The role of anaemia in the genesis of cardiac abnormalities in patients with chronic kidney disease

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Introduction

The relationship of anaemia to the pathogenesis of cardiac abnormalities in patients with kidney disease has been the focus of much clinical and basic science research over the past two decades. There is extensive data to support the important contribution of anaemia to multiple morbidities in patients with kidney disease, not only cardiovascular disease (CVD). Anaemia impacts cognitive function, quality of life, exercise capacity, and sexual function in patients with kidney disease, and has been clearly linked to mortality in dialysis populations. Since the advent and availability of effective treatments for anaemia, there has been enormous interest in further understanding the role of anaemia in various pathophysiological processes.

The focus of this article is to detail the current state of knowledge with respect to anaemia and CVD and to identify areas of potential future research.

Anaemia and chronic kidney disease

Since the first observations of Bright [1], it is well recognized that patients with chronic kidney disease (CKD) have low haemoglobin (Hgb) levels. The aetiology of the anaemia was eventually determined to be primarily due to the reduction of erythropoietin production and activity. Other causes or contributors to anaemia are well known, and include deficiencies of important substrates (iron, carnitine and folic acid, B12), the presence of inhibitors (e.g. hyperparathyroidism), blood loss (overt and covert), and shortened red cell life span [2].

Importantly, any discussion about anaemia in patients with kidney disease must first define anaemia, and secondly define kidney disease. It is only with clear definitions of these two terms that we can begin to appropriately define the issue of anaemia and CVD in this population.

Anaemia is defined, according to World Health Organization (WHO) criteria, to be that level of Hgb below age- and gender-determined normal ranges. Thus, for males and non-menstruating females, anaemia is defined as Hgb < 13.5 g/dl, while in pre-menopausal women, anaemia is defined as a Hgb < 11.5 g/dl. Using these definitions, a large proportion of patients with chronic kidney disease have anaemia, and most dialysis patients remain anaemic throughout the course of their dialysis life.

Chronic kidney disease is best defined relative to estimated or measured glomerular filtration rate (GFR). While clearly those patients on dialysis have...
little or no GFR, the prevalence of CKD defined as reduced GFR < 60 ml/min is significant in both the general population and the post-transplant population. Recent reviews, consensus opinion, and KDOQI guidelines, suggest that individuals with an estimated GFR of less than 60 ml/min can be classified as having CKD. This level is chosen as that below which the prevalence of abnormalities associated with CKD is evident, and that level below which 'normal' ageing processes would not have impacted. Importantly in this group of patients, we must include those with reduced GFR who have both native and transplanted kidneys.

The prevalence of anaemia in patients with CKD prior to dialysis can be determined using population data [3], and data available from observational studies. Using WHO definitions of anaemia, 87% of patients with GFR below 25 ml/min, but not yet on dialysis have anaemia [4]. In the current era, 85% of patients are commencing dialysis with Hgb levels below 10.0 g/dl [5].

There is definitely a consistent relationship between degree of kidney dysfunction and degree of anaemia, but there is also a large degree of individual variation at any level of kidney dysfunction, among dialysis patients and in transplant patients. These individual variations have not been well studied.

## Anaemia and cardiovascular disease

Cardiovascular disease can be simplistically defined as including two basic processes: (a) disorders of cardiac function and structure; and (b) disorders of perfusion or vasculature [6, and Parfrey, personal communication]. The association of anaemia with CVD has been noted in dialysis patients by numerous investigators [7–12]. It is clear that there is excessive cardiovascular morbidity in association with anaemia in dialysis populations. In addition, Hgb levels have been shown to be associated with cardiac hospitalizations in patients prior to dialysis [4,13], and to predict morbidity and mortality in HD patients [14].

Most consistently, anaemia is associated with left ventricular hypertrophy (LVH), with congestive heart failure and to a lesser extent with ischaemic heart disease. The strong associations between level of Hgb and LVH or heart failure is described in dialysis patients and in those prior to dialysis [4,7–11]. Recent publications by Rigatto et al. [15,16], extend these observations of a consistent relationship of Hgb and heart disease/function in transplanted patients. In a cohort of patients followed post-transplant, Hgb level predicted the advent of de novo CHF events.

Importantly, there is a less clear association of Hgb and ischaemic heart disease events (angina and myocardial infarction) than there is with heart failure. The relationship to ischaemic events may be confounded by survival bias in cohort studies, or over-ridden by other factors contributing to atherosclerosis per se. Thus, anaemia may impact on CV disease in two ways: firstly by its indirect effect on cardiac structure, through the induction of LVH; and secondly indirectly by limiting oxygen delivery in the presence of atherosclerotic or arteriosclerotic lesions.

