

# Should the Hematocrit (Hemoglobin) Be Normalized in Pre-ESRD or Dialysis Patients? Yes!

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## Introduction

The major issues regarding recombinant human erythropoietin (rHuEpo) use in patients with chronic kidney disease (CKD), particularly those receiving dialysis, have been cost-effectiveness, dosage, route of administration and resistance to therapy [1]. Anemia management has been optimized by using the subcutaneous route [2] and by using intravenous iron in a timely fashion [3, 4]. Optimal treatment of anemia has assumed greater importance with the increasing age of the end-stage renal disease (ESRD) and progressive CKD (pCKD) populations. This fast-growing segment is increasingly composed of diabetic patients and has more frequent and greater degree of ischemic heart and peripheral vascular disease. Those with pCKD all too often present for dialysis with well-established comorbidities of uremia, such as anemia, left ventricular hypertrophy (LVH), congestive heart failure, malnutrition, or debilitation. It is the purpose of this discourse to make the argument that many of these comorbidities, often seen as inevitable components of kidney failure, could be prevented if relatively normal hemoglobin concentration were maintained during the entire period of pCKD.

The optimal hemoglobin (Hb)/hematocrit (Hct) during EPO therapy in both ESRD and pCKD patients should be

one that maximizes cardiovascular function and activities of daily life (ADL) while minimizing risk. Different organs respond differently to correction of anemia, an effect that confounds the search for optimum Hb. Very few studies have directly addressed the negative impact of the severity of anemia in those with pCKD. In such patients, it is difficult to separate the effects of anemia from those due to mild azotemia. This difficulty does not justify the improper treatment of anemia. Using data from the US Renal Data System, Obrador et al. [5] demonstrated that the majority of patients with pCKD who initiate dialysis in the USA receive suboptimal care. Acceptance of a certain degree of anemia as the norm may explain the finding that the mean Hb in pCKD patients beginning dialysis was only ~9 g/dl [5]. Many patients with pCKD may not receive optimal therapy as a result of cost concerns or fear of adverse effects of anemia correction.

The role of preventive medicine is underappreciated. In the Canadian study on pCKD, patients with creatinine clearances <25 ml/min averaged a Hb of 10.9 g/dl and showed a progressive decline in mean Hb at each level of kidney disease [6]. Development of long-acting erythropoietin (novel erythropoietic stimulating product) [7] and the wide availability of safe iron preparations permits maintenance or correction of Hb at any desired level

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0253-5068/01/0192-0168\$17.50/0

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including normal. Indeed, several authors have suggested that normalization of Hb in patients with chronic renal failure might produce greater benefits than those currently achieved [8–10]. Four prospective studies of nearly normalizing Hb have been completed, mostly in ESRD patients. All have shown improvements in quality of life (QOL). Only one has shown a risk. Intuitively, normalization should benefit because in all other forms of hormone deficiency, replacement is given to fully correct the deficiency.

The definition of normal Hb differs for patients with pCKD and those on peritoneal dialysis from that of hemodialysis patients. The later have recurrent changes in weight between dialysis sessions. Because of hemoconcentration during dialysis, the 'normal' Hb measured predialysis in hemodialysis patients is 1–1.5 g lower than in the other two groups.

### **Historical, Economic, Philosophic, and Research Perspectives**

When the protocols for the initial clinical rHuEpo trials were being developed, hematologists argued for full normalization of Hb. In contrast, nephrologists argued for incomplete correction [11]. Initial clinical trials [12, 13] achieved mean Hb of about 12 g/dl (Hct 33–38). Marketplace economics in the USA produced a relatively low target Hb of 9.5–11 g/dl for its ESRD population [1]. It is now possible to maintain a 3-month rolling average of <12.5 g/dl. European nephrologists apparently also prefer a target of 10–12 g/dl [14]. The rationale for these levels is not clear since they are short of the normal ranges of 12.0–16 g/dl for menstruating women and 13.5–17.5 g/dl for men and postmenopausal women.

