Anemia With Impaired Erythropoietin Response in Diabetic Patients

Merlin C. Thomas, MBChB, PhD; Mark E. Cooper, MBBS, PhD; Con Tsalamandris, MBBS; Richard MacIsaac, MBBS, PhD; George Jerums, MBBS, MD

Background: Diabetes mellitus is associated with an increased prevalence of anemia, particularly in patients with nephropathy. We undertook this survey to determine the relationship between anemia and the renal production of erythropoietin in patients with diabetes mellitus.

Methods: The clinical data of 722 patients were obtained, including markers of diabetic complications. Erythropoietin levels were measured in the same samples. Patients with a full blood cell count, iron indexes, and renal function within the normal range (n=151) were used to define the reference range for this population. Anemic patients who had erythropoietin levels within this range were defined as having an "inappropriate erythropoietin response to anemia."

Results: Of the 722 patients, 168 (23.3%) had anemia, of whom 130 (77.4%) had erythropoietin levels inappropriately within the normal range. Although 55.4% of anemic patients had moderate renal impairment, erythropoietin levels were also inappropriately low in 69.2% of anemic patients with normal renal function. However, most of these patients (17 of 26) had diabetic kidney disease, as denoted by albuminuria.

Conclusions: The failure to produce erythropoietin in response to a declining hemoglobin level is a common contributor to anemia in patients with diabetes mellitus. This seems to be a manifestation of diabetic kidney disease, in the presence or absence of renal impairment.

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Diabetes mellitus is the single most common cause of end-stage renal disease and consequently the most common cause of renal anemia. Patients with diabetes mellitus are also twice as likely to have anemia as those with renal impairment from other causes. Declining hemoglobin (Hb) levels may be observed before changes in renal function. A cross-sectional series, involving patients with type 1 and type 2 diabetes mellitus, that revealed that 23% of unselected outpatients have Hb levels below the normal range (men, <13 g/dL; and women, <12 g/dL) has been published. In these patients, the additional burden of anemia may influence their clinical outcome.

The renal production of erythropoietin in response to changes in tissue oxygenation is an important regulator of hemopoiesis. It has been speculated that anemia may arise in those with diabetes mellitus from dysfunction of the erythropoietin-producing cells in the cortical interstitium. Indeed, erythropoietin production has been proposed as a functional marker of the tubulointerstitium. While previous series have documented reduced erythropoietin levels in patients with diabetes mellitus, these studies have selected patients with established complications, such as autonomic neuropathy or proteinuria. However, before clinical guidelines for the management of anemia can be developed, the contributors to anemia in those with diabetes mellitus need to be established in a population of patients without preselection for complications.

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erythropoietin, was calculated according to standard formulas. As in the general population, iron deficiency was defined as the presence of a transferrin saturation level of less than 16% or a ferritin level of less than 15 ng/mL, although higher thresholds are used in patients with end-stage renal disease. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease Study equation 6 in all patients. In 457 patients (66%), the isotopic GFR was also directly measured using technetium 99m-labeled diethylene triamine pentaacetic acid. The presence of renal impairment was defined categorically according to National Kidney Foundation guidelines. The same serum samples were used to determine circulating erythropoietin levels using a erythropoietin assay (IMMULITE 2000; Diagnostic Products Corporation, Los Angeles, Calif), performed according to manufacturer’s instructions. Because there is no clear laboratory definition of what constitutes a normal erythropoietin level in patients with diabetes mellitus, all patients with normal renal function, normal iron indexes, and an Hb level within the normal range were defined as a “reference” population for this study. Patients with an erythropoietin level more than 2 SDs above the mean for this population were defined as having elevated erythropoietin levels. Patients with anemia and erythropoietin levels within the normal range were regarded as having an “inappropriate renal response to anemia.”

