

What should the optimal target hemoglobin be?¹

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What should the optimal target hemoglobin be? Partial correction of anemia in patients with chronic kidney disease (CKD) improves anemia-related symptoms. However, controversy remains as to whether total correction of anemia provides benefits over and above those afforded by partial correction. There is some evidence showing that normalization of hemoglobin (Hb) concentrations may improve the cardiac hyperdynamic state in CKD patients and reduce the diameter of the left ventricle. Further studies have shown that normalization of Hb improves cognitive function and physical capacities as measured by quality of life (QoL) tests. Large studies have shown that in dialysis patients there is a close inverse relationship between hematocrit (Hct) levels and mortality and morbidity. Moreover, there is evidence suggesting that Hct levels higher than those recommended by European Best Practice Guidelines (EBPG) and the National Kidney Foundation Dialysis Outcome and Quality Initiative (NKF-DOQI™) provide better outcomes for patients with CKD. However, when Hb concentrations are increased to normal in selected patients with cardiac disease, congestive heart failure, or ischemic cardiopathy, higher mortality rates are evident. Therefore, while the majority of patients with CKD may experience significant benefits when Hb is normalized, it seems prudent to recommend individualized target Hb concentrations for each patient, taking into account factors such as age, sex, employment status, physical activity, and co-morbidities.

Anemia is a very frequent complication in patients with chronic kidney disease (CKD). It affects over 90% of patients undergoing renal replacement therapy with dialysis, but it may begin in the early stages of renal insufficiency, well before the initiation of dialysis. The prevalence of anemia in CKD correlates inversely with residual renal function. In the Canadian multi-center study of renal anemia, the prevalence of anemia was found to be approximately 25% when creatinine clearance is higher than 50 mL/min. Anemia progressively

worsens as renal function declines, such that when creatinine clearance is below 25 mL/min, the prevalence of anemia is approximately 87% [1]. These findings suggest that patients with CKD may be anemic for a long time during the progression of the disease. If this is the case, then patients are exposed to an important risk factor that could influence clinical outcomes.

As oxygen supply to the tissues decreases due to anemia, several compensatory mechanisms develop, including cardiovascular adaptations [2]. Owing to these systems of adaptation, anemia is largely responsible for the significant detrimental cardiac effects occurring in CKD patients (Table 1).

Treatment of CKD patients with epoetin leads to an increase in hemoglobin (Hb) concentrations, which improves anemia-related symptoms. At present there is no clear evidence as to what the target Hb concentration for these patients should be. The EBPG [3] and the NKF-DOQI™ Guidelines for the treatment of anemia of CKD [4] establish a minimum Hb concentration of 11 g/dL. Importantly, the EBPG features an open-ended target Hb that includes the provision to normalize Hb. However, some recent studies have reached controversial conclusions on the benefits of normalizing Hb concentrations. On the one hand, some authors have witnessed an increase in the beneficial effects of anemia therapy when Hb is normalized [5–8] while other authors have experienced conflicting results in selected groups of patients [9]. The aim of this review is to summarize the advantages and disadvantages of normalizing Hb levels in CKD patients.

EVIDENCE IN FAVOR OF A NORMAL TARGET HEMOGLOBIN

Left ventricular hypertrophy

Anemia is a very important risk factor in the occurrence of left ventricular hypertrophy (LVH). Anemia creates a hyperdynamic state that increases cardiac preload. This situation causes a proliferation of the sarcomeres of myocardiocytes with an increase in diameter and thickness

¹This article is dedicated to the memory of Fernando Valderrábano, who, over the last decade, was involved in the study of renal anemia with the goal of achieving optimal care and improved quality of life for all patients with CKD.

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Table 1. Detrimental effects of anemia in patients with chronic kidney disease

Decreased	Increased
Exercise capacity	Depression
Skeletal muscle oxidative capacity	Sleep/awake pattern
Coagulation	Cardiac output
Immune response	Angina
Cognitive function	Left ventricular hypertrophy
Sexual function	Cardiac failure
Appetite/nutrition	Myopathy
Quality of life	Morbidity
Growth in children	Mortality

of the left ventricle (eccentric LVH), where the diameter/wall thickness ratio remains constant.

