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The relationship of haemoglobin level and survival: direct or indirect effects?

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Abstract
The relationship between haemoglobin (Hb) level and survival in patients with chronic kidney disease (CKD) is complex. This paper explores the physiological basis for the hypothesis that Hb level and survival are causally related in this patient group, and assesses the current state of knowledge from clinical studies. Issues related to the methodology and analysis of clinical studies limit the certainty with which conclusions regarding the direct relationship between Hb level and survival can be drawn. The data support the concepts that Hb level is associated with survival in patients both with and without CKD, that changes in Hb level are associated with cardiovascular disease (CVD), and that CVD is prevalent in patients with CKD. Hb level is affected by nutritional status, inflammation, and the availability and effectiveness of human recombinant erythropoietin (rHuEPO) therapy, as well as by the degree of kidney function. Thus, the complexity of the relationships between Hb level, CVD and survival in patients with CKD requires further study from both the mechanistic and the clinical perspective. Properly designed clinical trials with survival as an endpoint, as well as data from prospectively measured modifiers of Hb levels and other markers of CVD, are needed to determine the physiological and statistical interaction of these factors in clinical practice.

Keywords: anaemia; cardiovascular disease; chronic kidney disease; erythropoietin; haemoglobin; survival

Introduction

The common finding of anaemia in patients with chronic kidney disease (CKD) has generated much interest over the last two decades. The adverse consequences of anaemia in patients with CKD have been well documented [1–7], and treatment strategies for anaemia have been developed as a consequence. The optimal haemoglobin (Hb) target continues to be debated [8–11], and the complexity of the relationship between Hb levels and specific physiological processes is still being investigated. This review addresses the question of whether Hb level is directly or indirectly related to survival in patients with CKD by examining data on the pathophysiology and consequences of anaemia, as well as relevant issues related to clinical study design.

It is clear that lower Hb levels are associated with adverse outcomes in patients with CKD; specifically, lower Hb levels are related to changes in cardiac structure and function in populations prior to dialysis, receiving dialysis, and after kidney transplant [12–16]. Other adverse effects include impaired cognition, reduced quality of life, sleep disturbances, and decreased exercise tolerance [7,17,18]. Importantly, the presence of cardiovascular disease (CVD) is associated with reduced survival in patients with CKD, and is the leading cause of death in patients on dialysis. The association of CKD with lower Hb levels, higher prevalence of CVD, and poor survival lends support to the hypothesis that Hb level and survival may be directly related.

Improving poor survival rates for patients with CKD is an important objective and one that requires an improved understanding of those factors that impact on survival. In reviewing accumulated data, investigators have focused on a variety of factors thought to contribute to reduced survival in patients with CKD. In addition to CVD and lower Hb levels, markers of inflammation [such as C-reactive protein (CRP)], markers of disturbed endothelial function, markers of malnutrition, parathyroid hormone abnormalities, calcium phosphate abnormalities, homocysteine levels, dyslipidaemias, and asymmetrical dimethylarginine (ADMA) levels have all been associated with reduced survival or cardiovascular events in patients with CKD. This points to a complex relationship between Hb level, CVD and mediators

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of inflammation, atherosclerosis, and malnutrition in patients with CKD.

The specific nature of the relationship between Hb level and survival has yet to be established. Understanding of the physiological and pathophysiological processes is growing but is limited by statistical and methodological flaws in the accumulating clinical data.

Physiology/pathophysiology

Hb in patients with CKD

It is well known that a decrease in Hb level is predictable in CKD. This decrease appears to be related to many factors including a reduction in red blood cell life span, lack of substrates (iron), inflammation, malnutrition, and most importantly, to reduced erythropoietic response [19]. The decrease in Hb level appears to commence quite early in the course of CKD, thus exposing patients to a prolonged period of anaemia. The third National Health and Nutrition Examination Survey (NHANES III) demonstrated that the median Hb level for those with glomerular filtration rate (GFR) estimated at around 60 ml/min/1.73 m^2 was below physiological norms for both men and women [20]. Hb is essential for oxygen transport to organs and thus for tissue health. Cytokine release and activation of neurohormonal systems are secondary in importance to reduced oxygen delivery, but subsequently impact on the physiological response [21–23].

