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Anemia and Heart Failure in Chronic Kidney Disease

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Cardiovascular disease is mainly responsible for the poor long-term survival observed in chronic kidney disease (CKD) patients on dialytic treatment. Anemia is an early complication of CKD and, by inducing important cardiovascular alterations, first of all left ventricular hypertrophy, it does not only impair quality of life, but has also been shown to be an independent risk factor for adverse cardiovascular outcomes in CKD patients. Clinical studies, although with discordant results, have shown that cardiovascular benefits, mainly in terms of left ventricular hypertrophy regression, may be achieved by a partial correction of hemoglobin levels, however, it still is unclear whether starting anemia correction in a very early phase of CKD or aiming for complete normalization of hemoglobin levels higher than the targets recommended by current guidelines may provide further cardiovascular advantages. Results of ongoing, large-scale, prospective, randomized, clinical trials therefore are awaited with much interest to clarify better which practices of anemia correction may provide the best results on the improvement of cardiovascular status and thus of long-term survival of patients with renal disease.

KEYWORDS anemia, chronic renal failure, congestive heart failure, left ventricular hypertrophy

Because of important technologic advances achieved over the past decades, dialysis increasingly has become a relatively safe and well-tolerated long-term therapy for patients with end-stage renal disease (ESRD). Nevertheless, the life expectancy of patients on chronic dialysis still is rather disappointing when compared with a general population with similar demographic features. Cardiovascular disease emerged as the main factor responsible for this gap because deaths from cardiovascular causes occur nearly 20 times more frequently in dialysis patients than in the general population, and cardiovascular disease is also the leading cause of both mortality and morbidity in these patients.[1,2]

The enormous impact of cardiovascular morbidity in chronic kidney disease (CKD) is underlined further by the observation that cardiovascular conditions severely are compromised already before the initiation of dialysis. In particular, clinically evident congestive heart failure is observed in more than 30% of patients starting dialysis in the United States, and a similar proportion of patients show echocardiographic findings suggestive of an impaired heart function.[3,4] The same data in European patients, although slightly less impressive, indicate that up to one quarter of patients are affected by congestive heart failure at the time of starting dialysis.[5,6] The importance of such a considerable percentage of incident dialysis patients with heart failure is not limited simply to its prognostic meaning, given that the presence of congestive heart failure at the beginning of dialysis has been shown to be an extremely unfavorable prognostic factor on the long-term outcome of patients,[5] because it suggests that pathogenetic factors primarily involved in the impairment of cardiac function begin to operate well before ESRD is reached, namely since the earliest stages of the natural history of CKD. In this setting, the contribution of CKD-related anemia is substantial, mostly because of its primary role in promoting the development of left ventricular hypertrophy (LVH). Bearing this in mind, anemia therefore is considered not simply as a potentially worsening factor on patients' quality of life but also as a serious threat to dialysis patients' cardiovascular conditions and long-term survival.

Epidemiology of CKD-Related Anemia

All epidemiologic analyses performed to date in CKD patients fully agree in describing anemia as a very frequent and at the same time rather early complication of chronic renal dysfunction. In a Canadian multicenter study performed in a sample of 446 CKD patients, the proportion of anemic patients, defined as those having a hemoglobin level of less than