From the very first clinical experiences with epoetin, various studies have shown that partial correction of anemia is accompanied by the partial regression of LVH [10–13]. However, these studies were conducted on relatively small groups of patients, and did not aim to fully normalize Hb concentrations. A Spanish multi-center study of 91 hemodialysis patients has also shown that the increase in Hb concentrations with epoetin reduces the severity of LVH. This improvement is due to a significant decrease in left ventricular diameter, but the overall thickness of the left ventricular walls does not change (abstract; López Gómez et al, *J Am Soc Nephrol* 11:A1488, 2000).

It is unclear whether Hb normalization may have an added advantage to such patients. The Canadian multi-center study has shown that complete correction of anemia fails to induce regression of well established concentric LVH or left ventricular dilation, but it appears to prevent left ventricular dilation in patients with normal left ventricular volume [15]. However, in a prospective, randomized, and doubled-blind cross-over study of 14 hemodialysis patients, Hb normalization was followed by a reduction in left ventricle end diastolic diameter with a 5% reduction in left ventricular mass index that was not statistically significant [8].

The US Normal Hemocrit Trial showed that complete correction of anemia in hemodialysis patients with symptomatic heart failure or ischemic heart disease was associated with a trend towards higher mortality rates compared with similar patients in the low target Hct group [9]. These studies suggest that when there are important alterations in cardiac structures, the beneficial effect of the total correction of anemia is very limited, although the results of the Canadian study have shown a favorable effect on the prevention of LVH once the developing anemia is corrected.

LVH may be evident very early in the progression of CKD [16]. The US and Canadian data combined suggest that the prevention of structural heart changes should be initiated early, i.e., in the pre-dialysis phase. However,

there have been few studies specifically investigating this phase of CKD. Portolés et al have shown that in 11 patients with CKD, the improvement in Hct is accompanied by a significant reduction of cardiac index and of left ventricular mass, despite not achieving normal Hb concentrations [17]. Hayashi et al showed that in 9 pre-dialysis patients the normalization of Hb resulted in a complete regression of LVH without negative influence on the blood pressure or on the rate of progression of renal failure. [18]. A multi-center Spanish study of 102 pre-dialysis patients showed that partial correction of anemia (Hb from 9 to 11 g/dL) resulted in a decrease in left ventricular mass index at 6 months. The most promising effect was in patients without basal LVH who remained normal when treated with epoetin, while non-treated patients experienced increased left ventricular mass (abstract; Valderrábano et al, *Nephrol Dial Transplant* 15:A114, 2000). These data suggest, once again, that early anemia correction protects against the development of LVH.

An observational study of 4866 pre-dialysis patients was recently published by Fink et al, showing that the mortality risk after initiating dialysis was lower for patients treated with epoetin before dialysis compared with patients who were not treated. However, there was no relationship between pre-dialysis Hct and mortality rate, suggesting that epoetin therapy prior to dialysis confers an increased probability of survival when the patients reach end-stage renal disease (ESRD) [20]. Thus, it seems that correction of anemia must be initiated early in the progression of CKD, and that complete correction may add complementary beneficial effects. However, new trials are necessary to confirm this hypothesis. Accordingly, several studies currently underway in Australia, Canada, and the UK, which, along with the Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial [21], are attempting to assess the effect of earlier anemia treatment on cardiac function. The results are promising and could show clear evidence of the preventive effect of early anemia correction in LVH and cardiovascular morbidity. They could also answer the question of whether or not achieving normal target Hb concentrations has beneficial effects on long-term outcomes for CKD patients.

Cognitive function

Various studies using different neuropsychological and neurophysiological tests in dialysis patients have demonstrated that raising Hb/Hct to the levels recommended by the EBPG (Hb \geq 11 g/dL in \geq 85% of patients with uncomplicated anemia) [3] and the NKF-DOQI™ Guidelines (Hct between 33% and 36%) [4] is accompanied by an improvement in cognitive function [22–24] and in electroencephalogram (EEG) characteristics [22, 25].