The increased cost incurred to maintain Hb at normal levels requires that cogent arguments be made for doing so. If anemia treatment is begun predialysis and extends over years, the costs become important considerations. Until recently there have been few studies investigating outcomes and effects of increasing Hb to 13–15 g/dl. We do need more studies that extend correlation of Hb concentrations to outcome, particularly in those with pCKD. In ESRD patients, Hb of 11–12 g/dl produces a survival advantage [15–17] and lower overall hospitalization [18, 19]. Collins and Keane [20] believe that keeping Hb at 11–13 g/dl is cost-effective with reduction of long-term costs for caring for ESRD patients. Will normalization of Hb produce even greater effects? LVH is a negative predictor of survival in dialysis patients [21]. If anemia were

not allowed to develop, could the severity of LVH in patients with pCKD be reduced?

The purpose of the remainder of this discourse is to make an argument for normalization of Hb in almost all patients and to start before the ESRD stage is reached. Studies have documented that oxygen transport to many organs decreases rapidly as Hct falls to less than 40%. These organs function better at higher Hb levels [22]. With progression of chronic renal failure and worsening anemia, the opportunity to maintain organ function is lost. Once lost, subsequent interventions may never restore full functionality (as with LVH). As a result, QOL, exercise performance and rehabilitative potential are adversely affected. Maintenance of normal Hb may prevent the maladaptive compensations.

### **Cardiovascular Function**

Patients with progressive anemia develop a series of compensations. Cardiac output increases by 20% and a rightward shift in the oxygen dissociation curve occurs. The increase in cardiac output is mediated by both an increase in stroke volume and heart rate. There is a reduction in afterload from hypoxic vasodilatation and decreased viscosity, an increase in preload, and an initial increase in contractility from increased sympathetic activity [23]. Eventually, anemia produces both eccentric LV as well as left ventricular (LV) dilatation. Hb concentrations correlate with both LV end-diastolic volume and LV mass. LVH is associated with the de novo development of ischemic heart disease. LVH, LV dilatation and ischemic heart disease produce cardiomyopathy [24]. Anemia decreases cardiac reserve in hearts with LVH in which the maximum vasodilatory reserve of the coronary circulation is already reduced.

Coronary reserve in the patient with renal insufficiency is decreased by anemia because compensatory vasodilatation uses up a portion of the reserve. In 'uremia' tolerance for ischemia is further reduced because of arteriolar wall thickening and inadequate capillary growth producing a cardiomyocyte/capillary mismatch [25]. Hypertrophic myocytes become at risk for hypoxia because of the increased diffusion distance. The importance of the above observations is most apparent in those who have angina pectoris but normal coronaries [26]. Seemingly, the myocardium of the renal patient increasingly lives on the brink of anoxia as anemia develops.

LVH per se also predisposes to ventricular arrhythmia [27] in part through this effect on coronary reserve and in

part through interstitial fibrosis [28]. Ischemia and the high resistance to electrical conduction establish a stage for re-entry pathways and re-entry arrhythmia [29, 30]. Many 'sudden deaths' in dialysis patients probably result from arrhythmia.

The risk of LV dilatation, heart failure and premature death increases as the anemia of pCKD worsens. Levin et al [6] have demonstrated that the development of LVH is closely related to the decrease in Hb in patients with progressive renal disease. Prevalence of LVH is related to the degree of renal dysfunction; 26% at creatinine clearance of 50–75 ml/min, 33% at 25–50 ml/min, 41% at <25 ml/min [31]. By logistic regression, each 1 g/dl decrease in Hb increased the risk of LVH by 6%. Hb level and systolic hypertension are the only two variables that are significant predictors of LVH in these nondialysis patients. When followed over 12 months, an increase in LVMI of 20% or 20 g/m<sup>2</sup> correlated only with lower Hb and higher blood pressure. Thus cardiovascular consequences begin early in pCKD and are closely linked to changes in Hb over time. These abnormalities worsen as patients approach dialysis. Approximately 70–75% of patients entering dialysis programs have LVH [32]. Once dialysis is initiated, subset analysis by Foley et al. [24] has shown that a further increase in LVH occurs during the first year of dialysis.

