AN EPIDEMIC OF END-STAGE RENAL DISEASE

The number of patients enrolled in Medicare’s end-stage renal disease (ESRD) program has increased in near-exponential fashion over the past 30 years — from approximately 10,000 beneficiaries in 1973, to more than 86,000 in 1983, to an estimated 400,000 in 2003. As documented by data from the US Renal Data System (USRDS), about 100,000 new patients with ESRD enter the program every year, and the overall prevalence of ESRD in the United States is expected to reach 661,330 by the year 2010. In the late 1990s, 72% of these patients were being treated by dialysis, and 28% had received functioning kidney transplants. The costs for this highly sophisticated ESRD care were an estimated $17.9 billion in 1999, which represents about 6% of the entire Health Care Financing Administration budget and more than the National Institutes of Health’s total annual budget of $15.6 billion.

Despite the tremendous investment of resources in ESRD treatment programs, the...
RENAL ANEMIA

Cardiovascular disease is the leading cause of death in patients with kidney failure. As shown in Figure 2, the risk of cardiovascular death is 500 times higher in dialysis patients aged 25 years to 34 years than in similarly-aged persons in the general population. Even among elderly patients with ESRD, cardiovascular mortality is approximately 5 times higher. These elevated mortality rates in patients with ESRD have occurred despite technological improvements in both dialysis and transplantation. In their own practices, clinicians are aware of the high morbidity associated with kidney failure. The typical patient with ESRD has 4 comorbid conditions, spends 15 days in the hospital each year, and reports a generally low quality of life.

The ever increasing costs and continuing suboptimal outcomes of renal replacement therapy have caused more attention to be focused on the earlier stages of chronic kidney disease (CKD). More aggressive management of the complications that often develop during these early stages may ultimately result in improved survival rates in patients who progress to ESRD. An estimated 5.6 million to 20 million people in the United States have CKD, and another 20 million are at risk to develop the disease — with the estimates varying according to the definitions used. Even the lowest prevalence estimates support the view that a vast underdiagnosed and undertreated population exists, and this group constitutes a critical target for future efforts to improve kidney disease outcomes.

Effective control of diabetes mellitus and hypertension will remain as starting points in any attempts to prevent initiation and progression of CKD, but managing these common underlying causes of kidney deterioration is only a beginning. The latest treatment guidelines from the National Kidney Foundation also call for earlier testing to detect the silent stages of kidney damage in a wide range of groups at high risk for developing CKD and to treat any reversible kidney complications.

In this article, anemia is examined as one of the key modifiable risk factors predisposing individuals to severe late-stage complications of CKD. In particular, the article reviews the association between renal anemia and the development of cardiovascular disease and accelerated morbidity and mortality in patients with early CKD. As data illustrating the connections between anemia and poor clinical outcomes are reviewed, practical suggestions for early diagnosis and treatment of renal anemia will be presented.
begins with an initiation factor, usually caused by diabetes, hypertension, autoimmune disease, systemic infection, or drug toxicity and results in kidney damage, a progressive decrement in glomerular filtration rate, and finally the development of uremia. While the uremic complications can be attenuated somewhat by dialysis, mortality at this late stage is greatly accelerated.

Over the past several years, however, researchers have discerned that the complications of CKD begin before the patient has reached the final stage of kidney failure. In fact, by the time dialysis is initiated, patients are already dying from accelerated cardiovascular disease. This evolving view of the natural history of CKD explains why high-technology interventions at the end stage have failed to slow mortality rates and exposes the need to target for intervention patients in the earlier stages of CKD. Anemia and other potential complications such as malnutrition, bone disease, and neuropathy are conditions that nonspecialist clinicians must now consider when evaluating patients with suspect kidney function tests. Without increased attention to the contributing factors that increase the risk of complications — especially cardiovascular risk — the dismal prevalence and mortality statistics seen in patients with ESRD will not improve.

**Anemia in Kidney Disease: An Early Red Flag for Cardiovascular Complications**

Anemia is a common problem in patients with progressive kidney disease. Even those with moderate CKD are at risk of anemia — a recent analysis of patients seen at a nephrology clinic revealed that almost one half of the patients with a serum creatinine level of 2.0 mg/dL or less had a hematocrit of less than 36%. The primary cause of the renal anemia is insufficient production of erythropoietin by the diseased kidney, although additional factors such as erythropoietin resistance, iron deficiency, or blood loss due to occult gastrointestinal bleeding may also contribute.