Metry et al suggest that maximal level of oxygen deliv-

ery to the brain occurs when Hct levels are higher than 36% [26]. This hypothesis brings once more to the fore the question: does normalizing Hb concentrations have benefits additional to achieving existing agreed targets? To this end, Pickett et al studied the effects of raising Hct from 31.6% to 42.8% in a group of 20 hemodialysis patients. EEGs revealed significant improvement, and improvement was also shown in electrophysiological tests mainly affecting P300 latency and amplitude [7].

A study of the effects of epoetin therapy on sleep, sleep disorders, and daytime sleepiness on hemodialysis patients (the SLEPO trial), conducted by Benz et al showed that after increasing mean Hct from 32.3% to 42.3%, some parameters of quality of sleep such as periodic leg movement, arousing periodic limb movements in sleep (PLMS), or maintenance wakefulness assessed by polysomnography were significantly improved (abstract; *J Am Soc Nephrol* 7:1473, 1996). These results suggest that normalization of Hct may have an added beneficial effect on improving cognitive function and the quality of sleep in dialysis patients.

Physical function

Anemia therapy with epoetin results in an increase in working capacity and aerobic exercise [13, 28, 29] as the result of an increased transport of oxygen to the muscular tissue. Suzuki et al show that the VO_2 is higher at a Hct level of 35–40% than at 30% [30]. In a multi-center study of 11 pre-dialysis patients, greater improvement in energy and work capacity was observed when Hct was increased from 28% to 38%. In these patients, oxygen consumption at anaerobic threshold and at maximal exercise capacity increased, but did not reach normal values. This suggests that poor physical performance in renal patients is not only due to anemia, but that other factors such as neuropathy, cardiovascular disease, and poor conditioning may also contribute [31].

The effect of different Hb concentrations on maximal exercise performance has also been studied in 14 hemodialysis patients. The results show that peak work rate and peak VO_2 significantly increase after normalization of Hb with no difference observed between young and older patients [32].

Quality of life

In recent years, the evaluation of health-related QoL has emerged as an important and useful tool for studying the efficacy and net benefit of medical therapies. In ESRD patients, QoL has been shown to be worse than that of the general population and anemia has been implicated as one of the main related factors [33].

The partial correction of anemia with epoetin is accompanied by an improvement in the QoL in both pre-dialysis [34] and dialysis [35–37] patients, and the aspects related to the physical dimension of the QoL score

are believed to be the most apparent. A comparison of very anemic patients with those treated to levels recommended by the EBPG [3] and NKF-DOQI™ [4] (Hb 11–12 g/dL) shows that the QoL scores are strongly related to Hb concentrations [38]. However, an aspect that is not so well studied is the evaluation of QoL when Hb concentrations reach normal values. The US Normal Hematocrit Trial showed that physical function, assessed by SF-36 questionnaire increased 0.6 points for each percentage point increase in Hct [9]. In the Canadian multi-center study, fatigue, depression, and relationship capacities improved significantly when normal Hb concentrations were achieved [15]. The Spanish Co-operative Renal Patients QoL Study Group examined the effect on the QoL and functional status in 156 hemodialysis patients after achieving an Hct close to normal. After increasing the epoetin dose by approximately 50%, QoL was measured using the Sickness Impact Profile (SIP) and functional status was measured using the Karnofsky scale. The results show that normalized Hct is associated with an improvement in physical and psychosocial scores as well as in the mean global SIP score and functional status. No adverse effects of epoetin therapy were observed [6]. Similar results were found in the Australian study [8].

Mortality and morbidity

Anemia has been shown to be a predictive risk factor of mortality and morbidity [39–41]. In a Canadian study of dialysis patients, each 1 g/dL decrease in Hb concentration was independently associated with an improvement in the relative risk of death of 1.14 [39]. Ma et al studied the relationship between mortality and Hct in a group of 75,283 Medicare patients and found that the relative risk of death decreased in patients with increased Hct. All causes of death (including cardiac causes) in diabetic and non-diabetic patients were found to be at the lowest incidence when Hct levels were in the range 33–36% [40]. In the study by Besarab of 1233 hemodialysis patients with cardiac disease, patients in whom Hct was increased to normal levels ($42 \pm 3\%$) had higher rates of mortality than the control group (Hct $30 \pm 3\%$). However, this study included only patients with congestive heart failure or ischemic heart diseases and deaths were due to cardiovascular causes [9]. The study has been analyzed and criticized in two interesting editorials [42, 43].

