large difference in the total hospital stays (34.5 ± 16.3 days for the late referral group and 5.8 ± 3.0 for the early referral group), with clear differences in costs. Finally, Khan et al. showed that a larger proportion of patients who died during the first 90 days after the initiation of dialysis received emergency dialysis via temporary venous access and had a median follow-up of 1.1 month before the initiation of chronic dialysis (48).

Perhaps the explanation of these findings is that patients started earlier on dialysis may be in better nutritional health and better able to manage the occurrence of hypercatabolism from infections and other comorbid complications. Although a number of studies demonstrate that nitrogen balance can be maintained in patients with CRF with protein intake as little as 0.6 g/kg per day (or even less with supplementation with keto amino acids), this is marginal replacement in the patient under stress. Once patients are stable on dialysis, they are often allowed (in fact, are encouraged to consume) a more liberal diet of at least 1 to 1.2 g of protein/kg per day. Thus, increased protein/energy intake in "healthier" dialysis patients reduces the risk of malnutrition and its associated morbidity and mortality. Patients benefit from the increased safety margin, as well as from consuming a near-normal diet—for most patients, a very pleasurable experience. Indeed, our patients have commonly and spontaneously commented on how much better they felt after starting dialysis, despite the additional commitment of time and effort on their part.

Another advantage of the early initiation of dialysis is easier and more effective management of hypertension, by control of the excess intravascular volume, generally found in chronic renal failure patients. Whereas more than 80% of patients with advanced renal failure require antihypertensive medications for the adequate control of blood pressure, a considerably lesser percentage of patients on chronic dialysis require antihypertensive medications. These medications often cause central nervous system symptoms or gastrointestinal upset, and their discontinuation is often welcomed by patients.

In summary, there are no truly randomized prospective studies of early versus late initiation of dialysis. The available evidence however favors early initiation of dialysis. Despite the drawbacks of many of the studies that have examined the issue, all have shown improved mortality, morbidity, and cost effectiveness in patients starting dialysis earlier. Delay of dialysis by 1 yr would save approximately $25,000 to $30,000. If one does not include the costs of clinic visits, dietary counseling, etc. On the other hand, when one considers that the average daily cost of an intensive care unit stay in our hospitals is approximately $1,089 and a non-intensive care unit bed is $240/day, it is clear the increased hospitalizations or prolongation of hospitalization related to malnutrition or complications of inadvertent uremia may obliterate any savings and, more important, will significantly reduce the quality of life of patients.

RECOMMENDATIONS REGARDING INITIATION OF DIALYSIS

The above considerations demonstrate the problem in defining objective criteria for the initiation of dialysis. However, the following recommendations seem reasonable:

1. If protein restriction is to be implemented in patients before dialysis, it is essential that the patient be monitored carefully for clinical signs and symptoms and laboratory evidence of malnutrition. Delays in starting dialysis should not occur at the expense of adequate nutrition. Current consensus, based on the outcome of the MDRD study, suggests that for patients with a moderate loss of renal function, the evidence that the prescription of a low-protein diet slows the progression of renal failure is inconclusive (63).

2. Definite or absolute signs or complications of the uremic syndrome should be anticipated and avoided.

3. Relative indications affect the quality of life in patients and should be strongly considered as indications for the initiation of dialysis. To these, we would add the following important indications.
4. Before the patient develops a GFR of 10 mL/min, initiation of dialysis should be initiated whenever indices of malnutrition develop in patients with CRF, whether as the result of the spontaneous reduction of protein intake or from dietary prescription.

b. The best index of malnutrition established at this time is an SBP lower than 4.0 g/dL. In the absence of severe liver disease or nephrotic syndrome, decreases in muscle mass, serum prealbumin, IGF-1, serum transferrin, or total lymphocyte count, along with weight loss (nonfluid) and an unsupervised decrease in dietary protein intake as measured by urinary nitrogen appearance, are harbingers of malnutrition and should trigger intensive dietary counseling. We propose that in patients on unrestricted dietary protein prescriptions, the finding of a decline in daily protein intake of less than 0.8 to 0.7 g/kg per day should be viewed with concern. Follow-up should occur as often as once every 3 to 4 wk, and if reduced protein and calorie intake persists, the patient should be started on dialysis. In particular, renal failure patients with diabetic nephropathy, gastroparesis, and enteropathy may experience not only a more rapid decline in renal function but also increased susceptibility to malnutrition. These patients should be considered for early dialysis and more aggressive feeding.

c. Waiting for unequivocal signs and symptoms of malnutrition may significantly worsen the morbidity and mortality of patients once they start dialysis. It is perhaps fortunate that many of the symptoms and signs of uremia overlap those of common viral infections, and at present, many patients probably start dialysis therapy when the signs and symptoms of an upper respiratory tract infection (“flu”) worsen their symptoms of incipient uremia. This phenomenon may help explain the 20% higher national incidence of the initiation of dialysis during the month of January compared with the month of July (F.K. Port, personal communication).

4. Before the patient develops a GFR of 10 mL/min, the maintenance dialysis must be initiated. These include, in addition to the discussion of the available treatment options (hemodialysis at home, in-center hemodialysis, PD, and transplantation), the creation of an arteriovenous fistula either with native vessels or prosthetic grafts. The placement of a PD catheter can be performed later just before the need for dialysis. However, we recommend native vein arteriovenous fistula placement (but not prosthetic grafts), even for patients electing PD, because the technical failure rate of PD remains high after the loss of residual renal function (64). Should patients have a related donor for transplantation, then early tissue typing and subsequent transplantation should be carried out, obviating the need for either hemodialysis or PD.

5. A common reason that patients are reluctant to initiate dialysis is their lack of understanding of the process and procedures and fear of the unknown. It is necessary that patients meet and talk with other patients who are undergoing hemodialysis or PD or those who have undergone transplantation. They should visit a hemodialysis unit and PD program and meet with transplant coordinators. There are several videotapes and much reading material available that inform patients of their disease, its progress, the various treatment options, and the particulars of each treatment option. Once exposed to a formal teaching program of the various types of dialysis and transplantation, patients are much less reluctant to start and experience a more positive result, both long and short term. The team approach, including a nephrology nurse, social worker, diettian, transplant coordinator, and nephrologist, is essential to this process.

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