The consequences of renal anemia have been captured best in the data-rich environment of ESRD and dialysis. In this setting, renal anemia has been associated with decreased health-related quality of life, reduced exercise capacity, cardiomyopathy, increased hospitalization rates, and congestive heart failure. Some of these negative outcomes linked with anemia are confounded by shared comorbidities; however, for cardiomyopathy and congestive heart failure — which are extremely common among patients with ESRD — anemia has been documented as an independent risk factor.

A prospective cohort study involving 432 Canadian patients with ESRD illustrates the extent of cardiomyopathy even at the initiation of dialysis. Echocardiograms at baseline showed that 74% of patients had left ventricular hypertrophy (LVH) and 36% had left ventricular (LV) dilation. Over a mean follow-up period of 41 months in these patients, the mean hemoglobin level was independently associated with progressive LV dilation (OR 1.46 per deciliter, \( P = .02 \)). The hemoglobin level was also independently associated with de novo congestive or recurrent heart failure, as well as all-cause mortality.

More recent evidence indicates that cardiomyopathy develops well before the initiation of dialysis in patients with CKD. In a Canadian multicenter study, 246 patients with renal insufficiency (mean creatinine clearance of 36.8 mL/min) underwent echocardiography at baseline and at 1 year of follow-up. The study quantified the predictors of change in left ventricular mass index (LVMI) over the 12-month follow-up period. Although only 15% of patients experienced progressive cardiac symptoms during this period, one quarter of the subjects had a significant increase in LVMI. After adjusting for baseline LVMI, both hemoglobin level and systolic blood pressure were found to be important predictors of LV growth. Each 0.5 g/dL decrease in hemoglobin level produced a 32% increase in progression of LV growth ( \( RR = 1.32, 1.1-1.59; P = .004 \) ). Thus, many patients with CKD have evidence of elevated cardiovascular risk in the predialysis period. This risk is strongly associated with an increase in systolic blood pressure and a decline in hemoglobin levels.

**Correcting Anemia in CKD: Goal versus Reality**

Because anemia has an independent role in the genesis of LVH and subsequent cardiovascular disease, correction of anemia in its early stages has gained momentum as a strategy for preventing the cardiovascular consequences of CKD. For more than 15 years, recombinant human erythropoietin (Epoetin alfa) has been the main therapy for CKD-related anemia. The recombinant protein can be administered subcutaneously or intravenously and is typically prescribed in hemodialysis settings 3 times per week. Administration in peritoneal dialysis usually involves weekly administration, the prescribing schedule most often used with patients before dialysis is initiated.

Erythropoietin replacement therapy is generally well tolerated. The main adverse effects are what might be predicted given the physiology of hemo-
The current goals for erythropoietin therapy are a hemoglobin concentration of 11 to 12 g/dL or a hematocrit of 33% to 36%, levels clearly not indicative of complete correction of the anemia. The US government set these targets to meet Medicare reimbursement goals rather than to reflect scientific consensus. Concerns related to iron deficiency, vascular access, and use in patients with pre-existing cardiac disease also contribute to subnormal hemoglobin targets. The ideal hemoglobin target for CKD remains a topic of much debate. However, most patients who require anemia correction are not receiving any antianemia therapy, and the movement toward any treatment goal remains a priority education message for most clinicians.

Erythropoietin promotes both the production and prolonged survival of red blood cells. Although erythropoietin levels actually increase as a patient progresses from mild to moderate stages of CKD, the rate of this increase in blood-stimulating hormone is markedly subnormal, given the low levels of hemoglobin present in that setting. Erythropoietin levels also show wide inter-individual variability. For these reasons, measurement of the erythropoietin level is not useful in trying to diagnose anemia in patients with CKD.

Darbepoetin alpha is a hyperglycosylated recombinant human erythropoietin analogue recently approved for the treatment of anemia in CKD (with or without dialysis) and cancer. The approved starting dose is 0.45 mcg/week, administered either intravenously or subcutaneously. The addition of carbohydrate chains to the Epoetin core molecule results in a longer serum half life and increased biologic activity. This longer half life facilitates a less frequent dosing schedule, advantageous to patient convenience and compliance. Since Medicare mandates that erythropoietin be administered in a physician’s office or in a medical clinic (ie, no home self-administration), the need for frequent clinic visits has discouraged some patients from adhering to their treatment plan. Thus, an extended dosing schedule would make anemia therapy more convenient and more effective. Only further postmarketing surveillance will prove if this new product with its attractive pharmacokinetic properties will share the benign side-effect profile of unmodified recombinant erythropoietin.

The established benefits of erythropoietin in CKD include improved quality of life and sense of well-being, boosted exercise tolerance, and elevated cognitive function. Correcting anemia has had such a dramatic impact on symptoms classically equated with progressive uremia that nephrologists often have difficulty convincing patients their CKD has advanced to the point of requiring dialysis.