RESULTS

Endogenous erythropoietin levels were measured in 722 patients with diabetes mellitus whose clinical characteristics have been previously reported. In this population, 168 (23.3%) of the patients with diabetes mellitus (75 women and 93 men) had anemia (Hb level, <12 g/dL for women and <13 g/dL for men). More than 80% of anemic patients had evidence of diabetic kidney disease, including 51.4% with elevated albumin levels in the urine (albumin excretion rate, >20 µg/min) and 55.4% with moderate renal impairment (estimated GFR, <60 mL/min per 1.73 m²). Although the Modification of Diet in Renal Disease Study equation 6 may be less accurate in patients with normal renal function, it was closely correlated with isotopic measurements ($R^2=0.73$, $P<.001$).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Anemia (n = 554)</th>
<th>Anemia and Normal Erythropoietin Level (n = 131)</th>
<th>Anemia and Increased Erythropoietin Level (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin level, mU/mL†</td>
<td>15 ± 8</td>
<td>16 ± 7</td>
<td>74 ± 112‡§</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL‡†</td>
<td>14.1 ± 1.1</td>
<td>11.6 ± 1.0‡</td>
<td>11.0 ± 1.1‡§</td>
</tr>
<tr>
<td>Age, y†</td>
<td>61 ± 13</td>
<td>66 ± 12‡</td>
<td>65 ± 13‡</td>
</tr>
<tr>
<td>Male sex</td>
<td>310 (56.0)</td>
<td>74 (56.5)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Duration of diabetes mellitus &gt;10 y</td>
<td>288 (52.0)</td>
<td>89 (67.9)‡</td>
<td>25 (67.6)‡</td>
</tr>
<tr>
<td>Macraalbuminuria</td>
<td>39 (7.0)</td>
<td>33 (25.2)‡</td>
<td>10 (27.0)‡</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m²†</td>
<td>79 ± 26</td>
<td>57 ± 28‡§</td>
<td>66 ± 28§</td>
</tr>
<tr>
<td>GFR&lt;60 mL/min per 1.73 m²</td>
<td>111 (20.0)</td>
<td>77 (58.8)‡</td>
<td>16 (43.2)‡</td>
</tr>
<tr>
<td>C-reactive protein level &gt;10 U/mL</td>
<td>83 (15.0)</td>
<td>41 (31.3)‡</td>
<td>16 (43.2)‡</td>
</tr>
<tr>
<td>Transferrin saturation &lt;16%</td>
<td>83 (15.0)</td>
<td>40 (30.5)‡</td>
<td>27 (73.0)‡§</td>
</tr>
<tr>
<td>Ferritin level &lt;15 ng/mL</td>
<td>9 (1.6)</td>
<td>9 (6.9)</td>
<td>13 (35.1)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>177 (31.9)</td>
<td>55 (42.0)‡</td>
<td>16 (43.2)‡</td>
</tr>
<tr>
<td>Ischemic heart disease‡</td>
<td>150 (27.1)</td>
<td>54 (41.2)‡</td>
<td>16 (43.2)‡</td>
</tr>
<tr>
<td>Peripheral vascular disease§</td>
<td>55 (9.9)</td>
<td>29 (22.1)‡</td>
<td>8 (21.6)‡</td>
</tr>
<tr>
<td>Any macrovascular disease¶</td>
<td>188 (33.9)</td>
<td>75 (57.3)‡</td>
<td>20 (54.1)‡</td>
</tr>
</tbody>
</table>

Abbreviation: GFR, glomerular filtration rate.

*Data are given as number (percentage) in each group unless otherwise indicated.
†Data are given as mean ± SD.
‡P<.05 for this group vs the no anemia group.
§P<.05 for this group vs the anemia and normal erythropoietin level group.
¶Patients with a clinical history of myocardial infarction, angina, or coronary revascularizations (angioplasty, stenting, or coronary artery bypass grafting).
†Data are given as number (percentage) in each group unless otherwise indicated.
‡P<.05 for this group vs the no anemia group.
§P<.05 for this group vs the anemia and normal erythropoietin level group.
¶Patients with a clinical history of ischemic heart disease, cerebrovascular disease, or peripheral vascular disease.

