Anaemia after renal transplantation

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Abstract

Although the presence of anaemia after renal transplantation is well known, specific data on the prevalence and risk factors are scarce. Results from the recent TRansplant European Survey on Anemia Management (TRESAM) survey, conducted in 4263 recipients of a renal transplant from 72 centres in Europe, revealed that 38.6% of patients were anaemic [haemoglobin (Hb) concentrations ≤13 g/dl for male patients and ≤12 g/dl for female patients]. Of these patients, 11.6% had moderate anaemia (Hb concentrations >11 and ≤12 g/dl for male patients and >10 and ≤11 g/dl for female patients), while 8.5% had severe anaemia (Hb concentrations ≤11 g/dl for male patients and ≤10 g/dl for female patients). A strong association existed between Hb concentration and renal graft function. Of the patients with a serum creatinine level >2 mg/dl (which indicates impaired kidney function), 60.1% were anaemic, compared with 29.0% of those with a serum creatinine level ≤2 mg/dl (P<0.01). Other risk factors for anaemia include therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, the use of azathioprine or mycophenolate mofetil, kidneys from older donors and recent infections. Furthermore, only 18.8% of patients with severe anaemia were treated with erythropoietic therapy. The findings from the TRESAM survey are in agreement with the results from another recently published study that included 128 renal transplant patients from two centres in the USA, who were followed for 5 years after transplantation. It was found that 30% of patients were anaemic at some point after transplantation. The prevalence increased with time after transplantation, with 26% of patients being anaemic 5 years post-transplant. A multivariate logistic regression model identified three risk factors for post-transplant anaemia: serum total CO2, blood urea nitrogen and creatinine. There is an unexpectedly high incidence of anaemia in patients with a functioning renal transplant: around one-third of these patients are anaemic. Most of the evidence suggests that impaired erythropoietin production by the renal allograft is the most important pathogenic factor of post-transplant anaemia. Whether this high incidence of anaemia may be an additional cardiovascular risk factor in renal transplant patients remains to be proven. However, there does not appear to be any reason why anaemic renal transplant recipients should not be treated like any other patients with renal anaemia.

Keywords: anaemia; prevalence; renal transplantation; risk factors; treatment

Introduction

Renal transplantation is considered to be the treatment of choice for patients with chronic renal failure. A successful renal graft will correct not only the excretory functions of the kidney but also the endocrine functions (through the restored synthesis of erythropoietin and vitamin D). However, in the majority of transplant recipients, the renal graft does not function optimally. It is well known that renal excretory functions are not restored completely, but the extent to which renal endocrine functions are restored is less well understood. In addition, data regarding the factors involved in a potential incomplete correction of, for example, post-transplant anaemia are almost non-existent.

Although the presence of anaemia after renal transplantation is well known [1–4], this article aims to provide insight into the condition by answering the following questions:

- What is the prevalence of anaemia after renal transplantation?
- What are the risk factors for the development of anaemia after renal transplantation?
- How can post-transplant anaemia be treated?
Prevalence of anaemia after renal transplantation

Despite the existence of several large international transplant registries, no information regarding the correction of renal endocrine functions following transplantation is available from these sources. (The Scottish Renal Transplant Registry has collected data relating to the incidence of anaemia in their patients, but these data had not been published at the time of writing this article.) To date, only three publications [5–7] present the results of studies of anaemia following renal transplantation; these are summarized in Table 1 and are discussed below.

The first study [5] included 60 renal transplant patients. As the study was performed in Japan, most of the patients were recipients of kidneys from living donors. Patients with a serum creatinine level >3 mg/dl were excluded from the study. The authors reported a 20% prevalence of anaemia [defined as haemoglobin (Hb) concentrations <12.8 g/dl for male patients and <11.5 g/dl for female patients].

