Anemia With Erythropoietin Deficiency Occurs Early in Diabetic Nephropathy

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OBJECTIVE — The normochromic normocytic anemia of erythropoietin (EPO) deficiency is recognized in advanced renal failure but not in early renal disease. The aim of this study was to determine whether anemia with EPO deficiency is found in type 1 diabetic patients with diabetic nephropathy in the absence of advanced renal failure and to compare them with patients with nondiabetic renal disease of similar severity.

RESEARCH DESIGN AND METHODS — A total of 27 type 1 diabetic patients with diabetic nephropathy (DN), defined as having persistent proteinuria (mean 1,086 mg/day [CI 120–5,190]), a serum creatinine ≤180 μmol/l, and retinopathy, were compared with 26 nondiabetic patients with glomerulonephritis (GN) and persistent proteinuria (1,874 mg/day [349–5,005]). The Hb concentration, red cell indexes, and serum EPO levels were measured, and other causes for the anemia were excluded. The EPO values were compared with a normal reference range obtained from nondiabetic patients with a microcytic anemia. The DN patients were tested for signs of diabetic peripheral and autonomic neuropathy.

RESULTS — We found that 13 of the 27 DN patients were anemic (Hb 10.6 ± 0.9 g/dl) in marked contrast to none of the GN patients (Hb 13.7 ± 1.4 g/dl, $P < 0.005$). In the DN group, serum EPO concentrations failed to increase in response to anemia compared with the response seen in patients with microcytic anemia. Thus, the anemia of the DN group was associated with EPO deficiency. The anemic DN patients showed evidence of more severe proteinuria and diabetic neuropathy than the nonanemic DN patients.

CONCLUSIONS — Anemia associated with EPO deficiency can occur early in DN before the onset of advanced renal failure, but does not normally occur in nondiabetic renal disease of similar severity. The pathogenesis requires elucidation.

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Erythropoietin (EPO), a 30.4-kDa glycoprotein, is produced mainly by the peritubular fibroblasts of the renal cortex in adult life (1). The actions of EPO include stimulation of erythroid progenitor cells and differentiation of normoblasts to increase the red cell mass in response to tissue hypoxia precipitated by anemia, hemorrhage, or altitude (1–3).

An anemia with EPO deficiency has recently been described in some type 1 diabetic patients with severe symptomatic diabetic autonomic neuropathy (4,5). EPO release is thought to be modulated by the splanchnic innervation of the kidneys because renal denervation in animal models leads to a loss of EPO production in response to hypoxic stimuli (6–8). It has been postulated that EPO deficiency in these patients may be caused at least in part by efferent sympathetic denervation of the kidney leading to the loss of appropriate EPO production (5), and there is some clinical and experimental evidence that this may be the case (6–11). However, all of these autonomic neuropathy patients also had evidence of diabetic nephropathy (DN) with persistent proteinuria, although some had only microalbuminuria. Because the lesion of DN may involve not only the glomeruli but also the renal interstitial area (12), it is possible that the EPO deficiency of these patients results from damage to the EPO-producing fibroblasts and is not a consequence of the neuropathy itself.

The aim of this study was to determine whether an EPO-deficient anemia exists in patients with DN without severe renal function impairment and to compare them with a group of patients with nondiabetic renal disease of comparable severity.

RESEARCH DESIGN AND METHODS

— Patients were recruited from the King's Diabetes Center and the renal clinic at King's College Hospital, London. The study was approved by the local ethics committee, and all patients gave their informed consent. We identified 27 consecutive type 1 diabetic patients aged <60 years with persistent proteinuria and retinopathy. Persistent proteinuria was defined as positive (1+ or more) Albustix readings for >1 year. Patients with a serum creatinine level of >180 μmol/l were excluded. A diagnosis of DN was assumed because all of the patients showed evidence of diabetic retinopathy. We also recruited 26 patients aged <60 years with glomerulonephritis (GN) if there was evidence of proteinuria (more than one positive Albustix reading) and a serum creatinine level ≤180 μmol/l. Causes of GN confirmed by renal biopsy included IgA nephropathy (6), minimal change nephropathy (1), focal segmental glomerulosclerosis (2), mesangiocapillary GN (1), secondary interstitial nephritis (1), IgA-negative mesangioproliferative GN (4), and membranous GN (7). Patients with vasculitic causes for GN, such as systemic lupus erythematosis, and those with concomitant diabetes were excluded.