ERYTHROPOIETIN LEVELS

Of the patients, 151 (85 men and 66 women) had normal renal function, normal iron indexes, and an Hb level within the normal range. Their mean ± SD level of endogenous erythropoietin was 16±7 mU/mL. Of these patients, 2.5% had a level greater than 30 mU/mL. This level was used to define the upper limit of the normal range for patients in our survey. This is similar to a 97.5% upper limit of 29 mU/mL reported in healthy volunteers.

Of the 168 anemic patients, 130 (77.4%) had erythropoietin levels within the study-defined reference range for patients with diabetes mellitus, denoting an inappropriate renal response to anemia. More than three quarters of these patients (100 [76.9%] of 130) had moderate renal impairment and/or albuminuria. Of the 168 patients with anemia, 38 (22.6%) had endogenous erythropoietin levels of more than 30 mU/mL. Most of these patients (27/38) had iron deficiency (transferrin saturation level, <16%), 4 had chronic lung disease, and 4 had other identifiable causes of anemia. Other characteristics of these patients, who were able to increase their erythropoietin levels in response to anemia, are shown in the Table. Notably, the more severe the anemia, the less likely that patients had anemia associated with inappropriate renal erythropoietin response to anemia (Figure).

ASSOCIATIONS WITH AN INAPPROPRIATE RENAL RESPONSE TO ANEMIA

The presence of nephropathy was the strongest predictor for anemia associated with normal erythropoietin levels. However, in 74 anemic patients without renal impairment (GFR, >60 mL/min per 1.73 m²), 56 (75.7%) had erythropoietin levels that remained within the normal range. Indeed, even in 26 patients with anemia and normal renal function (GFR, >90 mL/min per 1.73 m²), 18 (69.2%) had erythropoietin levels within the normal range. Notably, more than half of these patients (17 of 26) had diabetic kidney disease, as denoted by an elevated albumin level in the urine. All 18 of the anemic patients with elevated erythropoietin levels and a GFR greater than 60 mL/min per 1.73 m² were iron deficient. Consistent with the known effect of iron defi-
Anemia is common in those with diabetes mellitus and is associated with a high prevalence of an inappropriate renal response to reduced Hb levels. The mechanism of dysfunction remains to be established but is clearly associated with diabetic kidney disease. However, unlike other forms of renal disease, the presence of renal impairment is not a prerequisite for erythropoietin-dependent anemia, because even in patients with normal renal function, the failure of the kidney to produce erythropoietin in response to a decreasing Hb level is still the major cause of anemia. Nevertheless, most of these patients have diabetic kidney disease, because they also have an elevated albumin level in the urine.

Iron deficiency was the most common cause of anemia in patients with elevated erythropoietin levels. Transferrin saturation levels were also reduced in many patients with normal erythropoietin levels (Figure). It is conceivable that patients with diabetic kidney disease may be more sensitive to reduced iron availability, which is normally compensated by increased renal production of erythropoietin. Consequently, the thresholds used by this study to denote absolute iron deficiency may be inappropriate low. The same situation is seen in patients with end-stage renal disease taking erythropoietin, who may still be responsive to iron supplementation despite relatively normal iron indexes (functional iron deficiency). However, iron supplementation may negatively impact glyce-mic and lipid control and contribute to oxidative injury in those with diabetes mellitus.

Once other causes of anemia are excluded, these data suggest that most patients with diabetes mellitus and anemia may be responsive to supplementation with erythropoietin or related analogues. Correction of anemia may confer particular benefits in patients with diabetes mellitus. Treatment with erythropoietin in diabetic patients with heart failure may also have beneficial effects on tissue oxygenation and end-organ function. In addition, cognitive and sexual function, exercise tolerance, and ability to work may all be favorably influenced by the correction of anemia. These potential advantages must be carefully balanced against the costs involved in treating many patients with anemia and the possibility for deleterious effects, including a higher blood pressure. Hopefully, upcoming trials involving the correction of anemia in patients with diabetes mellitus will help clarify the optimal approach to this disorder. Meanwhile, the detection of anemia should identify patients with diabetes mellitus at increased risk of adverse clinical outcomes.3,4

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REFERENCES