In terms of cardiovascular improvements, some data indicate that erythropoietin can prevent further LV dilation. Small uncontrolled studies also show that correcting anemia may actually contribute to the regression of established LV dilation. Although these positive changes in a key surrogate marker of cardiovascular function are intriguing, larger studies in populations of patients prior to undergoing dialysis will be required to establish the actual clinical benefit. Similarly, although a retrospective cohort study indicates a survival benefit associated with early erythropoietin use in CKD patients, the confirmation of this potential benefit — and its potential mechanism — are still to be determined. Ongoing multicenter randomized trials now under way in both the United States and Europe should provide answers to these questions in about 2 years.

Despite the availability of an established treatment rationale and a goal for correcting anemia, as well as a highly effective therapy, many patients with CKD-related renal anemia remain untreated. Data from the USRDS show the mean hematocrit level at the start of dialysis in the year 2000 increased only 1% or 2% from the mean 28% level of the mid-1990s, well below the 33% to 36% goal. Thus, despite sustained educational efforts during several years, patients beginning dialysis still commonly present with a prolonged history of anemia that predisposes them to cardiomyopathy. Overall, only about 25% of patients with CKD who are beginning dialysis have received erythropoietin treatment. Even in those geographic regions where erythropoietin usage is highest (eg, the Northeast, the West Coast, Texas), only about one third of the patients receive key intervention that would impact their quality of life and long-term prognosis.
BEHIND THE ANEMIA TREATMENT GAP: UNDERDIAGNOSIS OF CKD

Because CKD is not accurately diagnosed, most patients with CKD do not receive appropriate therapy for renal anemia. In one review of hospital discharge records, of the 537 Medicare patients with diabetes or hypertension, 67 (12.5%) had serum creatinine levels of over 1.5 mg/dL. However, only 8 discharge summaries from these patients mentioned the presence of CKD. Such results highlight the consequences of the pervasive overemphasis on ESRD in medicine today. With attention and funding traditionally focused on end-stage kidney disease, early renal disease still lacks an effective disease management framework for detecting and controlling other chronic diseases such as diabetes and hypertension.

Disease management requires a simple and accurate test for diagnosing disease. Such a test is not available for detecting CKD, contributing to the disease's underdiagnosis. In many settings, serum creatinine remains the basic screening test for kidney disease, despite its poor ability to predict glomerular filtration rate (GFR). Proper interpretation of any serum creatinine test result requires a detailed knowledge of the patient's muscle mass, dietary intake, and medication use. Also, because the relationship between serum creatinine and GFR is exponential, the marked decrements in GFR associated with early CKD produce only very slight increases in serum creatinine.

Over-reliance on this poor screening test explains why many patients are referred to renal clinics with supposedly mild renal insufficiency when, in fact, they already have lost 50% or more of their kidney function. These difficulties in interpreting the serum creatinine assay are compounded by the nonspecific nature of symptoms associated with mild to moderate kidney damage and help to explain why this condition is so frequently underdiagnosed. However, as explained earlier, this early progressive period of CKD lays the groundwork for the accelerated mortality in patients once they require dialysis.

Estimated creatinine clearance is an improvement over the serum creatinine test. The Cockcroft-Gault formula, for example, is commonly used to calculate GFR based on a patient's age, weight, gender, and serum creatinine. The 24-hour urine collection method is also used; however, it is inconvenient and difficult to perform accurately in an ambulatory nonhospitalized patient. The MDRD equation, a new GFR estimation based on data from the Modification of Diet in Renal Disease study, is increasingly used. This equation shows excellent accuracy and good precision in calculating GFR; does not require a patient body weight as a variable; and works better for African Americans and females, as compared to the Cockcroft-Gault formula. Although the original 6-variable formula was a concern for many clinicians, the 4-variable MDRD equation is easier to use and still shows excellent accuracy with the patient equation (Table). Thus, some medical centers will use the creatinine result, along with the patient's age, gender, and race and will report an estimated GFR, a more informative indicator of renal status than is serum creatinine alone.

Improved recognition of anemia by generalists and specialists, while extremely important, represents only 1 aspect of the problem of undertreatment of renal anemia. The current Medicare (Centers for Medicare and Medicaid Services) reimbursement policy is an additional factor preventing the optimal management of renal anemia, even in patients who are appropriately diagnosed. In most instances, this policy requires that relatively severe anemia, with a hemoglobin of less than 11 g/dL, develops before epoetin therapy may be initially reimbursed — even though once therapy is started, the target hemoglobin goal thereafter is greater than 11 g/dL. Physicians are thus obliged to delay treatment until the patient's hemoglobin level drops below the target range, rather than commencing at the appropriate time so the hemoglobin can be maintained within the target range.