### Treatment trials

The results of interventional studies in patients with CKD have been limited by sample size, use of surrogate measures for CVD, duration or targets of therapy, or selection of specific populations. In haemodialysis patients, anaemia therapy has been demonstrated to reduce LV dilatation in asymptomatic patients with LVH [17]. In the oft quoted Normalization of Haemoglobin study published in New Engl J Med, normalization of Hgb did not improve, and in fact, was associated with a reduction in survival [18]. Of key importance, this study targeted individuals with severe cardiac disease: in retrospect those in whom the process of cardiac disease(s) had been well established, and unlikely to benefit from late intervention.

Most studies examining anaemia therapy in nephrology patients not on dialysis are (a) non-randomized and (b) of small sample size. Most have used LVH as the surrogate marker, given its strong association with outcomes, CHF and death in particular. Smaller studies in patients prior to dialysis [19–21], targeting patients prior to dialysis, have demonstrated some regression of LVH in those with anaemia who, on average, were treated to obtain Hgb levels of 12 g/dl from 10 g/dl.

To date, no long-term study has evaluated the impact of anaemia therapy on morbidity and mortality in patients with kidney disease prior to dialysis, though several are in progress internationally.

### Kidney function and cardiovascular disease

Interestingly, as recently reported by Mann et al. [22] in a sub-analysis of the HOPE study, the outcomes of CVD are adversely impacted by the presence of even 'minimal' kidney dysfunction. Others have reported similar findings in cohort or observational studies which underscore the importance of kidney function on predicting outcomes of CVD events [23,24]. We too have reported the high prevalence of CVD in patients prior to dialysis, and also the impact of the presence of CVD on time to renal replacement therapy [25].

Importantly, most studies do not differentiate ischaemic disease from heart failure, which, as noted above, may or may not be due directly to ischaemic or atherosclerotic disease. This simple, yet important, distinction is the shortcoming of studies to date, and does limit our current understanding of the complex pathophysiology of CVD in this group of patients.
Why should it be that anaemia impacts CVD so dramatically and consistently in patients with kidney disease?

The relationship between low Hgb levels and CVD outcomes (LVH and CHF or hospitalizations for cardiac problems) is consistently demonstrated in a number of populations: prior to dialysis, on dialysis and post-transplant. The impact of level of Hgb has been shown to be independent of kidney function, in non-dialysis patients, and thus not simply a marker for poor kidney function. Haemoglobin is well recognized as essential for oxygen delivery to tissues and vital organs, thus reduction in oxygen delivery stimulates a variety of adaptive responses which ultimately culminate in processes related to CVD expression. Hypoxia will necessarily stimulate compensatory mechanisms at both whole organ and cellular levels. Increase in cardiac output, heart rate and contractility is achieved through vasodilatation and increase in sympathetic activity. These ultimately lead to volume-mediated LV dilatation (eccentric LVH). The increase in oxygen extraction facilitated by the increase in 2,3 DPG and cellular adaptation can compensate for approximately 1–2 g/dl changes in Hgb, but after that, the increases in sympathetic system activation, mediated by cytokines and growth factors, become prominent. Superimposed on this set of anaemia related events, are those related to kidney disease itself: increases in plasma volume and hypertension, mediated in part by the renin-angiotensin system, lead to pressure-induced (concentric) LVH. As well, other factors (such as hyperparathyroidism, abnormalities of calcium and phosphate metabolism) may contribute to the process of LV growth and the change in myofibril constitution or orientation. Usually these processes of concentric and eccentric LVH occur concomitantly and continuously throughout the duration of kidney disease [26–29].

The consequences of LVH are subsequently exacerbated by lower Hgb, especially in the presence of established CVD (both micro- and macro-vascular disease) [30]. The increase in number of myocardial ischaemia events has been shown to increase 3- to 6-fold [10], as has the incidence of heart failure. While the issues of factors affecting cardiac structure/function versus those affecting perfusion (atherosclerosis and arteriosclerosis) may well be separate, they are undoubtedly related in patients with kidney disease [6].

Conclusions

Cardiovascular disease is responsible for 50% of the mortality of dialysis patients, and accounts for a similar proportion of death in patients with transplant kidneys [31–33]. The prevalence of CVD in all populations with kidney disease is approximately 35–40%, depending of course on definitions and invasiveness of documentation. Anaemia, as defined by WHO criteria, is pervasive in our patient populations. There is an epidemiological link and a plausible biological link between anaemia and CVD in patients with kidney disease. Studies are currently underway to establish the safety and utility of ‘normalizing Hgb levels’ in dialysis and non-dialysis populations, as well as to determine the impact of treatment on CV outcomes. We eagerly await the results of those studies. It is clear that we need to understand the appropriate timing of anaemia therapy or prevention in the course of a chronic disease process, be that CVD or CKD.

In the interim, it is important that clinicians and researchers alike remain clearly focused on accurately defining anaemia, CKD and CVD in nephrology patients. It is only in so doing that we will appropriately translate the findings of ongoing studies, and the data accumulating, into meaningful clinical practice.

References

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