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13 g/dL, was found to be 87% in the subgroup with the most severe impairment of renal function (glomerular filtration rate <25 mL/min) and 25% in the subgroup with only mild renal dysfunction (glomerular filtration rate >50 mL/min).[7] In a different retrospective analysis the presence of severe anemia (hemoglobin <9.5 g/dL) was observed in 4.7% of patients with serum creatinine levels less than 3.6 mg/dL and in 11.6% of those with higher serum creatinine levels.[8] Similar findings as to the presence of a clear correlation between the degree of renal dysfunction and the prevalence of anemia have been observed recently in a large study performed in the United States on a sample population of more than 15,000 units, in which the percentage of patients who could be defined as anemic (hemoglobin level <12 g/dL in men, <11 g/dL in women) ranged from less than 2% in those with glomerular filtration rate more than 60 mL/min/1.73 month^2 to almost 45% in those with glomerular filtration rate between 15 and 30 mL/min/1.73 month^2.[9] The impact of anemia therefore becomes most evident in patients reaching ESRD as a direct consequence of hugely deficient recognition and correction of anemia during the conservative phase of CKD, despite the fact that management of renal anemia has been revolutionized over the past 15 years since the introduction of recombinant human erythropoietin and specific clinical guidelines were developed with the aim of optimizing the quality of anemia management secondary to CKD.[10,11] An analysis of more than 155,000 patients starting dialysis in the United States found that 67% had a hematocrit level of less than 30% and 51% had a hematocrit level of less than 28%.[12] However, the most detailed information as to the prevalence of anemia in patients with ESRD has been made available by the results of the Dialysis Outcomes and Practice Patterns Study (DOPPS). DOPPS was a prospective observational study of nationally representative samples of randomly selected hemodialysis facilities and patients that was developed to provide information on current practices in hemodialysis management, including the treatment of renal anemia, based on data collected from 101 representative dialysis facilities from 5 European countries (France, Germany, Italy, Spain, and the United Kingdom) between 1998 and 2000 (DOPPS I) and from 309 representative dialysis facilities from 12 countries (Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, United Kingdom, and the United States) between 2002 and 2003 (DOPPS II). As the results of the DOPPS clearly show, large variations in anemia management in dialysis patients may be observed among different countries, but the overall results are disappointing considering that the percentage of patients starting dialysis with a hemoglobin level less than 11 g/dL (namely the target recommended by current international guidelines) ranges from 55% to 95%, depending on the country, along with a relatively small proportion of patients (from 27% to 65%) on erythropoietin therapy at the same time.[13] Therefore, it is evident that despite the early onset of anemia throughout the course of CKD, the chance of making an early diagnosis and the availability of a safe and effective treatment for anemia, such as recombinant human erythropoietin, still largely is unsatisfactory in CKD patients. A large proportion of patients persist in an anemic state for a prolonged time during their disease, prolonging their dangerous exposure to the detrimental pathophysiologic consequences of anemia on their cardiovascular system.

Cardiac Implications of Anemia in CKD

The deeply negative impact of anemia on cardiac function in CKD patients is caused mostly by its primary role in promoting the development of LVH, the most typical cardiac alteration observed in CKD. As for anemia itself, the prevalence of LVH also is prominent in ESRD patients on dialytic treatment, 70% of whom have echocardiographic evidence of LVH at the time of the beginning of dialysis.[3] However, there is evidence that this phenomenon begins well before ESRD is reached. The Canadian Multi-Center Study of Renal Anemia, an echocardiographic analysis of predialysis patients with various degrees of CKD, showed that the prevalence of LVH increases progressively with decreasing renal function, however, 30% already belong to the subgroup of patients with mild renal insufficiency (creatinine clearance, 50-75 mL/min).[7] In a recent echocardiographic analysis of 581 CKD patients with moderately advanced renal dysfunction (creatinine clearance, 15-35 mL/min) and moderate anemia (hemoglobin level, 11.0-12.5 g/dL) enrolled in the Cardiovascular Reduction Early Anemia Treatment with Epoetin beta; study, only 36% of the patients had normal echocardiographic findings, whereas 49% had LVH.[14]

The possibility of a cause-and-effect relationship between anemia and LVH, as suggested although not shown by the similar patterns of development of these 2 complications throughout the natural course of CKD, is suspected further when looking at the results of several observational studies. These studies show the existence of a clear association between the degree of anemia and the tendency to develop LVH in CKD patients.

London et al,[15] in an echocardiographic analysis of 57 hemodialysis patients, showed for the first time the existence of a significant inverse association between left ventricular end-diastolic diameter and hematocrit levels in dialysis patients. Subsequently, in a cross-sectional study of 175 CKD patients attending a kidney disease clinic, 39% of whom had echocardiographic evidence of LVH, Levin et al[16] evaluated the relationship of hemoglobin levels with echocardiographic findings and found that anemia, together with systolic blood pressure, was the most important modifiable risk factor associated with the presence of LVH. They found that at multiple logistic regression analysis each 1-g/dL decrease in hemoglobin level was associated with a 6% increased risk for having LVH. The same investigators,[7] in a prospective analysis of 246 CKD patients echocardiographically studied at baseline and after 12 months of follow-up evaluation, found that left ventricular growth occurred in one quarter of the patients and that at multivariable regression analysis each 0.5-g/dL decrease in hemoglobin level was associated with a 32% increased odds of developing left ventricular growth,

thus strongly suggesting that the presence of anemia may be a crucial risk factor for the development of LVH early in the course of CKD. Decreased hemoglobin levels also have been associated with a higher risk for developing cardiac alterations in dialysis patients. In particular, in a prospective study of 432 dialysis patients followed-up for an average of 41 months, each 1-g/dL decrease in hemoglobin level was associated with an almost 50% increased risk for developing a dilation of the left ventricle, together with a 28% and 20% increased risk for developing de novo and recurrent congestive heart failure, respectively, even after adjustment for potential confounding factors.[17]