Data are emerging that support the role of erythropoietin as an anti-apoptotic hormone. The protective effect of erythropoietin in situations of trauma, ischaemia, or inflammation, as demonstrated in animal models, is intriguing [24–26]. It is possible that in patients with CKD, the interaction between lower Hb levels and reduced erythropoietin production contributes to poor survival. In other words, in addition to the negative effect of low Hb levels, the reduced levels of erythropoietin contribute to the poor outcome in patients with CKD. Support for this hypothesis comes from a recent study by Fink *et al.* [27] who reported improved outcomes with pre-dialysis rHuEPO therapy in a cohort of more than 3000 patients, but could not demonstrate a relationship between survival and Hb levels *per se*.

The haemodynamic consequences of prolonged low Hb levels are evident from numerous studies of patients with and without CKD. Cardiac consequences, such as left ventricular hypertrophy (LVH) and exacerbation of coronary artery disease, are clearly linked consistently to low levels of Hb, irrespective of the cause [4,28]. Thus, given the physiological importance of Hb level in sustaining tissue health, and the association with erythropoietin as a 'mediating' hormone, it is biologically plausible that Hb level is directly linked to patient survival. However, statistical and methodological issues in clinical studies performed to date have limited the ability to define the specific nature of this relationship.

Statistical and methodological issues: limitations to our knowledge

The majority of studies to date have been observational allowing only tentative causal relationships to be suggested [1,4,29–31]. Even in observational studies of a substantial size [28,29], only those variables for which data have been collected can be analysed. Associations between other variables, interactions, or independence of specific variables cannot be demonstrated. Therefore, conclusions from such studies are limited. Many studies are cross-sectional or retrospective, relying on information retrieved from administrative databases [27,30,32]. Most prospective studies are of insufficient duration to assess survival outcomes and instead, use surrogate markers for CVD (such as LVH or even congestive heart failure), thus limiting their value. Interventional studies performed to date have used inclusion and exclusion criteria that limit the ability to form generalizations with other populations [5,9,33]. More importantly, no study has been of sufficient duration to address the issue of survival. Few of the new markers of CVD or reduced survival have been assessed in conjunction with the 'classic' variables associated with outcome. Therefore, the potential interaction or competing significance of these newer markers in relation to previously described predictors (such as Hb level) is not known. These limitations in published clinical data make it difficult to clearly define the nature of the relationship between Hb level and survival.

Despite the above limitations, some consistent information has accumulated over the past few decades.

Survival in patients without CKD: Hb is important

A well-reported association between lower Hb levels and reduced survival in groups of patients without CKD has emerged over the last 8 years [34–41]. Response to interventions such as HIV therapy, radiation and chemotherapy, and surgery has been reported to be associated with Hb level. However, in these studies kidney function was not measured. This may have had a confounding effect on the results as poor or impaired kidney function often accompanies ageing, HIV, and chemotherapy. Data are accumulating that suggest CKD, even at mild stages, is a predictor of poor prognosis [42–45].

Survival in patients with CKD

(i) Without consideration of Hb levels

Seven studies published over the last 2 years [46–50] have demonstrated relationships between survival and specific measured factors, such as ADMA, hepatocyte growth factor, homocysteine, nutrition, low

parathyroid hormone (PTH), high calcium phosphate product, abnormal kidney function *per se*, and aortic stiffness. However, Hb level was neither measured nor used as a variable in predictive models, in any of these of these studies.

