Managing anaemia and diabetes: a future challenge for nephrologists

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Abstract
The combination of diabetes and chronic kidney disease is associated with increased mortality and reduced quality of life. Recent studies have shown that, in general, late referral of patients to the renal unit increases mortality, and that patients with diabetes who are referred late have a particularly poor prognosis. Several co-morbid conditions have been shown to contribute to poor patient outcomes, including both cardiovascular disease and anaemia. In patients with diabetic nephropathy, anaemia is more severe and is seen earlier than in patients with non-diabetic renal disease. Although the treatment of anaemia with recombinant human erythropoietin (rhEPO; epoetin) is well established, the only data currently available concerning the effects of early intervention in patients with diabetic nephropathy are from small-scale studies. Therefore, two large-scale studies have been designed to provide information on the efficacy of epoetin treatment and on how current management strategies might be improved. The Anaemia CORrection in Diabetes (ACORD) study will provide information on the potential cardiac benefits of early anaemia management in patients with early, type 2 diabetic nephropathy. The Individualised Risk-profiling In DiabEtes Mellitus (IRIDIEM) study will provide evidence-based guidance in risk factor management, by assessing the efficacy of individualized interventions.

Keywords: diabetic nephropathy; epoetin-β; renal anaemia

Introduction
The risk of complications, such as cardiovascular disease (CVD) and other organ damage, is strikingly higher in patients who suffer from both diabetes and chronic kidney disease (CKD) than in patients suffering from CKD alone [1]. Diabetes is now recognized as the most common primary co-morbid condition associated with end-stage renal disease (ESRD) [2–4], and increasing numbers of patients with diabetic nephropathy present to the nephrologist. This combination of CKD and diabetes has become a major health problem. The World Health Organization (WHO) estimated that in 2000 there were 151 million patients with diabetes (mainly type 2) worldwide. This figure is expected to increase by 46% to 221 million by 2010 [5]. The estimated prevalence of diabetes in Germany is 8.2% [6], and this figure is consistent with observations in other developed countries [7]. In the USA, it has been estimated that 19.2 million people over the age of 20 years have reduced kidney function [8], while almost 0.4 million patients suffer from ESRD [4].

The increasing number of patients with ESRD is partly attributable to improved management of the disease and its co-morbidities, prolonging the life expectancy of these patients [2,9]. Two of the main complications of CKD are CVD, which is the leading cause of death in dialysis patients [10], and anaemia [11]. As the major cause of renal anaemia is a decrease in the production of red blood cells resulting from inadequate erythropoietin (EPO) production, treatment with recombinant human erythropoietin (rhEPO; epoetin) effectively abrogates anaemia [9].

Two of the main aims in CKD management are to reduce complications and to delay the progressive loss of kidney function. Guidelines on anaemia management [12,13], nutritional therapy [14] and vascular access placement [15] have been published (summarized in St Peter et al. [9]). There is great variation in the timing of patient referral to nephrologists, largely because the individual roles of physicians and specialists are not well defined.

The current paper discusses the influence of diabetes and the consequences of late referral on the mortality of patients with CKD. Specifically, the co-morbidity and mortality associated with the management of diabetic nephropathy will be addressed. Two large-scale studies...
currently underway, investigating the management of diabetic nephropathy, will also be considered.

Late referral and survival

The prevalence of CKD with diabetes has increased in recent years, resulting in a progressive increase in the number of patients with diabetic nephropathy being referred to renal units. This escalation was highlighted in a recent, retrospective analysis of 280 patients with CKD, which demonstrated that 49% of patients referred to a renal unit over a 4 year period had diabetes, primarily type 2 [16]. The analysis demonstrated earlier death and higher cumulative mortality in patients with diabetes ($P = 0.01$; Figure 1a). Although the average systolic blood pressure and creatinine clearance rates were similar in both groups, serum creatinine concentrations were lower in patients with diabetes (Table 1). This disparity in serum creatinine concentrations may reflect the reduced muscle mass associated with neuropathy and may also partially explain why the degree of renal malfunction tends to be underestimated by primary care physicians. It also lends support to the argument for evaluation not only of serum creatinine concentrations but also of estimated serum creatinine clearance. These findings are supported by several other studies. The Third National Health And Nutritional Examination Survey (NHANES III) reported that anaemia was more prevalent in patients with a glomerular filtration rate (GFR) $< 60\text{ ml/min/1.73 m}^2$ (49.3%) [17]. A recent publication by Thomas et al. [18] also showed that anaemia, according to the WHO definition [19], was more prevalent (35–55%) in patients with diabetes who had a creatinine clearance rate of $< 60\text{ ml/min/1.73 m}^2$ [18].

