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Anemia, Renal Transplantation, and the Anemia Paradox

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Anemia is prevalent in renal transplant recipients (RTRs), as it is in all chronic kidney disease (CKD) populations. Mild anemia occurs in up to 40% of RTRs, and more severe anemia (110 g/L) occurs in about 9% to 22% of patients. As in CKD, impaired graft (renal) function is a major predictor of anemia identified in nearly all studies, suggesting a major role for erythropoietin deficiency. Chronic inflammation, malnutrition, iron deficiency, and medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mycophenolate, azathioprine, and sirolimus) are contributory factors seen in some, but not all, studies. Although pathophysiologic and observational data strongly support a causal association between low hemoglobin levels and cardiovascular outcomes in RTRs, no randomized controlled trial to date has been able to show a clear benefit of anemia treatment on cardiovascular outcomes or mortality in either RTR or other CKD populations. This important paradox has led some investigators to question the causal nature of the association between anemia and heart disease. Resolution of this paradox, at least for patients with stage 2/3 CKD, will depend on the outcome of randomized controlled trials currently in progress. Similar trials sorely are needed in renal transplant populations. In the interim, current opinion favors treating persistent anemia in RTRs to achieve targets similar to those recommended for dialysis and CKD patients.
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Anemia is a common complication of chronic kidney disease (CKD), but until recently its importance among renal transplant recipients (RTRs) has been underappreciated. Several lines of evidence suggest that anemia is an important risk factor for cardiovascular morbidity and mortality in various CKD populations. Anemia may affect cardiac and vascular structure via several proposed mechanisms. Observational studies have suggested a strong relation between anemia and cardiovascular outcomes. Nonrandomized interventional studies have observed improvement in cardiac structure and function and in quality of life. However, most randomized clinical trials of anemia treatment have failed to observe the benefit predicted by observational and nonrandomized studies. The present article discusses the clinical burden and possible importance of anemia in RTRs, and some of the major controversies in the field of renal anemia.

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Clinical Epidemiology of Anemia in RTRs: Burden and Risk Factors

The prevalence of anemia in RTRs varies between 15% and 40% depending on several factors including the definition of anemia, the timing of the measurement with respect to transplantation, and the population studied.

Vanrenterghem et al[1] conducted a cross-sectional survey of more than 4,000 RTRs in Europe who were transplanted 6 months, 1, 3, or 5 years before study enrollment [Transplant European Study on Anemia Management (TRESAM) study]. Anemia was defined as a hemoglobin (HGB) concentration of less than 130 g/L in males and less than 120 g/L in females. Thirty-nine percent (39%) of patients in the entire cohort had some degree of anemia. The prevalence of severe anemia, defined as a HGB level of less than 110 g/L in males or less than 100 g/L in females, was 8.5%. The mean HGB level was

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similar in the 6-months, 1-, 3-, and 5-year cohorts. The level of graft function was the dominant correlate of anemia; a serum creatinine level of more than 2 mg/dL conferred a 3- to 4-fold increase in the odds of having anemia independently of other variables. Other factors associated with low hemoglobin level were age, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers, mycophenolate (MMF) or azathioprine treatment, and infection. Polycystic kidney disease was associated with lower odds of anemia.

Fernandez-Fresnedo et al[2] reported on the prevalence of anemia in a cohort of more than 2,000 prevalent Spanish RTRs. Anemia was defined as a HGB level of less than 120 g/L in men or less than 110 g/L in women. The prevalence of anemia was 23% in men and 22% in women. Besides gender, graft function and MMF use were associated with anemia in a cross-sectional analysis.

Molnar et al[3] reported on the prevalence of anemia in a cross-sectional analysis of 959 prevalent RTRs in Hungary. Twenty-seven percent of patients met the definition of mild to moderate anemia in that study (HGB level, 100-120 g/L in females, 110-130 g/L in males), and 7% met the definition of severe anemia (<100 g/L in females, <110 g/L in males). Eleven percent of patients had a HGB level of less than 110 g/L, the lower target of HGB level for patients on dialysis. On multivariate analysis, estimated glomerular filtration rate (GFR), serum albumin, and transferrin saturation were the only independent predictors of anemia.