(ii) Hb level and CVD in patients with CKD

Ample data demonstrate that Hb levels predict CVD, particularly left ventricular mass index, LVH, congestive heart failure and cardiac-related hospital admissions in patients prior to dialysis, patients receiving dialysis, and those with a transplanted kidney. However, as mentioned above, the majority of the data are from studies that were observational, of relatively short duration, and did not consistently measure all other explanatory variables. Small studies have demonstrated the reversibility of LVH or improvement in cardiac function in patients prior to dialysis or receiving dialysis [18,26,31,51–53]. In a trial by Besarab *et al.* [9], raising Hb levels in haemodialysis patients with severe cardiac disease did not demonstrate benefit and resulted in higher mortality. Thus, results from the one study that *did* use survival as an outcome did not favour the treatment of anaemia in a high-risk group of patients.

It is interesting to note that in a recent study by London [28], raising Hb levels did result in an improvement in LVH, and associated mortality. However, this trial was neither randomized nor controlled and used target Hb levels outside currently recommended ranges [54–56].

Certain animal and human data provide support for the important role of Hb in CVD, particularly with respect to LVH [57,58]. A study in 299 women with iron-deficiency anaemia reported structural changes in the myocardium that were reversed with correction of anaemia by i.v. iron supplementation [38]. Thus, the relationship between Hb level and CVD is relatively consistent over different population groups.

CKD and survival

The presence of CKD predicts poorer survival relative to the absence of the condition. In studies of patients with CVD, those with impaired kidney function also had a greater burden of CVD and poorer outcomes [42–45,59]. Unfortunately, Hb levels are not reported in these studies. As a consequence, the relationship between Hb, CKD, and survival cannot be fully assessed. There is also accumulating evidence that the treatment of patients with CVD and CKD is often inferior to that of patients with CVD but without CKD [60–62].

Progression of CKD in relation to CVD and Hb levels

A correlation has been established between CKD, Hb level, and CVD in all populations. A high burden of co-morbidity, particularly CVD (angina, myocardial infarction, chronic heart failure, transient ischaemic attack, or peripheral vascular disease) at all levels of GFR (calculated by creatinine clearance rate) has recently been described in patients with CKD [63]. The prevalence of co-morbidity was at least 45% at all levels of kidney dysfunction. Moreover, in a multivariate model, the presence of CVD predicted time to renal replacement therapy (RRT), as did level of kidney function, PTH level, and Hb level. While the multivariate model demonstrated the statistical independence of these variables, it is unlikely that they are physiologically independent. For example, it is clear that anaemia can exacerbate symptoms of CVD, and that PTH contributes to a fall in Hb levels and myocardial fibrosis, as well as LVH. While no statistical relationships were found in the model, the existence of all of these conditions within one individual or group of patients emphasises the complexity of the pathophysiology of CVD in patients with CKD.

Table 1. Impact of Hb* on predicting RRT event

	Level of kidney function	
	30–60 ml/min	10–30 ml/min
Hb 130	1.00	1.00
Hb 120–129	1.06	1.62
Hb 110–119	3.21*	1.45
Hb 100–109	6.62	3.51*
Hb <100	8.72*	4.64*

Risk ratios: each level of Hb at baseline by level of kidney function. *Adjusted for age, gender, and diabetes; stratified by kidney function.

In a Canadian cohort of patients with CKD [4,59], we examined the impact of Hb on progression to RRT. We were able to determine that, for any given level of kidney function, the relative risk of progression to RRT was highest for the lowest decile of Hb level (Table 1). Others have demonstrated similar associations in the context of retrospective or case control studies [64,65]. Thus, it appears that Hb levels *per se* may impact on progression of CKD. Whether this is due to lack of erythropoietic effect on tissue, low Hb levels (and thus reduced capacity to carry oxygen to damaged tissue), or a combination of the two, cannot be determined without appropriately designed clinical studies.