It is well known that the outcome of dialysis is more favourable in patients without diabetes than in diabetic patients. The timing of consultation with a nephrologist is also an important determinant of dialysis outcome. The retrospective analysis of CKD patients conducted by Schwenger et al. [16] investigated survival rates according to the interval between referral and start of dialysis (average interval 17 weeks). The results demonstrated that survival was significantly ($P < 0.001$) better in patients who were referred early (≥17 weeks before start of dialysis) than if they were referred late (<17 weeks before start of dialysis) (Figure 1b). Indeed, the impact of late referral persisted beyond the first 12 months: excess mortality was still noticeable in the second year of dialysis (15.3% mortality with late referral vs 11.4% with early referral). Importantly, this analysis showed that late referral had the greatest impact on mortality in patients with diabetes (risk of mortality: 37% late vs 7.3% early) compared with those without (risk of mortality: 30.6% late vs 4.1% early).

Data from this analysis are supported by a recent review [20], which emphasized that patients who were referred later had less chance of avoiding ESRD and had poorer results on renal replacement therapy (RRT). This paper highlighted that late referral meant that patients missed the chance of early reno- and cardio-protective therapy and did not allow for adequate preparation for RRT.

These results clearly illustrate that late referral of patients, with or without diabetes, exposes them to a greater risk of death than early referral, presumably as a consequence of less efficient risk factor management. Late referral also represents a financial loss for society; it is estimated that an additional €30,000 are spent...
per patient at the start of dialysis following late referral, primarily because of longer periods of hospitalization [20]. Factors other than late referral, such as CVD and anaemia, are also associated with an increased risk of mortality in patients with diabetes.

Co-morbidity in CKD

Cardiovascular complications are important factors contributing to the increased risk of death in patients with diabetes. CKD is also a powerful risk factor for CVD. The net result is a particularly devastating frequency of cardiovascular events in diabetic patients, and the combination of diabetes and CKD has therefore become a major health problem. This was illustrated in a prospective study by Foley et al. [21], which compared the prevalence of cardiac abnormalities in patients with and without diabetes. The results showed that ischaemic heart disease, cardiac failure and concentric left ventricular hypertrophy (LVH) were significantly (P < 0.05) more prevalent in patients with diabetes (Figure 2), and that the incidence of de novo CVD was much higher, pointing to accelerated atherogenesis. The likelihood of overall and cardiovascular death was also significantly (P < 0.001) higher in patients with diabetes.

Coupled with the presence of diabetes, anaemia is thought to play a major role in augmenting the cardiovascular risk profile of CKD patients, including those with diabetes. Anaemia appears at an earlier stage of CKD in patients with diabetic nephropathy than in patients without diabetes [22]. Furthermore, Ishimura and colleagues [23] demonstrated that, for a given level of renal dysfunction, anaemia is more severe in patients with type 2 diabetes than in matched, non-diabetic, control patients (Table 2). In both groups, serum EPO concentrations were within the normal range, but the haemoglobin (Hb) concentration of anaemic diabetic patients was significantly lower than that of patients with non-diabetic renal disease (P < 0.01). These findings led the authors to conclude that both serum creatinine and the presence of diabetes are independent risk factors for the development of anaemia (r² = 0.49, P < 0.001).

Bosman et al. [22] demonstrated that anaemia occurs early in patients with type 1 diabetes with incipient diabetic nephropathy. They compared patients who had diabetic nephropathy with matched controls suffering from glomerulonephritis. Despite similar levels of proteinuria and serum creatinine in the two groups, nearly half of the patients with diabetic nephropathy were anaemic (defined as an Hb level ≤11.5 g/dl for women and ≤12.0 g/dl for men) compared with none of the patients in the control group. Early-onset anaemia in patients with diabetic nephropathy results from the kidney’s inability to increase EPO concentration appropriately [24,25]. This defect is apparently more pronounced in patients with diabetes than in those with renal disease but without diabetes.

Low baseline EPO concentrations can also be used to predict chronic renal failure in patients with diabetic nephropathy [26]. One of the hypotheses to explain this relationship is that EPO-synthesizing cells in the renal interstitium are more severely affected by diabetic nephropathy and are destroyed, such that they undergo phenotypic modulation or do not respond adequately to anaemia and hypoxia [27].

Fig. 2. Prevalence of cardiovascular abnormalities in patients with CKD with and without diabetes (adapted from Foley et al. [21] with permission).

Table 2. Severity of anaemia in patients with diabetic nephropathy vs patients with non-diabetic renal disease

<table>
<thead>
<tr>
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<th>Type 2 diabetes (n = 19)</th>
<th>Non-diabetic renal disease (n = 21)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 11</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/6</td>
<td>13/8</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>3.5 ± 1.6</td>
<td>3.8 ± 1.5</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.5 ± 2.1</td>
<td>11.2 ± 2.0*</td>
</tr>
<tr>
<td>Serum EPO (mU/ml)</td>
<td>19.8 ± 6.2</td>
<td>18.6 ± 5.6</td>
</tr>
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*P < 0.01 vs type 2 diabetes.