Lorenz et al[4] conducted a cross-sectional analysis of 438 prevalent RTRs in Austria. The prevalence of anemia, as defined in the 2 studies cited earlier, was 40%, while 16% of patients had a HGB level of less than 110 g/L. Again, low GFR showed the strongest association with low HGB level, suggesting a primary role for renal erythropoietin (EPO) deficiency. Other variables independently associated with lower HGB levels on multiple linear regression were as follows: female gender, EPO therapy, azathioprine use, high serum ferritin level, low serum transferrin level and low transferrin saturation, low body mass index, diagnosis of polycystic kidney disease, and older age. These associations provide evidence for the role of inflammation (increased ferritin levels), malnutrition (low body mass index), iron deficiency (low transferrin level, low transferrin saturation), and antimetabolite use (MMF, azathioprine) as additional risk factors for anemia. The association of EPO therapy with lower, rather than higher, hemoglobin levels in this study likely represented confounding by indication because low hemoglobin values provided the primary indication for starting EPO.

Winkelmayer et al[5] observed an overall prevalence of anemia (hematocrit [Hct] level < 33%) of 29% in 374 prevalent RTRs studied at a median of 7.7 years after transplantation. The major cross-sectional predictors of low Hct level were female gender, increased serum creatinine level, ACEI use, mycophenolate use, and tacrolimus use.

Mix et al[6] performed a retrospective cohort study on 240 prevalent RTRs in Boston to document temporal changes in the prevalence of anemia after transplantation. In their study, the prevalence of anemia (defined as Hct level < 36%) decreased from 76% at 1 month after transplantation to 21% at 1 year after transplantation, increasing again to 36% at 4 years after transplantation. Severe anemia (Hct level < 30%) was much less frequent, present in 20% of RTRs at 1 month but only 5% of RTRs at 1 and 4 years after transplantation. Cross-sectional analyses revealed the following univariate associations with occurrence of anemia (Hct level < 36%) at 6 months after transplantation: female gender, cytomegalovirus D+/R- status, nondiabetic status, and GFR at 3 months. However, female gender was the only predictor on multivariate analysis. At 1 year, similar univariate associations were found, whereas GFR at 6 months was the only multivariate association with anemia.

Mild anemia is common among RTR. Anemia prevalence is greatest immediately after transplantation, reaching a nadir at 6 months to 1 year, coincident with restoration of normal EPO secretion in the allograft. The prevalence then increases again after several years, presumably due to the increasing prevalence of chronic allograft nephropathy (CAN). Severe anemia that would meet current thresholds for EPO treatment in dialysis and nontransplant CKD (HGB level < 110 g/L or Hct level < 33%), occurs in 9% to 20%. The major determinant of anemia, at least cross-sectionally, is functioning renal mass, as estimated by GFR or creatinine level. In this sense, posttransplant anemia resembles anemia in CKD. Additional contributing factors appear to be inflammation; malnutrition; iron deficiency; medication use, in particular renin angiotensin system (RAS) antagonists (ACEI or angiotensin receptor blocker) and antimetabolites (MMF or azathioprine); and chronic viral diseases such as cytomegalovirus.

Anemia: A Risk Factor for Cardiovascular Disease

Possible Mechanisms

Effects on cardiac and vascular remodeling

Anemia appears to exert a primary effect on cardiac and vascular remodeling, with additional effects on endothelium and atherosclerosis.

Chronic anemia causes relative tissue hypoxia, leading to vasodilatation and a decrease in blood pressure. This triggers a neurohormonal response, with increased sympathetic drive and RAS activation.[7] The proximate cardiac consequences are an increase in heart rate and stroke volume, the latter achieved initially by an increase in the fractional shortening of the myocyte. In the kidneys, RAS activation leads to salt and water retention, diluting HGB levels further. Increased cardiac output as a result of the neurohormonal response and plasma volume expansion increases venous return, causing a primary myocardial stretch stimulus. The cardiomyocyte responds to this stimulus by adding sarcomeres in series, increasing myocyte length and thus increasing the volume of the heart cavities.[8,9] By Laplace's law, an increase in cavity dimensions necessarily results in an increase in wall stress, which in turn stimulates the cardiomyocyte to add sarcomeres in parallel, augmenting the cross-sectional area of the myocardium and returning wall stress back to normal. Ane-

mia thus promotes a form of eccentric left ventricular hypertrophy, characterized by primary cavity enlargement and a secondary parietal thickening in response to increased wall stress. These changes initially are adaptive, returning wall stress and fractional shortening back to normal values.[10] Hypertrophy, however, exacts its price because the hypertrophied myocardium is not normal and is characterized by a decreased capillary to myocyte ratio,[11] accelerated myocyte apoptosis,[12] impaired subendocardial perfusion,[8,10] and increased oxidative stress.[13,14] These derangements can promote progressive cardiomyocyte attrition and interstitial fibrosis, resulting in further hypertrophy and wall stress. Uremia and its derangements, such as hyperparathyroidism[15] and increased oxidative stress,[13] can contribute further to myocyte death. A progressive downward spiral of cardiac function can result, leading to heart failure and death.