The second study [6] was performed in the USA and included 128 renal transplant patients. This was a combined initiative from the University of Stanford (n = 88) and the University of North Carolina (n = 40), and was the first time that an American group had looked at the incidence of anaemia in renal transplant recipients. An interesting aspect of this study was that the patients were followed for 5 years after transplantation. The authors reported that 30% of patients were anaemic at some point after transplantation, and that the prevalence increased with time after transplantation, with 26% of patients being anaemic by 5 years after transplantation (anaemia was defined as haematocrit <33 volume percentage). In addition, anaemia occurred in 62.5% of patients whose immunosuppressive therapy was switched from azathioprine to mycophenolate mofetil.

The third study [7], which has been published recently in the American Journal of Transplantation, included 4263 renal transplant patients from 72 centres in 16 European countries [TTransplant European Survey on Anemia Management (TRESAM) survey]. The patients were divided into four cohorts and assessed 6 months (n = 1003), 1 year (n = 960), 3 years (n = 1254) and 5 years (n = 1046) after transplantation. Recipients of multiple organs, pregnant women and children aged <10 years were excluded from the study.

Demographic data indicate that the patients included in the TRESAM survey were representative of the European transplant population [7]. Approximately 60% of patients were male and 40% were female, and these proportions were similar in the four cohorts. The mean (SD) age of transplant recipients at transplantation was 45.5 (13.1) years, although patients who had received their transplant more recently were significantly (P = 0.01) older at transplantation than patients who had received their transplant 5 years ago. In addition, a greater proportion of the more recent transplants were recipients of a second transplant.

The proportion of patients in this survey who had received their kidney from a living donor was rather low (~10%), which is typical of the situation in Europe. The distribution of donor age showed that, as expected, the living donors were significantly older than the cadaverous donors [mean age, 49.0 (11.5) years vs 42.9 (16.1) years; P < 0.01], and also that the donors being used today are older, compared with those used 5 years ago.

The most prevalent underlying kidney disease in the TRESAM survey was chronic glomerulonephritis (29.8–37.0% across the four cohorts). The prevalence of diabetic nephropathy was rather low (6.5–7.5%), but one explanation for this may be that patients with multiple organ transplants (i.e. combined kidney–pancreas transplants) were excluded from the study. The most frequently occurring co-morbidities were coronary artery disease (13.0–16.1%), hepatitis B/C (9.3–10.8%) and type 2 diabetes mellitus (8.7–10.1%).

Serum creatinine levels were lowest in the cohort who underwent transplantation most recently: mean levels were 1.6 (0.6) mg/dl in the 6 month cohort and 1.8 (1.0) mg/dl in the 3 year cohort (P < 0.01). The opposite was true for creatinine clearance: mean clearance rates were 62.4 (28.2) ml/min in the 6 month cohort and 57.7 (26.4) ml/min in the 5 year cohort (P < 0.01).

Pre-transplant Hb concentrations were significantly higher in patients who had received their transplant more recently than in patients who had received their transplant 5 years ago [mean Hb concentrations were 11.9 (1.7) g/dl in the 6 month cohort vs 10.8 (1.8) g/dl in the 5 year cohort; P < 0.01], which suggests that anaemia in dialysis patients is managed better today, compared with 5 years ago. Figure 1 shows mean pre-transplant Hb concentrations along with mean Hb concentrations at the time of enrolment in the survey.

Table 1. Summary of publications presenting the results of studies of anaemia following renal transplantation [5–7]