From Ishimura et al. [23] with permission.
Another marker of future deterioration is a low Hb concentration, which has been shown to be predictive of rapid renal disease progression [28]. The Reduction of End points in the NIDDM with the Angiotension II receptor Antagonist Losartan (RENAAL) trial demonstrated that Hb concentrations were lower in patients reaching a pre-defined renal end-point (i.e., a doubling of serum creatinine, the onset of ESRD or death) than in those who did not [28].

Research is currently underway to determine whether anaemia is a non-modifiable consequence of renal dysfunction or if the rate of renal disease progression can be affected by treatment with epoetin.

Epoetin and the management of diabetic nephropathy

As well as affecting the progression of renal disease, the question arises of whether epoetin administration is beneficial in the treatment of late complications of diabetes. Many such complications are ischaemic in nature, as exemplified by proliferative retinopathy, in which capillary closure and loss of the capillary lumen creates hypoxia of the retina. This process leads to the upregulation of vascular endothelial growth factor expression and provokes neo-angiogenesis [29]. It has yet to be determined whether epoetin can prevent this deleterious sequence, but there is a strong possibility that it can prevent late complications, not only in terms of retinopathy but also in terms of cardiac sequelae.

The efficacy of epoetin in correcting and maintaining Hb levels in patients with anaemia is well established, yet few data are available in patients with diabetes, apart from some small-scale studies [30–32]. To address this dilemma, two studies are currently underway, designed to investigate management strategies for patients with diabetic nephropathy.

The ACORD study

The Anaemia CORrection in Diabetes (ACORD) study has been designed to provide information on the effects of early anaemia correction compared with current treatment practices. The effects of subcutaneous epoetin-β (NeoRecormon®; Roche Pharmaceuticals) on cardiac structure, function and cardiovascular outcomes will be investigated in ~160 patients with early type 1 or 2 diabetic nephropathy over a 15 month, randomized treatment period. The rationale for this study is that early intervention might prevent target organ damage, which can result in anaemia and dialysis, by avoiding the drop in Hb concentrations.

Patients will receive epoetin-β at an initial dose of 2000 IU/week, once weekly, self-administered via the Reco-Pen® (Roche Pharmaceuticals). Patients randomized to the early treatment group will be started immediately on epoetin-β to reach the target Hb level of 13–15 g/dl at the end of the correction period. Patients in the conventional treatment arm will only be started on epoetin-β once their Hb level has dropped below 10.5 g/dl, to achieve and maintain target Hb levels of 10.5–11.5 g/dl.

To be eligible for inclusion, patients will be required to have an established diagnosis of diabetes with stable glycaemic control and clinical evidence of proteinuria for at least 3 months before enrolment. Other inclusion criteria include a creatinine clearance rate ≥30 ml/min and anaemia (Hb level ≥10.5 and <13.0 g/dl). The primary efficacy variable will be the change in left ventricular mass index from baseline to 15 months post-randomization. Secondary efficacy variables include left ventricular volume, fractional shortening, changes in renal function, mean weekly dose/kg of epoetin, and the percentage of patients with stable Hb levels (13–15 g/dl).

The IRIDIEM study

The Individualised Risk-profiling In DIabEtes Mellitus (IRIDIEM) study will investigate the current management of diabetic nephropathy, examining the effect of individualized and evidence-based cardio- and reno-protective interventions in patients with diabetes and CKD. The main objectives of this study are to describe the epidemiology of CKD and co-morbidities in elderly patients with type 2 diabetes, and to document current management practices. Actual management will be compared with current, evidence-based treatment guidelines, and risk profiles will be developed for these patients.

The first phase of the IRIDIEM study will be a pharmaco-epidemiological assessment of ~2500 patients, aged >60 years, with an established diagnosis of type 1 or type 2 diabetes for at least 5 years before enrolment. An assessment of risk factors will be performed to obtain baseline information. In the second phase, risk factors in a subgroup of ~700 patients with CKD stage III or IV [1] will be evaluated in two study arms (evidence-based treatment vs standard care). Patients and physicians in the evidence-based treatment arm of the study will receive additional education and training in accordance with current guidelines.

Results from this study will be used to determine whether educational guidance given by the treating physician and patient instruction on evidence-based, individualized, reno- and cardio-protective interventions is superior to standard care. Risk factors will be reassessed 3, 6, 9 and 12 months after enrolment.

Conclusions

The combination of diabetes and CKD is an important health problem. The poor outcomes of this condition result from several co-morbid conditions, including CVD and anaemia. Although effective treatments are available, one of which is epoetin administration, a delay in referral of patients may imply that they are not managed in the most appropriate way. Indeed,
recent evidence suggests that patients with CKD and diabetes require referral, treatment and disease management to be instigated earlier than current practice dictates, as these are all areas in which there is huge potential to improve patient outcomes. To this end, the results of the ACORD study will provide information on the cardiac benefits of early anaemia management, and the IRIDIEM study will provide evidence-based guidance in risk factor management.

Conflict of interest statement. None declared.

References