In the conduit arteries, chronically increased stroke volume and blood flow result in dilation and medial thickening of the arterial walls by processes similar to those occurring in the ventricle. This stiffens the conduit arteries, increasing the velocity and amplitude of the reflected arterial pulse wave, and thus augmenting systolic and diminishing diastolic pressure. The increase in systolic pressure worsens left ventricular (LV) afterload and thus further exacerbates the stimulus to LV hypertrophy, whereas the decrement in diastolic pressure compromises coronary perfusion, which occurs during diastole.[16]

The complement of an increased reflected wave is a decreased conducted wave perfusing the tissues, which theoretically can compromise distal perfusion even in the absence of arterial occlusion.

Anemia and oxidative stress

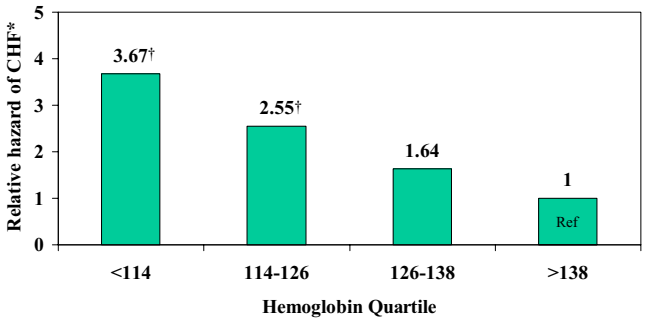
Anemia is associated with increased oxidative stress.[17] In evolutionary terms, hemoglobin-like compounds likely arose as a potent mechanism to bind oxygen and thus mitigate oxidative stress in primordial organisms. Oxidative stress is an important feature of cardiac failure, and abrogation of oxidative stress improves cardiac function in animal models of overload cardiomyopathy.[18-23] Oxidative stress also promotes atherosclerosis via endothelial injury and lipid oxidation[24-26].

EPO deficiency and cardiovascular disease

Transplant anemia is, inter alia, a reflection of inadequate renal EPO secretion. EPO recently has been shown to increase circulating endothelial progenitor cells. These cells have been shown to be involved in vasculogenesis and repair. Decreased number and/or function of endothelial progenitor cells has been associated with increased cardiovascular event rates in several settings, including uremia.

Cardio-renal-anemia syndrome

Iaina et al have pointed out the heightened sensitivity of the failing heart to anemia.[27] Experimentally, congestive heart failure (CHF) can develop with milder anemia than is the case with normal hearts.[28,29] Clinically, both anemia and reduced GFR are associated with CHF. CHF can induce anemia and reduce GFR. Anemia can exacerbate CHF and may worsen renal function. Finally, renal function can contribute to volume stress on the heart and anemia. These 3 positive-feedback loops constitute the cardio-renal-anemia syndrome and can result in a downward clinical spiral. The treatment of anemia in this setting appears to improve symptoms and reduce mortality.[30]



* Adjusted for age, diabetes, systolic blood pressure, donor status, and serum albumin
† p<0.03 with respect to reference quartile
Adapted from Rigatto et al. See reference 42 in text

Figure 1 Relative risk of de novo CHF as a function of hemoglobin quartile. *Adjusted for age, diabetes, systolic blood pressure, donor status, and serum albumin level. †$P < .03$ with respect to reference quartile. Adapted from Rigatto et al.[42] (Color version of figure is available online.)

Clinical Studies

Observational studies in RTRs

Anemia has been shown to be a risk factor for cardiac disease in many clinical settings. Anemia has been associated with LV dilation and LV hypertrophy in chronic renal insufficiency and in dialysis patients [relative risk for left ventricular hypertrophy (LVH) progression, per 10 g/L decrease, is 1.74 in CKD and 1.48 in dialysis].[31-36] Anemia is also a risk factor for the development of de novo cardiac failure and death in dialysis.[33,37] Partial correction of anemia is associated with regression of hypertrophy in cohort studies.[38,39] Several newer studies have shown that anemia increases the risk of cardiovascular disease in patients with CKD.[40,41]