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>No. of patients</th>
<th>Definition of anaemia</th>
<th>Prevalence of anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al. [5]</td>
<td>Japan</td>
<td>60</td>
<td>Hb &lt;12.8 g/dl for male patients and</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;11.5 g/dl for female patients</td>
<td></td>
</tr>
<tr>
<td>Yorgin et al. [6]</td>
<td>USA</td>
<td>128</td>
<td>Haematocrit &lt;33 volume percentage</td>
<td>30% at some point post-transplant, 26% at 5 years’ post-transplant</td>
</tr>
<tr>
<td>Vanrenterghem et al. [7]</td>
<td>Europe</td>
<td>4263</td>
<td>Hb ≤13 g/dl for male patients and</td>
<td>38.6% (of these patients, 11.6% had moderate and 8.5% had severe anaemia)</td>
</tr>
</tbody>
</table>
Anaemia, defined as Hb concentrations ≤13 g/dl for male patients and ≤12 g/dl for female patients according to the Clinical Practice Guidelines for Outpatient Surveillance of Renal Transplant Recipients [8], was present in 38.6% of patients in this survey, and was equally distributed between the sexes. Of these patients, 11.6% had moderate anaemia (Hb concentrations >11 and ≤12 g/dl for male patients and >10 and ≤11 g/dl for female patients), while 8.5% had severe anaemia (Hb concentrations ≤11 g/dl for male patients and ≤10 g/dl for female patients). In patients with a serum creatinine level >2 mg/dl, 60.1% were considered anaemic, whereas in patients with a serum creatinine level ≤2 mg/dl, only 29.0% of patients were considered anaemic (P < 0.01). The findings of the TRESAM survey are in agreement with the results published by the American group [6].

Risk factors for the development of anaemia after renal transplantation

In an overview of erythropoietin and renal transplantation published in Kidney International [1], Muirhead notes that: 'A number of factors have been suggested as influencing the recovery of anaemia after renal transplant, including the development of initial non-function, acute rejection, intercurrent illness, and iron deficiency’. Although these risk factors have been suggested, none has yet been proven.

The American group [6] examined their data for risk factors for the development of post-transplant anaemia. A multivariate logistic regression analysis performed 1 year after transplantation identified three risk factors: serum total CO₂, blood urea nitrogen and creatinine (Table 2). The authors interpreted this result as renal dysfunction—or diminished function of the renal allograft—being the most important risk factor for the development of anaemia after transplantation. The low total CO₂ (in other words, the presence of metabolic acidosis) was considered a surrogate marker for impaired kidney function.

A logistic regression analysis looking at risk factors for post-transplant anaemia was also performed in the TRESAM survey [7]. The risk factors identified in this group of >4000 patients are shown in Table 3. A strong association is seen between Hb concentration and renal graft function: patients with a serum creatinine level >2 mg/dl (which indicates impaired kidney function) were more than three times more likely to be anaemic than those with a level ≤2 mg/dl. In addition, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists was associated with a higher likelihood of being anaemic, as was donor age.

### Table 2. Risk factors for post-transplant anaemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (±1 SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum total CO₂</td>
<td>−0.402±0.131</td>
<td>0.0021</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>0.069±0.034</td>
<td>0.0392</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.136±0.567</td>
<td>0.0451</td>
</tr>
</tbody>
</table>

Reproduced, with permission, from Yorgin et al. [6].

### Table 3. Risk factors for post-transplant anaemia in the TRESAM survey [7]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio 95% CI of ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine &gt;2 mg/dl</td>
<td>3.48</td>
<td>2.92–4.14</td>
</tr>
<tr>
<td>ACE inhibitors or angiotensin II</td>
<td>1.55</td>
<td>1.34–1.80</td>
</tr>
<tr>
<td>Receptor antagonists</td>
<td>1.41</td>
<td>1.16–1.72</td>
</tr>
<tr>
<td>Age of donor &gt;60 years</td>
<td>1.34</td>
<td>1.13–1.64</td>
</tr>
<tr>
<td>Mycophenolate mofetil or azathioprine</td>
<td>1.24</td>
<td>1.05–1.47</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>0.70</td>
<td>0.56–0.88</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CI = confidence interval.
>60 years (because age was an independent factor, this finding cannot be explained by these patients having a lower creatinine clearance rate). Recent infection was also a risk factor for anaemia, and the use of azathioprine or mycophenolate mofetil was associated with an odds ratio of 1.24 for being anaemic (the result for mycophenolate mofetil is perhaps surprising because this drug is not expected to have a major effect on the proliferation of bone marrow cells except lymphocytes [9]). However, the presence of polycystic kidneys in the recipient after transplantation had the opposite effect (indeed, the incidence of anaemia in patients with polycystic kidneys as their underlying kidney disease was lower than in patients with renal failure due to other diseases). These data [6,7] indicate that renal allograft dysfunction is probably the most important aetiological factor in the development of post-transplant anaemia.