ANEMIA DEVELOPS EARLY IN CKD

With limited awareness and testing for early CKD, the detection of anemia in these patients has also been neglected. The Canadian cohort

Table. Modification of Diet in Renal Disease (MDRD) Equations*

| GFR(ml/min/1.73m²) = 170 x (SCr^-0.999 x (Age)^-0.176 x (SUN)^-0.170 x (Alb)^-0.318 x (0.762 if female) x (1.180 if black) |

GFR = glomerular filtration rate; SCr = serum creatinine; SUN = serum urea nitrogen; Alb = albumin.
* A simple calculator for MDRD GFR is now available online at http://www.nephron.com/cgi-bin/MDRD.cgi.
study cited earlier, for example, showed that a low GFR was a strong indicator of anemia in early renal disease (Figure 3).

Recent epidemiologic data from the Third National Health and Nutrition Examination Survey (NHANES) confirm the association between mild renal deficiencies and the development of anemia. This 1988 to 1994 survey, representative of the non-institutionalized US population, included over 15,000 subjects who were older than 20 years and had a serum creatinine measurement. The 4-question MDRD equation was used to convert serum creatinine results into estimated GFRs, which were then compared in a cross-sectional fashion with hemoglobin levels.

Approximately 31% of the surveyed population had mild renal insufficiencies, defined as a GFR between 60 and 90 mL/min/1.73 m². Extrapolated to the US population, the data indicate that 7.6 million individuals have mild renal disease. Another 4.3% of the NHANES population have moderate renal function, and 0.2% have severe renal insufficiency according to these calculated GFRs.

An analysis of the GFR relationship with anemia shows that median hemoglobin levels remain fairly stable until the GFR reduces to below 60 mL/min/1.73 m². Below this GFR cutoff, a level at which the unmodified serum creatinine result may remain within the population-based reference range, the prevalence of anemia increases significantly for some individuals, especially elderly patients with a low muscle mass. Based on these NHANES III data, for example, the probability of a man having anemia (defined by the World Health Organization as hemoglobin below 13 g/dL) is 7% at GFR 60, as compared to a probability of 12% at a GFR of 45 and 29% at a GFR of 30. Similar trends of increasing anemia can be seen in calculations for women and for anemia defined with

Figure 3. Anemia in Early Renal Disease

![Figure 3](image)

Data from the Canadian Multicenter Cohort Study (n=447).

Figure 4. The Prevalence of Anemia Increases Below GFR 60: NHANES Data from General US Population (Adjusted to Age 60 Years)

![Figure 4](image)

Source: Astor 2002
lower hemoglobin cutoffs (Figure 4). The multivariate logistic regression analysis shows that reduced renal function, as indicated by a GFR between 30 and 59 mL/min/1.73 m², was associated with a 2.5-fold higher odds of anemia in both men and women. For a GFR below 30 mL/min/1.73 m², the adjusted odds ratio is 36.9 in men and 44.9 in women. In addition to lower GFR, other factors strongly associated with anemia were older age, African American race, and iron deficiency.

These data are significant because they show a direct link between decreased hemoglobin level and kidney disease in the general population. In other words, anemia is not just a problem for those patients with advanced kidney disease. Even in the GFR range of 30 to 60 mL/min/1.73 m² — a grey zone through which most patients still pass silently and undetected — there are levels of anemia that are cause for concern. The results of large prospective studies are required to further define the relations between early CKD, anemia, and key clinical outcomes.

CONCLUSIONS

In summary, anemia develops in CKD long before dialysis is needed. In most cases, renal anemia will be present for prolonged periods before it or the underlying presence of kidney insufficiency is recognized. Even in hospitalized patients who are anemic and have moderately elevated creatinine levels, the diagnosis of early renal failure will often be missed, perhaps shrouded by the ubiquitous (and useless) diagnosis of anemia of chronic disease. These cases are missed opportunities to recognize and treat anemia, a serious and preventable complication of renal disease. While renal anemia is associated with increased morbidity and mortality, the available treatments for this common condition are highly effective. By detecting and correcting the anemia of CKD in its earliest stages, clinicians have the opportunity to improve the cardiovascular outcomes of these patients.

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REFERENCES

1. US Renal Data System. USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, Md; 2002. (The data reported here have been supplied by the United States Renal Data System [USRDS]. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.)