Relatively few studies have examined the impact of anemia on cardiovascular outcomes in RTRs. Rigatto et al[42] documented the impact of anemia on de novo CHF in a cohort of 638 RTRs transplanted in Manitoba and Newfoundland, Canada. The incidence of CHF was 1.26 per 100 patient-years of observation. CHF was associated with a 2-fold increase in mortality, and was as lethal an event as de novo ischemic heart disease. Anemia was a major risk factor for the development of CHF and all-cause and cardiovascular death. The relationship between hemoglobin level and the risk of CHF was smoothly progressive for any hemoglobin level that was less than normal. The risk was highest for patients in the lower hemoglobin quartiles (hemoglobin level < 126), indicating that even modest hemoglobin reductions might be associated with cardiac morbidity (Fig 1). In a subsequent analysis, the investigators documented a direct link between electrocardiographic LVH, anemia, and CHF in kidney graft recipients.[43] These observations can be integrated into a causal framework as shown in Fig 2. Under this hypothesis,

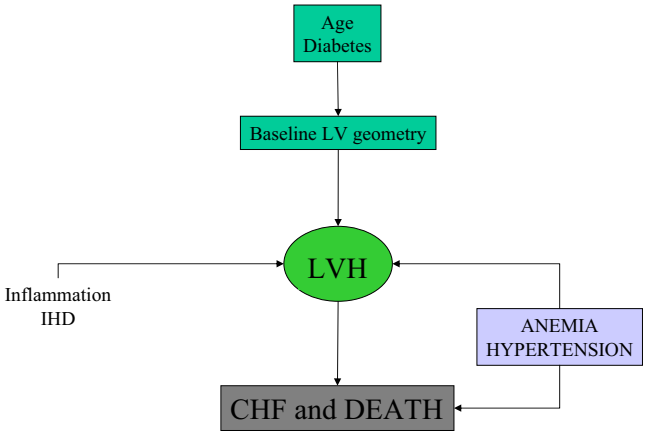


Figure 2 Pathogenesis of CHF in RTRs: a hypothesis. Adapted from Rigatto et al.[43] (Color version of figure is available online.)

anemia (and hypertension) promote ventricular growth and remodeling, leading to CHF and death.

Djamali et al[44] studied a cohort of 404 type 1 diabetics receiving either a kidney or kidney–pancreas transplant. They reported that anemia in the first 30 days after transplant was associated significantly with cardiovascular events occurring in the first 6 months after transplantation.

Randomized controlled trials

There are as yet no randomized controlled trials of anemia management in RTRs. Therefore, it is necessary to generalize from other populations.

Despite strong observational data suggesting smooth, graded, inverse associations between hemoglobin level, LVH, CHF, and death in dialysis, CKD, and RTR, most randomized controlled trials (RCTs) have failed to show a clear benefit of anemia treatment on cardiovascular event rates or mortality in renal patients. Early RCTs of anemia management compared EPO treatment with no EPO therapy.[45-48] The mean hemoglobin levels in the control groups typically were 70 to 80 g/L versus 100 to 110 g/L in the EPO treatment groups. A clinically important observation was a reduction in transfusion requirements (with a resultant reduction in risk of viral transmission and HLA allosensitization). A landmark study also showed improvements in quality of life and exercise capacity.[45] These results form the only basis for current recommended anemia treatment targets (HGB level, 110-120 g/L) in dialysis patients. Importantly, none of these studies either observed, or was powered to observe, a survival benefit of anemia correction. A recent RCT in CKD patients did detect an improvement in decrease in GFR with early versus delayed anemia management, but this trial was not powered to detect differences in cardiovascular disease event rates or mortality.[49]

More recent trials have compared partial (HGB level, 110-120 g/L) correction versus normalization (HGB level, 130-140 g/L) of anemia. In the landmark trial by Besarab et al,[50] no improvement in mortality was observed with normalization of hemoglobin in dialysis patients (n = 1,233). In fact, the trial was stopped early because of a persistent trend toward higher mortality rates in the normalization group. Patients included in this trial were older and had more cardiac disease than the average dialysis population. It was hypothesized that this group might be incapable of benefiting from anemia normalization because of the presence of advanced irreversible heart disease. A subsequent RCT performed by Parfrey et al[51] examined this hypothesis by studying whether normalization of HGB levels could arrest or reverse ventricular dilation and hypertrophy in dialysis patients without symptomatic heart disease at baseline. No differences in left ventricular volume index or mass index were observed between the partial and full anemia correction groups over the 72-week follow-up period. Levin et al[52] compared low (HGB level, 90-105 g/L) versus higher (HGB level, 120-140 g/L) anemia targets in 172 patients with CKD. No differences in LV mass index were seen after 24 months. Only 1 small RCT in a non-CKD cohort, performed in 34 patients with severe CHF and anemia, has been able to show that correction of anemia improved mortality rates.[30]

Anemia and heart disease in RTR: causation or association?