Furthermore, most of the evidence suggests that the leading cause of anaemia is impaired production of erythropoietin by the failing allograft. In his overview [1], Muirhead comments that: ‘Several studies have indicated that endogenous serum [erythropoietin] concentrations are low in anaemia related to allograft failure, as in other forms of renal anaemia, suggesting that [erythropoietin] deficiency is the dominant aetiological factor, despite concerns to the contrary [4,10]’. These concerns to the contrary have not yet been proven. If impaired production of erythropoietin by the failing allograft is the leading cause of anaemia, then treatment with erythropoietin may also be considered. Only few data on the efficacy of erythropoietic therapy in renal transplant recipients are available.

**Treatment of post-transplant anaemia**

Anaemia in kidney transplant recipients may have an adverse effect on long-term outcome. In particular, anaemia may contribute to cardiovascular risk, which is of concern because cardiovascular events are known to be the main cause of death in transplant patients [11].

The question of how to treat post-transplant anaemia was addressed in the TRESAM survey [7]. Surprisingly, of the 3969 patients for whom the use of erythropoietic therapy was documented, only 207 (5.2%) had received erythropoietic therapy for the treatment of anaemia (Figure 2). Even more striking was the fact that among the group of anaemic patients \( n = 1539 \), only \(~10\%\) had received erythropoietic therapy for their anaemia (Figure 2). Of the 343 patients with severe anaemia, 17.8% were treated with erythropoietic therapy.

Possible reasons for the reluctance of nephrologists to correct anaemia in transplant patients include the ‘psychological factor’, concerns regarding the safety of therapy and concerns regarding the efficacy of therapy. The ‘psychological factor’ appears to be of importance. If a transplant recipient is told that they need to restart erythropoietic therapy, the tendency is for them to assume that their kidney function is declining and that their transplant has been unsuccessful.

In terms of the safety of therapy, there have been concerns regarding the normalization of Hb concentrations. A few studies, involving small numbers of patients, have suggested that transplant recipients treated with epoetin develop hypertension, which requires treatment with antihypertensive drugs [1, 12,13]. However, to date, there have been no indications that patients treated with erythropoietic therapy after transplantation show a more rapid deterioration of their allograft function [1].

Several small-scale studies suggest that erythropoietic therapy may be an effective treatment for post-transplant anaemia [1,12–14]. In addition, Lezaic et al. provide a clear answer to concerns regarding the efficacy of therapy [10]. These authors studied three groups of patients: eight renal transplant patients

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Fig. 2. Epoetin treatment in the TRESAM survey [7]. *Patients for whom epoetin use was documented (yes/no).
(group A), 20 pre-dialysis patients (group B) and 17 haemodialysis patients (group C). Before starting erythropoietic therapy, the patients in groups A and C had the most severe anaemia [mean (SEM) Hb concentrations were 6.1 (0.2) g/dl in group A, 7.4 (0.1) g/dl in group B and 6.5 (0.1) g/dl in group C]. However, the correction of anaemia by erythropoietic therapy was the same in all three groups. These results suggest that the response to erythropoietic therapy of patients with anaemia post-transplant is comparable with that of anaemia due to other forms of renal failure.

Conclusion

There is an unexpectedly high incidence of anaemia in patients with a functioning renal transplant: around one-third of these patients are anaemic. Risk factors for low Hb concentrations in transplant recipients include impaired renal function, use of ACE inhibitors or angiotensin II receptor antagonists, kidneys from older donors, the presence of recent infections, use of azathioprine or mycophenolate mofetil and type of underlying kidney disease. The most important risk factor appears to be impaired renal function.

Most of the evidence suggests that impaired erythropoietin production by the renal allograft is the most important pathogenic factor of post-transplant anaemia. Whether the high incidence of anaemia may be an additional cardiovascular risk factor in renal transplant patients remains to be proven. However, there does not appear to be any reason why anaemic renal transplant recipients should not be treated like any other patients with renal anaemia.

Conflict of interest statement. None declared.

References