In a Medicare dialysis cohort of 71,717 patients, the probability of hospitalization was found to be less when Hct levels were in the range 33–36% than when Hct levels were lower [41]. Our co-operative Spanish group has also studied the effect of Hct $>36\%$ on hospitalization rates. It showed a significant decrease in the number of hospitalized patients and hospitalization length when Hct was normalized [6]. More recently, Collins et al have performed a retrospective study with incident hemodial-

ysis patients with Medicare insurance. The authors show that for those patients with Hct >36%, hospitalization rates were 16–22% lower than in the rest of the patients. However, the relative risk of death was not different between patients with Hct values of 36–39% compared with those with values of 33–36% [44].

In summary, partial correction of anemia in ESRD patients has a beneficial effect on mortality and morbidity, but complete correction may provide further improvements in some selected patients.

POTENTIAL ADVERSE EFFECTS OF A NORMAL TARGET Hb

High Hb concentrations increases blood viscosity and may potentially play a role in the coagulation and thrombosis of vascular access for hemodialysis. Very few studies have evaluated the role that normalization of Hct may have on vascular access. During a mean follow-up period of 49 months, the US Normal Hct Trial showed that high Hct levels are not associated with greater incidence of vascular access thrombosis [9]. Thrombosis of vascular access was evaluated during the 6-month period of the Spanish co-operative study on the normalization of the Hct. This study found that 5.7% of patients suffered a thrombosis of the vascular access. The cumulative vascular access survival at 6 months (CI 95%) was 0.93 ± 0.04 . Even though the complications of the vascular accesses are very different between centers, making comparisons between them difficult, it does not seem that correcting anemia has a detrimental effect on vascular access [45–47]. However, studies specially designed to research anemia and other potentially contributory factors to thrombosis are necessary. Currently, it seems reasonable to follow the NKF-DOQI™ guidelines that have established that there is no need for increased surveillance of access thrombosis in hemodialysis patients treated with epoetin [4].

Other possible adverse effects related to normalization of Hb concentrations include hypertension and the possible effect on silent cardiac ischemia. Conlon et al have reviewed both these parameters, and have found no evidence at all of either problem [48]. Additionally, the prevalence of hypertension remained stable during the 6 months surveillance of Hct normalization of the Spanish Multi-center Study [6].

The cost of the increased dosages of epoetin necessary to achieve normalization of Hct could be a limiting factor on treatment. However, not all clinical cases exhibit similar dose-response relationships. While Hb concentrations increase in some patients after a slight increase in epoetin dosage, other patients only show a slight increase in Hb after increasing the epoetin dose 2- or 3-fold. In the Spanish Multi-center study, the mean dose of epoetin increased

51% [6], whereas in the Besarab study, the mean dose of epoetin increased by approximately 200% [9].

OPTIMIZATION OF EPOETIN THERAPY

Currently, there is strong evidence that total correction of anemia by normalizing Hb concentrations offers clear benefits in selected patients with CKD. It no longer seems reasonable to allow the development of anemia and its deleterious effects on these patients. Thus, the most appropriate target Hb concentration should be correction to normal levels. The main concerns over this objective include the high costs and possible adverse effects on selected groups of patients. Consequently, the recommendation of normalizing Hb is not appropriate for all dialysis patients and the target Hb should be tailored to the clinical conditions of each individual patient, bearing in mind his/her age, sex, physical activity, dialysis modality, and co-morbidity factors. As Macdougall suggests, a normal Hb may be appropriate for young patients, in full-time employment, physically active, and with no severe co-morbidity, whereas partial correction of anemia would be reserved for elderly patients with significant co-morbidities [49].

Overall, we are seeing greater evidence as to the need to begin treatment with epoetin in the early stages of CKD, which has the potential to prevent anemia and its cardiovascular complications. To initiate therapy when Hb levels fall below 11 g/dL is probably too late. By then, many patients will have severe, irreversible LVH as well as other complications due to the effect of prolonged anemia.

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