As shown previously, a paradox exists between the results of observational and nonrandomized studies (strong positive association of anemia with cardiovascular outcomes and death) versus those of RCTs (no clear benefit of anemia treatment). This paradox is shown even within the same data set: in both the Besarab et al[50] study in dialysis patients and the Levin et al[52] study in CKD patients, a strong positive association between anemia and the study end point was seen within each treatment group (nonrandomized comparison), but not between groups (randomized comparison).

The implication of this paradox is central and profound: if anemia is associated with outcomes observationally, but experimentally manipulating it in a methodologically rigorous fashion (ie, RCT) truly does not change outcome, then the association between heart disease and anemia cannot be causal. A crisis exists, therefore, in our current frame theory of anemia and heart disease. This crisis can be resolved only by a RCT that definitively addresses the major shortcomings of existing RCTs of anemia management in uremia. These are as follows: (1) enrollment of populations with advanced and irreversible disease (eg, Besarab et al[50] study) and (2) inadequate statistical power owing to either (a) inadequate HGB separation between groups or (b) inadequate N, or (c) both. Large RCTs currently in progress are addressing these issues by (1) randomizing patients with earlier (stages 2-3) CKD who are more likely to have early reversible cardiac disease and (2) aiming for a HGB differential between trial arms of 25 g/L to maximize differences between arms. These trials either will support or refute the causal anemia hypothesis. Regrettably, similar trials in renal transplant have not been planned, nor have RTRs been included as a separate stratum in the current CKD trials.

Treatment of Anemia in RTRs

Given the uncertainties in the literature, firm evidence-based recommendations about anemia management cannot be

made. Consensus guidelines for the management of anemia in RTRs nevertheless have been published.[53] As in CKD and dialysis, reversible causes for anemia, such as iron deficiency, blood loss, infection, and chronic inflammation, should be sought and treated. Cytomegalovirus infection is associated frequently with anemia, but the diagnosis usually is straightforward because of the symptoms. Parvovirus B19 infection is a novel cause of graft dysfunction and anemia and should be considered in the differential of anemia. Many medications (azathioprine, MMF, sirolimus, and RAS system antagonist) can be associated with anemia. It is very unclear, however, whether discontinuation of these drugs to reverse the anemia is a better strategy than continuing the agent and either treating the anemia with erythropoietic agents or simply tolerating the anemia. Discontinuation of an ACEI, for example, assumes that the benefit of a higher HGB level outweighs the potential loss of the cardioprotective effects of RAS antagonism. Neither the risks nor the benefits are characterized adequately in this setting. Once reversible causes are ruled out, the prevailing view favors the use of erythropoietic agents to achieve HGB target levels as suggested for CKD and dialysis patients (hemoglobin level, 110-120 g/L). Whether higher targets are desirable is not known. Clinical trials are needed urgently to guide management of anemia in all CKD populations, especially in kidney transplant recipients.

Summary

Anemia is prevalent in RTRs, as it is in all CKD populations. Mild anemia occurs in up to 40% of RTRs, whereas more severe anemia (110 g/L) occurs in about 9% to 22% of patients. As in CKD, impaired graft (renal) function is a major predictor of anemia identified in nearly all studies, suggesting a major role for EPO deficiency. Chronic inflammation, malnutrition, iron deficiency, and medications (ACEI, angiotensin receptor blockers, MMF, azathioprine, and sirolimus) are contributory factors seen in some but not all studies. Although pathophysiologic and observational data strongly support a causal association between low HGB levels and cardiovascular outcomes, no RCT to date has been able to show a clear benefit of anemia treatment on cardiovascular outcomes or mortality. This important paradox has led some investigators to question the causal nature of the association between anemia and heart disease. Resolution of this paradox (at least for patients with stage 2/3 CKD) will depend on the outcome of RCTs currently in progress. Similar trials sorely are needed in renal transplant populations. In the interim, current opinion seems to favor treating persistent anemia in RTRs to achieve targets similar to those recommended for dialysis patients.

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