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Abbreviations: DN, diabetic nephropathy; EPO, erythropoietin; GN, glomerulonephritis; PH, postural hypotension.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and biochemical characteristics of the two groups*

	DN	GN
n	27	26
Sex (M:F)	10:17	16:10
Age (years)	41 ± 9	44 ± 12
Proteinuria (mg/day)	1,086 (120–5,190)	1,874 (349–5,005)
Creatinine (μmol/l)	96 (63–160)	93 (49–180)
Retinopathy (proliferative:background)	25:2	—
Use of ACE/angiotensin II inhibitors	22	21
Number of anemic patients	13	0

Data are *n*, means ± SD, or mean (range).

Methods

The patients with DN were assessed for all symptoms and signs of diabetic complications, including diabetic peripheral and autonomic neuropathy. Autonomic symptoms, as defined by Guy et al. (13), including postural hypotension (PH), diabetic diarrhea, gastroparesis, bladder paresis, and gustatory sweating, were recorded. All of the diabetic patients were examined for evidence of neuropathy and underwent a battery of peripheral nerve and cardiovascular autonomic function tests. All patients were screened for anemia (defined as an Hb level ≤11.5 g/dl for women and 12.0 g/dl for men), and those with identified causes (e.g., ferritin, B_{12}, folate deficiencies, thyroid dysfunction, and hemoglobinopathies) were excluded. Serum creatinine, liver function tests, albumin, and lipid profiles were recorded. Serum EPO levels were measured in all the DN patients and in most of the GN patients. The serum EPO levels of the anemic subjects were compared with values obtained from the control group (nondiabetic patients with and without microcytic anemia[s]).

EPO assay

EPO was measured using an enzyme-linked immunosorbent assay based on the double-antibody sandwich method (Quantikine IVD; R & D Systems, Minneapolis, MN). The within-assay precision was 3.1% (n = 30, mean 16.2 IU/l), and the between-assay coefficient of variation was 6.5% (n = 20, mean 10.6 IU/l). The laboratory normal range of EPO for nonanemic subjects is 3.3–16.6 IU/l. A small diurnal variation in EPO production has been recognized; therefore, all EPO measurements were recorded in the midday or early afternoon (14).

Peripheral nerve and cardiovascular autonomic function tests

Peripheral nerve tests. These included assessment using the 10-g Semmes-Weinstein monofilament at five points on the sole of the foot and scoring the number of points perceived, vibration perception at the grand hallux using a biosthesiometer (Biomedical Instruments, Newbury, OH), and thermal threshold assessment using the Thermotest (RDG Medical, Croydon, U.K.) at the lateral aspect of the foot. The values were compared with published normal ranges (15).

Cardiovascular autonomic function tests. These included heart rate variation on deep breathing, Valsalva maneuver (only performed when proliferative retinopathy was not present because of the increased risk of retinal hemorrhage), and heart rate change on standing. Standard methods were used (16). Postural hypotension was defined as a systolic blood pressure drop of ≥20 mmHg (17).

Statistical analysis

Normal distribution of parameters was assessed using diagnostic plots, and where no departure from normality was demonstrated, group differences in Hb and other baseline parameters were compared using the t tests for independent samples. Values were expressed as means ± SD. The data for serum creatinine, proteinuria, and serum EPO were expressed as the median (range). These data were compared using the Mann-Whitney U test for nonparametric values. The relationship of

Table 2—*Hematological characteristics of the different patient groups*

	DN (anemic)	DN (nonanemic)	GN
n	13	14	26
Sex (M:F)	2:11	8:6	16:10
Age (years)	41.3 ± 11.2	41.1 ± 5.1	45.0 ± 11.9
Diabetes duration (years)	25 ± 12	30 ± 9	—
HbA_{1c} (%)	11.3 ± 2.1	10.5 ± 2.1	—
Hb (g/dl)	10.6 ± 0.9 (8.7–12.0)†	13.7 ± 1.1 (11.8–15.1)†	13.7 ± 1.4 (11.6–16.3)
EPO (IU/l)	8.1 (2.5–19.0)	8.5 (2.5–17.5)	8.5 (2.5–17.0)
Mean corpuscular volume (fl)	87.3 ± 5.8	88.5 ± 4.3	89.4 ± 4.0
Mean corpuscular Hb (pg)	28.7 ± 1.8	29.8 ± 1.7	29.4 ± 2.0
B_{12} (pmol/l)	410.6 ± 137.9	—	—
Folate (nmol/l)	18.1 ± 7.0	—	—
Ferritin (ng/ml)	70.3 ± 52.9	—	—
Proteinuria (mg/day)	2,536 (130–5,190)‡	579 (120–2,876)‡	1,874 (349–5,005)
Creatinine (μmol/l)	110 (63–160)	88 (64–133)	93 (49–180)

Data are *n*, means ± SD, means ± SD (range), or median (range). *Our published data used here as reference data (5). †$P < 0.0001$; ‡$P = 0.01$.