In view of the above detrimental effects of LVH, every effort must be made to reduce it or reverse it. The strategy should be treatment at an earlier stage before fibrosis sets in. Maintenance of Hb in these patients before the need for replacement therapy may be the key to preventing progressive increase in LV mass. Partial correction of anemia to a Hct of 30–36% produces only incomplete reductions in LV hypertrophy [33, 34], volume [35], or mass [36] and incomplete improvement in exercise-induced ST-segment depression [37]. Since development of anemia during the predialysis period is a key, normalization of Hb should be begun when the opportunity still exists to maintain muscle function as well as prevent cardiac dilatation. Pharmaco-economic treatment choices should focus on prevention of cardiac complications during the development of renal insufficiency.

On the basis of the above discussion, it is useful to evaluate the studies that have attempted to normalize Hb. Eschbach et al. [38] increased the Hct from a mean of 32.6 to 42.0% and noted significant improvements in cardiac function and exercise capacity. Specifically cardiac output decreased and LV mass decreased. Major side effects or risks were not observed in this small uncontrolled study. By contrast, a controlled study of dialysis patients

with cardiac disease (Normal Hematocrit Cardiac Trial) arrived at the opposite result. The study was terminated after an interim analysis showed a tendency toward a higher death rate in the group whose Hb had been normalized [39]. Although the difference did not reach a predefined statistical boundary, the study was halted because of safety concern (access clotting) and the extreme unlikelihood of showing any benefit. Difference in outcome could not be explained by 11 prespecified baseline characteristics using Cox regression analysis. Higher Hb levels per se did not appear to be responsible for the death rate findings since post-hoc analysis showed that mortality decreased with higher Hb levels in both the control group as well as the normal Hct group. Overall there was a 30% reduction in mortality for a 10-point increase in Hct.

The Canadian Multicenter Trial [40] evaluated LVH and QOL in 159 anemic hemodialysis patients with asymptomatic LV disease. Two sets of patients were randomized; those with LVH and normal LV cavity and those with LV dilatation alone. In contrast to the Normal Hematocrit Cardiac Trial, patients with symptomatic cardiac disease were excluded. Normalization of Hb to 13–14.0 g/dl as opposed to maintenance at 10 g/dl for 48 weeks prevented progression of LV dilatation in those starting with a normal LV volume but did not reverse regression of pre-existing concentric LVH or LV dilatation. Along with the previous studies of Levin et al. [6, 31], the results suggest that early normalization may be a key strategy. In the Scandinavian Multicentre Trial [41], a total of 416 hemodialysis, peritoneal and pCKD patients with stable Hb levels between 9 and 12 g/dl were randomized into two Hb target groups, to remain at levels <12 g/dl or to be increased to 13.5–16 g/dl for a total duration of 18 months. This study found no difference in the two groups with regard to safety. In summary, normalization of Hb appears to be safe in patients who have asymptomatic cardiac dysfunction, a finding that differs from that of normalization in patients with symptomatic coronary artery disease and/or congestive heart failure.

Reversal of adaptive circulatory adaptations requires considerable time. In patients with symptomatic heart disease it is prudent to control blood pressure while slowly correcting the anemia. Several studies now indicate no or trivial differences in mean day or nocturnal blood pressure at Hb levels of 10 compared to Hb levels of 14 g/dl [42]. In the Normal Hematocrit Cardiac Trial, normalization did not produce an increase in BP as assessed by ambulatory monitoring nor was there a change in the diurnal pattern [43, 44].