The suspected favoring effect of anemia on the development of LVH has its pathophysiologic explanation in the hemodynamic adaptations occurring in the cardiovascular system when hemoglobin levels chronically decrease. In this condition, an adequate tissue oxygenation level is achieved only by means of an increased intraerythrocytic concentration of 2,3-diphosphoglycerate and, above all, systemic arterial dilation. The latter results in decreased vascular resistance and thus decreased cardiac afterload, at the same time activating the sympathetic nervous system, which in turn increases heart rate and cardiac contractility and leads to stimulation of the renin-angiotensin-aldosterone axis. Resulting increases in plasma volume and venous tone, together with the decreased blood viscosity directly secondary to anemia, augment cardiac preload. Together, reduced afterload and increased preload, heart rate, and cardiac contractility lead to the final result of increasing cardiac output. Although these adaptations, aimed at compensating the inadequate tissue oxygenation level induced by anemia, are appropriate initially, the chronic increase in cardiac output may lead, over the long term, to a remodeling of the left ventricle itself. This, ultimately, may result in eccentric hypertrophy that is characterized by increased ventricular internal dimensions and a normal ratio of wall thickness to cavity diameter and frequently is appreciated in anemic CKD patients. Other conditions, however, are supposed to be involved in promoting the development of LVH in CKD, and in particular eccentric hypertrophy in hemodialysis patients may be facilitated by volume overload induced by the vascular access. At the same time, thickening of the left ventricular wall so as to decrease the high wall tension typical of the dilated ventricle, together with frequently poor blood pressure control observed in CKD, account for the similarly high proportion of CKD patients with concentric hypertrophy.[14] The latter is characterized by thickening of the left ventricular wall predominating over cavity dilation. Furthermore, CKD patients often also have a high prevalence of comorbid conditions other than anemia and hypertension such as hyperparathyroidism and a high calcium $\times$ phosphate product. These comorbid conditions may contribute to myocardial fibrosis and calcification, thus making LVH caused by anemia and/or hypertension a more severe and less reversible condition.

Impact of Anemia on Cardiovascular Outcome of CKD Patients

The clinical relevance of the high prevalence of LVH observed in CKD patients is linked to the many detrimental consequences of LVH on cardiac function. These include a significant increase in the demand of oxygen by the hypertrophic myocardium, often aggravated in CKD patients because of a concomitant reduction in coronary reserve caused by coronary artery disease. These adaptive changes occur at a molecular and cellular level in LVH that, although well compensating at first, otherwise are destined intrinsically in the long term to impair both cardiac contractility and diastolic compliance. The favoring effect of LVH on the development of arrhythmias is likely a result of the detrimental mechanical consequences of hypertrophy on the nodal tissue of the heart. It is therefore not surprising that LVH significantly and independently contributes to increase the risk for cardiovascular death even in the setting of CKD, as pointed out by the results of several observational studies.

Stack and Saran,[18] in a recent prospective analysis of 2,584 patients starting dialysis in the United States found that LVH, echographically detected at the time of dialysis initiation, had an adverse impact on patient survival. The mortality risk, after adjustment for demographic variables was 61%, 36%, and 29% higher at 6 months, 1 year, and 2 years, respectively, in patients with LVH compared with those without. Interestingly, the impact of LVH on mortality in this study was reduced considerably, so as to decrease statistical significance, after adjusting for the presence of congestive heart failure and coronary artery disease. This strongly supported the previously discussed hypothesis that LVH increases mortality mainly by impairing cardiac pump function and promoting ischemic heart disease. The supposed basic role of anemia in promoting LVH, together with the detrimental consequences of LVH on heart function, is therefore the main factor accounting for the significantly negative impact of anemia on the prognosis of CKD patients. Additional factors also must be taken into account such as that chronic anemia impairs myocardial perfusion and therefore increases the risk for coronary events, independently from the presence or absence of LVH, as recently documented in a large cohort of patients both with and without CKD.[19] Indeed, several large observational studies on CKD patients have shown an inverse relationship between the degree of anemia on one side and mortality and/or morbidity on the other side. In an analysis of the Registro Lombardo Dialisi e Trapianto data performed some years ago, the existence of a clear inverse relationship between hematocrit levels and both overall mortality and hospitalization rates has been documented among ESRD patients on chronic dialysis.[20] The same findings have been observed in similar surveys performed in the United States in very large cohorts of dialysis patients.[21-23] More recently, the DOPPS, obtained data from a large European dialysis population and also showed that higher hemoglobin levels are associated with lower mortality and morbidity rates, with the

adjusted relative risk for death and hospitalization 4% and 5% higher, respectively, for each 1-g/dL increase in hemoglobin concentration.[24] Similar results, particularly as to the relationship between the level of anemia and the risk for hospitalization, also have been shown by observational studies dealing with patients in the conservative phase of CKD not undergoing the dialytic treatment.[7,8]