EPO with Hb was expressed by regression of the natural logarithm of EPO (lnEPO) on Hb of the DN group compared with the control group. The predictive power of the model was measured by percentage variance of lnEPO explained by variation in Hb and group membership. We performed *t* tests to determine whether the regression lines differed (in slope and intercept) and whether the individual slopes differed from zero. Significance was defined as $P < 0.05$.

RESULTS — We identified 27 patients with type 1 diabetes and nephropathy. All of the patients had proteinuria (1,086 mg/day, range 120–5,190), but none were in severe renal failure (creatinine 96 μmol/l, 63–160). The 26 patients with GN had similar levels of renal function in terms of proteinuria (1,874 mg/day, 349–5,005) and creatinine (93 μmol/l, 49–180). Proteinuria exceeded 3.5 g/day in only two of the DN patients and four of the GN subjects, but none had a low serum albumin. There was no significant difference between the characteristics of the two groups (Table 1).

Of the diabetic patients with DN, 13 were found to be anemic (Hb 10.6 ± 0.9 g/dl). The anemia was normochromic and normocytic, as evidenced by a normal mean corpuscular volume and mean corpuscular Hb (87.3 ± 5.8 fl and 28.7 ± 1.8 pg, respectively). There was no evidence of any hematinic deficiencies such as iron, B_{12}, or folate to explain the anemia. In marked contrast, none of the 26 patients with GN were found to be anemic (Hb 13.7 ± 1.4 g/dl); therefore, by implication, they were not EPO deficient, despite having the same severity of renal disease and use of ACE inhibition. Of the 26 GN patients, 17 had serum EPO levels of 8.5 IU/l (2.5–17.0), which is in the normal range for nonanemic subjects. Serum EPO levels were not measured in nine of the GN patients because of logistical problems in outlying clinics. The hematological characteristics of the groups are shown in Table 2.

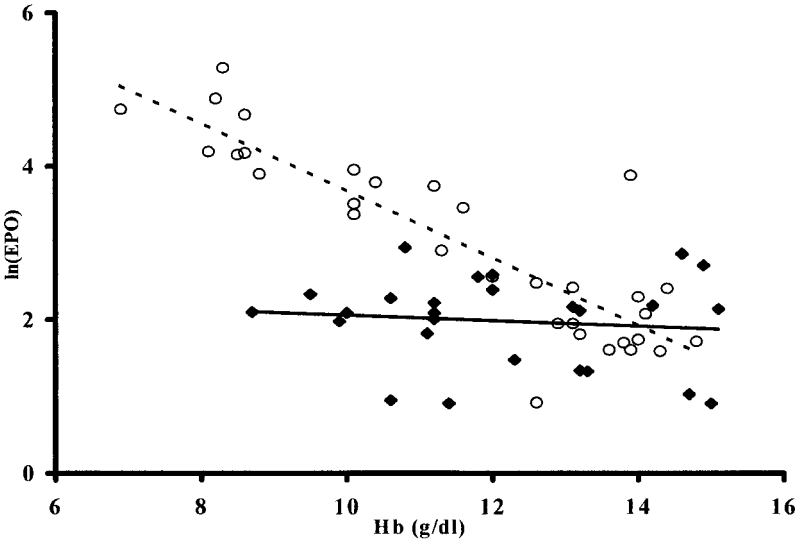

Figure 1—*Relationship between the natural logarithm of serum EPO and Hb concentrations in 26 of 27 DN patients (◆) compared with nonanemic and microcytic anemic control subjects (○) (one nonanemic DN patient not shown because serum EPO value not available). The best fitting regression lines are illustrated with solid and dotted lines, which are significantly different in both slope and intercept (P < 0.001). The dotted line shows the normal relationship of lnEPO to Hb in the control subjects, with a significant rise in EPO with decreasing Hb. This relationship is not found in the DN group.*

The serum EPO levels in the anemic DN patients were found to be inappropriately low compared with the results from a control group of iron-deficient anemic subjects (5). In comparing the regression lines for the whole DN group with those of the nonanemic and anemic control group, we found a difference in the slope of lnEPO in relation to Hb ($t = -5.359$, df = 62, $P < 0.001$) when allowing nonparallel regression lines in the model. The model was able to explain $r^2 = 72.7\%$ of the variation in lnEPO. There was no evidence at the 5% level of an EPO response to falling Hb in the DN group ($t = -0.522$, $P = 0.604$, 95% CI for the slope 0.166–0.098). In contrast, in the control group, lnEPO increased by 0.46 for a fall of 1 g/dl in Hb ($P = 0.001$; 95% CI for slope [−0.55 to −0.36]) (5). Thus, in the control group, the serum EPO levels rose appropriately with a decreasing Hb, whereas there was no appropriate rise in EPO with decreasing Hb concentrations in the DN group (Fig. 1).