## Cerebrovascular

Maximal delivery of O<sub>2</sub> occurs with Hb in the 13.5–15 g/dl range. Several studies have shown improvements in cognitive function on increasing the Hb above the levels currently recommended. Nissenson and co-workers [45] found better brain function at Hcts of 42% than at the lower clinical targets of 30–36%. Continuous performance tasks and P-300 latency in the auditory oddball task by electroencephalogram improved as Hb was normalized suggesting better signal transmission in the central nervous system. Normalization of Hb increases oxygen supply to the brain and oxygen extraction [46].

## Quality of Life

QOL is affected by the ability to perform physical ADL. The definition of what constitutes adequate ADL function differs among age groups, particularly when comparing older sedentary to younger more active-working or pediatric patients. In all age groups, CKD impacts QOL negatively [47, 48]. More than 25% of patients with pCKD reported important symptoms relative to general health, energy, fatigability, sleep disturbance, recreational activities, home management, and work [47]. A low Hb level was the only laboratory variable that correlated with poor QOL scores. Schidler [48] studied 50 patients with mild degree of CKD and found that such patients exhibited negative psychological reactions to their illness, associated with lower QOL and higher depression scores.

The Normal Hematocrit Cardiac Trial did report significant improvements in QOL parameters in the patients in the normal Hb group at the time the study was halted [39]. The observation by Valderrabano [49] that improvement in the sickness impact profile (SIP) and Karnofsky scores correlated with Hct over the full range of Hcts in 1,013 Spanish hemodialysis patients led to a prospective 6-month study (Spanish Quality of Life Study) to evaluate functional status and QOL resulting from a deliberate increase in Hct [50]. Only stable hemodialysis patients under the age of 65 were entered and those with diabetes, CVA, seizures or severe co-morbidity were specifically excluded. Although the study was designed to increase hematocrit by about 5 points, the mean increase was 7.5 points in the 115 patients who finished the study. Increasing the Hct from 31 to 39% in 117 patients statistically altered the SIP and Karnofsky scores. When Hb was increased from 10.2 to 12.5 g/dl, the overall SIP decreased from 7.8 to 5.7, the physical dimension component from

5.9 to 4.1, and the psychological dimension score from 8.9 to 7.3. The number of patients hospitalized and their length of stay decreased during the 6 months of the study when compared to the 6-month period preceding the study. The greatest benefit accrued in those having the lowest baseline QOL.

Similar results have been reported from the Scandinavian Erythropoietin study at 1 year of follow-up [51]. Physical symptoms were reduced with less fatigue, depression and frustration in the normal Hb group than in the lower Hb group. Similar trends occurred in the Leicester Uremic Symptoms Scale, the ADL scale, and Self-Image Scales. Of note, the dropout rate in those with pCKD was low. The Canadian Multicenter Trial has also reported on QOL outcomes. At 24 and 48 weeks into the study, improvements in the Kidney Disease Questionnaire and the SF-36 subscales have been noted without a change in the Health Utilities Index. Importantly, normalization had least effect in those with LVH and greatest impact in those with LV dilatation. Changes in depression, fatigue and relationships were the subscales showing the most effect from normalization.

Thus the data on QOL from normalization Hb is consistent. Normalization improves QOL. We believe that even greater potential exists for preventing disability by insisting on Hb normalization much earlier in pCKD.

## Physical Activity

During exercise, maximum oxygen uptake can increase 20-fold but cardiac output can only increase 6-fold. Increase in oxygen uptake is dependent on age, gender, height and weight, and habitual physical activity.

Reduced exercise capacity in patients with pCKD is commonly observed due to (1) reduction in oxygen delivery, (2) concurrent diseases such as peripheral vascular disease, heart failure, (3) increased proteolysis, (4) malnutrition, and (5) hyperparathyroidism. In addition, muscle abnormalities develop. Overall muscle strength of dialysis patients decreases to about half [52]. Lack of muscle strength may be the principal factor limiting exercise capacity of anemic renal failure patients. Reported increases in exercise and work capacity in ESRD patients are proportional to the Hct increases but show wide inter-individual variation.

