The High Prevalence of Anemia in Diabetes Is Linked to Functional Erythropoietin Deficiency

Merlin C. Thomas

Anemia is a common finding in diabetes, particularly in patients with albuminuria or renal impairment. We recently showed that at least 1 in 5 outpatients with type 1 or type 2 diabetes in tertiary clinics have anemia, in whom it constitutes a significant additional burden. Anemia is associated strongly with an increased risk of diabetic complications including nephropathy, retinopathy, and heart failure. Although a number of factors contribute to an increased prevalence of anemia in diabetes, an uncoupling of hemoglobin concentration and renal erythropoietin synthesis associated with tubular dysfunction appears to be the dominant factor. In our patients with diabetes and anemia, more than three quarters had functional erythropoietin deficiency. This association was most pronounced in patients with renal impairment, in whom nearly half of all patients had anemia. However, 70% of anemic patients without renal impairment also had inappropriately low erythropoietin levels. Consequently, the likelihood of functional erythropoietin deficiency, as a cause of anemia in patients with diabetes, is not dependent on the severity of renal impairment. Although there is a clear rationale for correction of anemia in diabetes, it remains to be established whether this will lead to improved outcomes. Some small studies suggest improvement in cardiac outcomes and hospitalization. It is anticipated that large ongoing studies will help define the optimal approach to the management of anemia in diabetes.

Semin Nephrol 26:275-282 © 2006 Elsevier Inc. All rights reserved.

KEYWORDS anemia, diabetes, diabetic nephropathy, hemoglobin, microvascular disease

Anemia is a common finding in patients with chronic kidney disease (CKD).1 This reflects the pivotal role of the kidney in the control of hemopoiesis, in sensing changes in tissue oxygenation, and subsequently in stimulating hemopoietic precursors in the bone marrow through the production of erythropoietin by peritubular interstitial fibroblasts of the renal cortex and outer medulla. Uremia is associated with a range of hemopoietic stressors including reduced red cell survival, occult blood losses, malnutrition, and systemic inflammation. However, the failure of the kidney to increase erythropoietin release in response to a decreasing hemoglobin (Hb) level appears to be the key contributor to the development of renal anemia.2-3 There is a direct relationship between the severity of the anemia and the decrease in renal function. A significant increase in the prevalence of anemia can be shown when the glomerular filtration rate (GFR) decreases to less than 70 mL/min/1.73m2 among men and less than 50 mL/min/1.73m2 in women.4 Although anemia may be seen in CKD regardless of the underlying renal disease, anemia is more common overall in nonglomerular renal diseases than in chronic glomerulonephritis.5 In addition, anemia is more common in patients with diabetic nephropathy.6 Anemia also develops significantly earlier in patients with diabetes, with the Hb concentration decreasing significantly when the GFR decreases to less than 90 mL/min/1.73m2 in men with diabetes and less than 70 mL/min/1.73m2 in women (Fig 1). This review examines recent evidence on the role of functional erythropoietin deficiency in the anemia of diabetic nephropathy, and its potential consequences for patient morbidity and mortality in diabetes.
In normal health, the kidney maintains an inverse relationship between plasma erythropoietin activity and Hb concentration. For example, a moderate reduction in Hb level resulting from blood loss of less than 500 mL is sufficient to increase erythropoietin messenger RNA and active erythropoietin expression in renal cells. In patients with anemia and CKD, renal erythropoietin production is uncoupled from the Hb concentration. Instead of increasing exponentially with a decreasing Hb concentration, erythropoietin levels in patients with CKD and anemia inappropriately remain in the normal range. This state may be defined as functional erythropoietin deficiency because erythropoietin levels conceivably could be adequate to maintain the Hb concentration in the normal range. However, in the setting of requirements for increased hemopoiesis and erythropoietin resistance associated with uremia, the compensatory renal response is overtly deficient.