Hb decline: impacting factors and complex relationships

The level of Hb, in the presence or absence of rHuEPO, is dependent on appropriate substrate availability, absence of inflammation, and good nutritional status. The fact that many patients with CKD have evidence of inflammation, malnutrition, underdialysis, or a combination thereof, further complicates the nature of the relationship between Hb level and survival.

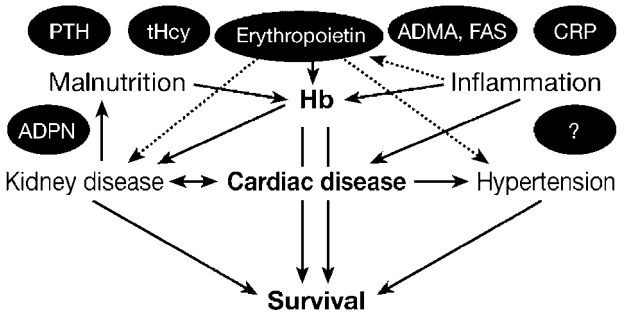

Fig. 1. The complex interaction between the many factors that contribute to survival in patients with CKD.

Serum markers of inflammation, malnutrition, and other processes have been demonstrated to predict survival or CVD events. Again, it is important that in most of the studies reported, Hb level was not included in the multivariate analysis. Thus, it is difficult to establish whether these predictive markers are affected by Hb levels, or if they act independently [66,67]. Zoccali *et al.* [68] have recently reported an inverse relationship between adiponectin (ADPN, a cardiovascular-protective adipocyte-derived substance), and CVD risk. Elaborate modelling, with and without conventional risk factors, uraemia-related risk factors (including Hb), and newer markers (tHcy and CRP) demonstrate the independent predictive value of ADPN on CVD events. It is interesting to note that the use of rHuEPO increased levels of ADPN. Thus, while no relationship between Hb and survival was demonstrated, an independent effect of ADPN on survival was observed: those patients with the lowest levels of ADPN had the worst outcome. Given that ADPN levels are affected by erythropoietin, the relationship between Hb level and survival may have been masked by the strength of the relationship with ADPN. Further investigation of this hypothesis is warranted.

Figure 1 depicts the complex interaction between the many factors that contribute to survival in patients with CKD.

Summary

This paper has attempted to address the fact that there are numerous methodological issues, that confound our ability to establish a conclusive relationship between Hb levels and survival in patients with CKD. There is also intriguing biological information that suggests a relationship between Hb level and survival in populations without CKD, between Hb level and erythropoietin and tissue health in a number of different biological models, and between Hb level and CVD in patients with CKD.

It is inescapable that Hb level and CVD are related in patients with CKD, and that CVD is the major cause of death in patients with CKD. The continuum of disease in patients with CKD occurs within the context of ongoing long-term exposure to multiple risk factors. It is imperative that we determine which risk factors (e.g. Hb level) are most important, and at which stage, to the patient outcome. The need for well-designed prospective mortality studies, enrolling patients with CKD prior to starting dialysis, and incorporating a 5–10-year follow-up, are essential if we are to answer the question of whether Hb levels are directly or indirectly related to survival in patients with CKD.

Key points

- CKD is associated with reduced survival.
- CKD is associated with high prevalence of CVD.
- Low Hb level, or fall in Hb, is associated with CKD.
- There is a clear relationship between erythropoietin deficiency and fall in Hb.
- The kidney is the major source of erythropoietin production. In the presence of impaired kidney function, the capacity for production of erythropoietin is reduced.
- Low Hb is associated with CVD in patients with CKD at all stages.
- Low Hb predicts structural and functional changes consistent with the pathophysiology induced by lower Hb.
- CVD is prevalent in patients with CKD.
- CVD is the major cause of morbidity and mortality in patients with CKD.
- Erythropoietin has effects on tissue health, independent of change in Hb.
- Given the importance of Hb in outcomes related to CKD, and its association with CVD in patients with CKD, the relationship of Hb to survival is likely to be both direct and indirect.

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