The effect of restoring full physical and intellectual performance derives from limited studies to date. Increasing Hb improves exercise-induced lactate concentration [53]. Lim [54] reported that energy and work capacity

improved more in those who were fully corrected (Hct 35–40%) than in those only partially corrected. Barany et al. [55] found that exercise capacity did increase further with normalization of Hb but that the increase remained subnormal compared to rHuEPO-treated healthy subjects. Although  $\text{VO}_2$  is higher at a Hct of 35–40% than at 30%, exercise ability is not fully corrected [56]. Eschbach et al. [38] showed a 24% increase in maximal oxygen uptake, a 20% increase in bicycle exercise, a 50–60% increase in pulmonary  $\text{CO}_2$  diffusion, and an increase in quadriceps isometrics with Hb normalization. Finally an increase in Hb from 10 to 14 g/dl produces a significant increase of maximal exercise performance in hemodialysis patients [57]. Although uremic factors may contribute to the pathogenesis of impaired exercise and muscle dysfunction even after full correction of anemia, one has to question whether the abnormalities would be less if anemia and deconditioning were not allowed to develop in the first place. With respect to the later aspect, Stray-Gunderson et al. [57] studied patients at a Hct of 30% and at 42%. At the higher Hct the subjects were examined after 15 weeks of exercise training.  $\text{O}_2$  uptake increased markedly after the exercise training. Thus poor conditioning of many dialysis patients contributes to the reduced exercise capacity in patients with pCKD.

### Morbidity and Risk

Patients on dialysis have an age-adjusted death rate 3.5 times that of the general population. Anemia predicts mortality independently of diabetes, cardiac failure, hypoalbuminemia, or blood pressure [24, 32]. It also independently predicts the development of congestive heart failure [32]. Many of these effects may result from the affect of anemia on LVH. The presence of LVH at the start of dialysis is independently predictive of mortality for the next 2 years with a relative risk of 2.9 for all-cause mortality and 2.7 for cardiac mortality. Silverberg et al. [58] reported that the patient whose LV mass exceeded the normal value had an actuarial survival of 25% compared to 55% in patients with normal LV mass. The morbidity and mortality data by Collins and co-workers [17, 19] and Locatelli et al. [16] indicate that no patient should have a Hct less than 30%. US studies were unable to demonstrate whether increasing Hb to  $>12$  g/dl prolonged survival due to the small number of subjects [15, 17] with such Hb levels due to the reimbursement system. As stated before, the Normal Hematocrit Cardiac Study did not show benefit. However, neither the Canadian nor the

Scandinavian Trials showed any risk of normalizing Hb in patients without symptomatic cardiac disease.

Normalization of Hb does not appear to have any negative impact on blood pressure stability [39, 43, 44]. In 20% of patients, additional antihypertensives may be necessary. If blood pressure is adequately controlled, rHuEPO does not accelerate progression of chronic renal insufficiency [59]. More recent studies using more accurate measurements of GFR ( $^{125}\text{I}$ iothalamate clearance) over a 1-year period in pre-dialysis patients have shown no evidence for a Hct-induced change in GFR nor was there any difference between the treated (Hct 35–36) and untreated patients in time to initiation of dialysis [60]. In some studies, therapy in pCKD even appeared to retard progression in nondiabetic patients [61]. Could this be an effect to reduce oxidative stress or ischemia within the kidney?

### Conclusions

The available evidence indicates that QOL, exercise capacity and cardiac function improve as Hb approaches normal values in patients with CKD. At present there is incomplete information on normalizing Hb in predialysis patients. Randomized studies are needed to identify appropriate endpoints (time to renal replacement therapy, rate of progression, exercise capacity, LV growth and geometry, cardiac events, morbidity and mortality).

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