Functional erythropoietin deficiency also appears to be a major contributor to anemia in individuals with diabetes, with and without nephropathy. For example, in a cross-sectional survey of more than 800 patients with diabetes in our clinic, we found that approximately 21% of patients had anemia, as defined by the World Health Organization criteria of a Hb concentration less than 12 g/dL in women and less than 13 g/dL in men. In these patients, we found that more than three quarters (78%) of the patients had erythropoietin levels that were the same as patients with diabetes without anemia, denoting functional erythropoietin deficiency (Fig 2). Clearly, most of the patients with functional erythropoietin deficiency had moderate to severe renal impairment and/or albuminuria (78%, n = 93/119). Similarly, 83% (n = 73/88) of patients with renal failure and anemia had erythropoietin levels that inappropriately remained within the range considered normal for patients without anemia (Fig 3). This finding is consistent with the key role of the diabetic kidney in the development of anemia associated with diabetes. Indeed, most diabetic patients with anemia can be identified readily by the presence of diabetic renal disease, manifested as impaired renal function and/or increased albuminuria. Overall, in our population, 60% of patients with World Health Organization–defined anemia had a GFR of less than 60 mL/min/1.73m2 and nearly half of all individuals (n = 88/185) with moderate to severe renal impairment or those with patients with macroalbuminuria (46%) were anemic.

However, unlike other forms of renal disease, moderate to severe renal impairment is not required for the development of anemia or functional erythropoietin deficiency. Even in anemic patients without renal impairment, more than 70% of those with anemia also had erythropoietin levels that remained inappropriately within the normal range. This finding is consistent with findings from other groups in which, even in the absence of overt renal disease, functional eryth-
ropoietin deficiency appears to be a key contributor to the pathogenesis of anemia. Because the likelihood of functional erythropoietin deficiency as a contributor to anemia in patients with diabetes is not dependent on the severity of renal impairment, prescribing restrictions that limit the use of erythropoietin solely to patients with severely impaired renal function regardless of the Hb concentration clearly is problematic. Moreover, because most patients with diabetes and proteinuria do not survive long enough to develop severe renal impairment, a high-risk group that clearly has demonstrable renal damage (and functional erythropoietin deficiency therein) may be missing out on appropriate interventions.

**Diabetic Tubulopathy and Anemia**

Diabetic renal disease originally was described as a glomerulopathy associated with diffuse or nodular glomerulosclerosis. However, fewer than one third of diabetic patients with microalbuminuria have this typical glomerulopathy. Moreover, it is now apparent that functional and structural changes in the proximal tubule and cortical interstitium, so-called diabetic tubulopathy, are more than just the aftermath of diabetic nephropathy. They may, in fact, be better correlated with progression of diabetic nephropathy than the classic changes of the Kimmelstiel-Wilson lesion. The dysregulation of tubular functions in diabetes may proceed on a number of levels, and compromise diverse actions including salt reabsorption, activation of the intrarenal renin angiotensin system, and apical and basolateral transport of organic molecules. The tubular synthesis of key physiologic mediators such as the circulating antioxidant, glutathione peroxidase, also is disrupted in the diabetic kidney, contributing to increased renal oxidative stress. Although the precise mechanisms by which diabetes impairs the renal erythropoietin response to reduced Hb levels remains to be established, in this setting it is hardly surprising that diabetic tubulopathy also is able to disrupt the delicate interaction between interstitial fibroblasts, capillaries, and tubular cells required for normal hemopoietic function within the kidney.

Diabetes is associated with a common pattern of interstitial fibrosis and nephron drop-out that ultimately characterizes advanced CKD of any cause. However, similar to anemia, tubulointerstitial damage in diabetes also may be seen, independent to and in advance of late changes of decreasing GFR. For example, thickening and reduplication of the tubular and epithelial basement membrane can be observed readily in the early diabetic kidney, even among normoalbuminuric patients. Maladaptive tubular hypertrophy in the diabetic kidney is followed by progressive and cumulative atrophy of tubular epithelial cells. Renal tubular cells also may lose their epithelial phenotype in response to injury and local activation associated with diabetes, and acquire features characteristic of a mesenchymal cell (tubular epithelial-mesenchymal transition). Stagnation of blood flow in peritubular capillaries, tubulointerstitial fibrosis, and, ultimately, loss of peritubular capillaries also is observed in the early diabetic kidney. It is conceivable that cumulatively these changes may disrupt hemopoietic functioning in the kidney. Indeed, endogenous erythropoietin production has been suggested as a marker of the severity of tubulointerstitial damage in diabetes.