Cardiac Benefits of Anemia Correction in CKD

It is suspected that anemia is involved in the deterioration of cardiac performance in CKD patients. Its correction is expected to lead to an improvement of cardiovascular status, thus ultimately leading to improved outcomes over the long term. In 2 small nonrandomized studies, an improvement of cardiac parameters with correction of anemia was shown in the earlier stages of CKD.[25,26] More recently, Silverberg et al,[27] in an open uncontrolled intervention trial performed on 179 patients with congestive heart failure and mild to moderate CKD, found that correction of anemia was associated with improvement of the New York Heart Association functional class by more than 30% and of left ventricular ejection fraction by more than 7% in nondiabetic patients and by more than 14% in diabetic patients.

Uncontrolled studies have suggested that the treatment of anemia is associated with reduction in left ventricular mass in dialysis patients as well. In a recent work by Frank et al,[28] normalization of hemoglobin concentration by recombinant human erythropoietin (mean achieved hemoglobin concentration after the treatment, 13.4 ± 3.1 mg/dL) in a group of 23 hemodialysis patients resulted in significantly decreased left ventricular mass index, together with a clear change in left ventricular geometry from an asymmetric to a symmetric configuration, as suggested by the decreased value of left ventricular relative wall thickness.

However, results from randomized controlled trials have been less conclusive. The United States Normal Hematocrit Trial, which enrolled more than 1,200 hemodialysis patients with clinical evidence of congestive heart failure or ischemic heart disease, was halted prematurely after the observation at interim analysis that patients in the normal hematocrit target group had an almost statistically significant higher risk for reaching the primary end point of death or first nonfatal myocardial infarction. In the low-hematocrit group a clear inverse relationship between mortality and achieved hematocrit levels was observed.[29] In the Canadian Normalization of Hemoglobin Study, a multicenter trial of 146 hemodialysis patients with asymptomatic LVH at baseline, even the complete correction of anemia failed to induce a significant regression of well-established LVH, even if patients with concentric LVH were less likely to progress to left ventricular dilation if they were randomized to the higher hemoglobin target.[30] In 155 CKD patients not yet on dialysis, with creatinine clearance between 15 and 50 mL/min, Roger et al[31] were not able to observe a significant decrease in left ventricular mass even in those patients randomized to achieve and maintain a target hemoglobin level of 12 to 13 g/dL over a follow-up period of 2 years.

Overall, the results of this studies suggest that the ability of anemia correction to prevent or correct, once developed, the cardiac changes occurring as renal function decreases therefore has yet to be shown, together with the definition of the hemoglobin target to be achieved in CKD patients to provide them the maximum cardiovascular benefit. For these reasons, results of ongoing, large-scale, prospective, randomized trials, such as the Cardiovascular Reduction Early Anemia Treatment Epoetin beta[32] and the Anemia CORrection in Diabetes studies,[33] both performed in patients with CKD in the conservative phase, are awaited with much interest to confirm the potentiality of anemia correction to reduce the high burden of cardiovascular comorbidity in CKD patients, as well as to define the best modalities of anemia treatment in terms of both time of intervention and target hemoglobin level.

Conclusions

Anemia is a rather frequent and relatively early complication of CKD, affecting a significant proportion of patients with even mild renal function impairment. By altering cardiac structure and function, in particular by promoting the development of LVH, anemia independently is associated with worse cardiovascular outcomes and thus poorer long-term survival in these patients. Clinical studies, although with nonunivocal results, have shown that correction of anemia by recombinant human erythropoietin may lead to at least partial regression of LVH in CKD patients. However, it still is unclear whether starting anemia correction in a very early stage of CKD or achieving a complete normalization of hemoglobin levels (correcting anemia far beyond what now is recommended by international clinical guidelines) are strategies that may be able to provide further advantages in terms of improved cardiovascular and overall outcome of the patients. Results of prospective, randomized, clinical trials performed on large populations of patients therefore are needed urgently to highlight the modalities of CKD-related anemia treatment that may provide the best cardiovascular benefit, so as to provide the nephrologist with a powerful therapeutic instrument to provide definitive improvement to the poor cardiovascular prognosis of these patients.

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