**Uncoupling of Erythropoietin Synthesis in Diabetes**

In some patients with diabetes and anemia, the renal capacity to produce erythropoietin is not simply abolished because the erythropoietin response to hypoxia may be preserved, even though erythropoietin levels are inappropriately low for their degree of anemia. This finding, together with the fact that erythropoietin levels remain in the normal range in most patients with diabetes and anemia, suggests that erythropoietin synthesis and release pathways are not simply lost in the diabetic kidney, but rather are uncoupled from changes in the Hb concentration (Fig 4). This uncoupling of the Hb-erythropoietin–feedback mechanism may be considered phenomenologically similar to impaired glucose sensing in diabetic islets, which may respond normally to acute stimulation with arginine or tolbutamide but inappropriately to a chronic hyperglycemia.

The mechanisms leading to the uncoupling of erythropoietin synthesis and hemopoiesis in diabetes remain to be established. However, it may be that continued hypoxic stress in the diabetic kidney has an important role in reducing its sensitivity to changes in Hb levels and other hemopoietic stressors. For example, the formation of radical species associated with nephron loss can induce degradation of hypoxia inducible factor (HIF)1-α, negatively influence erythropoietin gene expression, and thereby regulate the molecular adaptation of tubular cells to hypoxia. Increased energy demands in the diabetic kidney, associated with salt retention, also may serve to induce a functional hypoxia in the tubulointerstitium. Certainly, erythropoietin levels are correlated with fractional sodium reabsorption in the context of diabetic nephropathy, and blockade of proximal tubular reabsorption by acetazolamide causes a decrease in erythropoietin.
levels in normal individuals. Decreased Hb levels and increased sodium reabsorption therefore might represent opposing stimuli for erythropoietin production in the diabetic nephron, potentially resulting in normal erythropoietin levels as a counterbalance to salt retention, but at the expense of anemia.

At a local level, inflammatory cytokines and the accumulation of oxidized nucleic acids, endogenous polyamines, cobalt, and tryptophan metabolites may inhibit the production of erythropoietin in the diabetic kidney. We recently showed that advanced glycation end products, which are formed as a result of chronic hyperglycemia and oxidative stress, also are linked to Hb levels in diabetes. It also has been suggested that erythropoietin deficiency in patients with diabetes may result from autonomic dysfunction. Previous studies have found a strong correlation between polyneuropathy and the development of anemia in diabetes. Splanchnic denervation, as occurs in diabetes, is known to be associated with blunted production of erythropoietin in response to hypoxia. However, polyneuropathy also may be correlated closely with other diabetic complications, including nephropathy, making it difficult to separate cause from effect. Nonetheless, this hypothesis is supported by observations that patients with primary autonomic failure also have impaired erythropoietin release and an increased risk of anemia.

**Other Contributors to Anemia in Patients With Diabetes**

Although the uncoupling of erythropoietin production and the Hb concentration in diabetes appears to be a key component for the pathogenesis of anemia, it is not the only one. Because erythropoietin levels remain in the normal range and are not reduced, there must be additional hemopoietic stressors that reduce the Hb level in the first place. Nonetheless, if other primary (nonrenal) causes, such as iron deficiency, reduced red cell survival and resistance to erythropoietin, are to be invoked on their own, erythropoietin levels should be increased as the kidney attempts to compensate for decreasing tissue oxygenation. Therefore, it is likely that some combination of factors leads to a progressive decrease in Hb levels in diabetes. Moreover, it is conceivable that in the setting of impaired compensation by the diabetic kidney, even relatively minor changes in red cell turnover or substrate availability are sufficient to reduce Hb concentrations.

Patients with diabetes have several metabolic and functional abnormalities of their red blood cells including reduced erythrocyte survival and senescence. Diabetes also is associated with a number of potential sources of occult blood loss including gastritis, cancer, and hemoglobinuria. Patients with diabetes also may be faced with a large number of blood tests as part of their routine management, and regular self-assessment of glycemic control may contribute to blood loss. However, in our studies the Hb level in patients with diabetes was independent of the cumulative amount of blood drawn by venipuncture.

**Added Impact of Anemia in Diabetes**

A reduced Hb concentration, even within the normal range, identifies patients with diabetes at increased risk for hospitalization and premature death. However, because anemia for the most part may be considered a manifestation of renal injury, it is easy to see why diabetic patients with anemia (and therefore more severe end-organ damage) may be more prone to complications, without needing to invoke any direct consequences of a reduced Hb concentration. Nonetheless, untreated anemia is known to contribute to functional morbidity, including impaired cognitive function, poor sleep,
anorexia, depression, and reduced sexual function in patients with CKD. Physical activity, an important predictor of adverse outcomes and reduced quality of life in diabetes, is affected directly by the Hb concentration, contributing to tiredness, fatigue, and reduced physical independence.30 Moreover, those patients with diabetes and anemia are the same ones that have kidney disease, macrovascular complications, heart failure, and retinopathy. Consequently, anemia in these individuals comes as an unwelcome and additional burden. There also are data to suggest anemia directly may influence the development and progression of diabetic complications, which are detailed later.

Anemia and Diabetic Kidney Disease

More than 5% of newly diagnosed patients with type 2 diabetes already will have diabetic kidney disease and a further 30% to 40% will develop diabetic nephropathy, mostly within 10 years of diagnosis.31 For the hundreds of millions with diabetes worldwide, nephropathy constitutes one of the major risks for premature mortality. Anemia has been reported to be an important risk factor for progression to end-stage renal disease (ESRD) in patients with CKD, with or without diabetes.29,32,33 But does anemia (and, more importantly, the correction of anemia) actually modify the progression of diabetic renal disease? Clearly, anemia per se does not cause microvascular injury in the kidney or result in ESRD. However, there is some evidence to suggest that anemia may modulate the activity of pathways that lead to progressive renal damage in diabetes.

Hypoxia arising from anemia may have a variety of mitogenic and fibrogenic effects on the kidney, associated with expression of multiple growth factors, hormones, vasoactive reagents, and enzymes.34 HIF-1α regulates genes involved in angiogenesis (such as the prosclerotic mitogen, vascular endothelial growth factor), vasomotor response (inducible nitric oxide synthase, heme oxygenase-1, and endothelins), glycolysis (the glucose transporter GLUT-1 and glycolytic enzymes), matrix metabolism (transforming growth factor-β1, collagens, matrix metalloproteinases), and cell survival.35 all pathways implicated in the pathogenesis of progressive diabetic kidney disease. Hb levels also are correlated closely with oxidative stress because erythrocytes represent a major antioxidant component of the blood. Functional erythropoietin deficiency also may be important for tubular growth and development, angiogenesis, and response to injury in diabetes because erythropoietin has a range of renoprotective actions. It is conceivable that in the setting of diabetes, the combination of tissue hypoxia, oxidative stress, and reduced renoprotection associated with erythropoietin deficiency may act to enhance renal damage in the diabetic kidney.

There have been several small prospective clinical studies involving diabetic patients with advanced nephropathy in which correction of anemia with exogenous erythropoietin partly was able to attenuate the deterioration of renal function.36,37 This effect was overall less prominent in diabetic compared with nondiabetic patients, possibly reflecting the key adjunctive role of other nonrenal factors in the anemia associated with diabetes. More recently, 2 large studies, specifically in patients with diabetes and pre-ESRD (cardiovascular risk reduction by early anaemia treatment with epoetin beta (CREATE) and correction of haemoglobin and outcomes in renal insufficiency (CHIOR), failed to show any renoprotective actions arising from anaemia correction (unpublished data). The potential use of anemia correction in patients with earlier-stage renal injury will be tested in the ongoing trial to reduce cardiovascular events with aranesp therapy (TREAT) study.38 Because most patients with diabetic nephropathy do not survive long enough to develop ESRD, targeted intervention in these patients would seem more logical than delayed intervention in selected survivors with advanced disease. However, evidence for any direct action of anemia in clinical diabetic nephropathy is lacking.

Anemia and Macrovascular Disease

Patients with diabetes and CKD are 20 times more likely to have a cardiovascular event than to develop ESRD. In the general population, a decrease in mean Hb concentration is associated independently with an increase in cardiovascular disease, stroke, and premature mortality. Patients with ischemic heart disease and anemia also are more likely to have an advanced degree of ischemic heart disease (IHD), congestive heart failure (CHF), rhythm disturbance, and a higher mortality rate than those with a Hb concentration in the normal range.39 Consequently, the additional burden of anemia also may be significant in determining the outcome of the hypoxia-induced organ damage in patients with diabetes and macrovascular disease. Although anemia does not cause atherosclerosis, it is conceivable that pre-existing tissue hypoxia may be accentuated by a reduction in the oxygen-carrying capacity of the blood or an increase in cardiac work and activation of the sympathetic activity related to anemia. In diabetes, cardiac ischemia often is silent, so that the potential contribution of anemia to myocyte loss and progressive fibrosis, associated with the diabetic heart, is difficult to assess. However, in patients with diabetes at our center, the prevalence of vascular complications was increased significantly in patients with anemia, regardless of cause and whether or not their erythropoietin levels were increased.3 This finding suggests that anemia per se is an independent risk factor for macrovascular disease in diabetes.

It is important to note that some studies have suggested that limited reductions in the hematocrit level may have a protective influence on cardiovascular mortality. For example, cardiovascular survival is improved in women and blood donors. Anemia is associated with decreased afterload owing to vasodilatation and reduced vascular resistance as a consequence of lower blood viscosity, hypoxia-induced vasodilation, and enhanced nitric oxide activity. Correction of anemia, on the other hand, may be associated with increased peripheral vascular resistance. Some retrospective studies
Anemia is a potent adverse risk factor for new-onset heart failure, and a marker for poor outcomes in patients with established cardiac dysfunction, even after adjusting for conventional risk factors. In a study of survival of patients with heart failure, the Hb level at the time of initial diagnosis of heart failure was a significant predictor of survival. Although a causal link remains to be established firmly, there is some evidence that anemia may contribute independently to the irreversible changes in cardiac function that is characteristic of patients with diabetes. Certainly, chronic anemia results in increased cardiac output, volume overload, increased heart rate, and, ultimately, progressive left ventricular hypertrophy and diastolic dysfunction. A modest decrease in Hb level (10.5 g/dL) may be associated independently with a 33% increase in LVH. At least a partial regression of left ventricular hypertrophy (LVH) may be possible after the correction of anemia in CKD. When anemia-related LVH develops in an otherwise healthy humoral environment, the lesions are reversible and the type of LVH primarily is physiologic and not associated with impaired diastolic function. However, in the setting of diabetes, cardiac remodeling may be maladaptive and ultimately contribute to cardiac dysfunction.

The use of anemia correction in individuals with heart failure is currently the matter of large and ongoing studies. Some small prospective studies, performed in diabetic patients with moderate renal impairment, already have shown an improvement in cardiac function with regression of left ventricular mass after erythropoietin treatment. In addition, there is evidence that the number of hospitalizations may be reduced by correction of anemia in diabetes. Correction of anemia also may play a significant role in improving exercise tolerance and patient well-being as well as maintaining patients in a community setting.

Should Functional Erythropoietin Deficiency Be Treated?

Our studies indicate that 7% to 8% of ambulatory patients with diabetes in tertiary clinics have a Hb concentration of less than 11 g/dL. Once iron deficiency is excluded, almost all of these patients have functional erythropoietin deficiency and consequently would be responsive to supplementation with erythropoietin or related analogues. But should functional erythropoietin deficiency in anemic patients with diabetes be treated? On the basis of currently available evidence, correcting anemia in these patients would improve their quality of life, their ability to work, their exercise tolerance, and their cognitive and sexual functioning. Considering that these are severely incapacitated patients who carry the burden of a number of diabetic complications, including the liability of a shortened life expectancy, it has been suggested that, in these circumstances, a performance-enhancing drug may be completely appropriate. However, any potential advantages must be balanced against the substantial costs involved in treating anemia—and the possibil-
ity for deleterious effects from erythropoietin such as increased blood pressure, blood viscosity, and peripheral vascular resistance. Iron supplementation also may impact negatively on glycemic and lipid control and contribute to oxidative injury in diabetes. It is hoped that upcoming trials involving the early correction of anemia in patients with diabetes will help clarify the optimal approach to this disorder. In the meantime, the detection of anemia should be used to identify those patients who are at increased risk of adverse clinical outcomes. Good metabolic and blood pressure control are still the best known way to prevent anemia by averting renal damage at the outset.

References

34. Fine LG, Bandyopadhay D, Norman JT: Is there a common mechanism for the progression of different types of renal diseases other than proteinuria? Towards the unifying theme of chronic hypoxia. Kidney Int Suppl 75:S22-S26, 2000