The DN groups were reviewed to determine whether there were any additional factors to explain the anemia. There was no difference in age, duration of dia-

Table 2—*Continued*

Nondiabetic (anemic)*	Nondiabetic (nonanemic)*	Normal values
14	18	—
4:10	3:15	—
46.7 ± 15.3	41.1 ± 10.8	—
—	—	—
—	—	3.8–6.4
9.3 ± 1.3 (6.9–11.6)	13.5 ± 0.8 (12.0–14.8)	11.5–15.5
57.7 (29.2–195.8)	6.6 (2.5–12.9)	3.3–16.6
69.9 ± 4.8	91.7 ± 2.8	79–96
21.3 ± 2.2	31.1 ± 1.5	27–32
—	—	165–835
—	—	7.0–28.1
—	—	10–200
—	—	<30
68 (59–148)	97 (51–108)	45–120

Table 3—*Results of peripheral and autonomic nerve function tests*

	Abnormal values	DN anemic	DN nonanemic	*P*
Vibration perception	≥15	33.4 ± 17.9	22.1 ± 13.6	—
Monofilament	<5/5	2 ± 2	4 ± 1	—
Thermal thresholds (°C)	>10	23.3 ± 7.3	16.9 ± 7.6	0.04
Heart rate variation (beats/min)	<10	6.0 ± 5.7	6.6 ± 4.1	—
Heart rate increase on standing	<12	6.0 ± 5.7	10.9 ± 3.6	0.028
Systolic blood pressure drop (mmHg)	>20	13.0 ± 9.2	2.2 ± 3.8	0.003

Data are means ± SD. Abnormal values according to Purewal et al. (15).

betes, or glycemic control between the anemic and nonanemic patients. The HbA_{1c} was high in many of the patients with DN, indicating the protracted poor control of these patients. There was a female preponderance in the anemic group (2 males vs. 11 females), but this was not evident in the nonanemic DN subjects (8 males vs. 6 females) The small differences in serum creatinine did not reach statistical significance (110 μmol/l [63–160] vs. 88 μmol/l [64–133]). There was no difference in the use of ACE inhibitors between the groups (9 of 13 vs. 13 of 14). However, the anemic group had worse proteinuria (2,536 mg/day [130–5,190] vs. 579 mg/day [120–2,876]) than the nonanemic group ($P = 0.01$).

Both groups of diabetic patients had evidence of peripheral and autonomic neuropathy (Table 3), although none of the patients had symptomatic disease. Nerve function is known to deteriorate with age. The mean age of both groups is similar, and thus the results of the neuropathy assessments of both groups can be compared. There was evidence of impaired vibration perception and monofilament perception in both groups, indicating impaired large-fiber function. Strikingly, the anemic group had evidence of more severely impaired thermal perception ($P = 0.04$). Both groups showed evidence of cardiac autonomic dysfunction with impaired heart rate variation (parasympathetic dysfunction). Although both groups showed impaired heart rate increase on standing (sympathetic dysfunction), this was worse in the anemic group ($P = 0.028$). The anemic group had evidence of some postural hypotension, which was more severe than in the nonanemic group ($P = 0.003$). This did not reach the severity classified as clinically relevant (17); however, it did suggest more severe sympathetic dysfunction in the anemic group compared with the nonanemic group.

CONCLUSIONS — We have shown that some type 1 diabetic patients with DN but without severe renal function impairment are anemic (normochromic and normocytic) and that this is associated with a relative EPO deficiency. This is in sharp contrast to the nondiabetic patients with a similar degree of renal damage (similar levels of proteinuria and creatinine), who did not develop anemia at the same stage of the disease. This anemia of early DN has long been suspected by clinicians but not documented. We cannot explain the apparent female preponderance; all of these subjects had a normochromic normocytic blood profile with a normal serum ferritin level, thus excluding iron deficiency. Given the remote possibility that the anemia may have had some other cause in these female patients, our study still shows that they are EPO deficient. Thus, EPO deficiency appears to occur early in diabetic renal disease.

The anemia of chronic renal failure is not normally observed until the glomerular filtration rate drops to <20–40 ml/min, which is equivalent to a serum creatinine of greater than ~177 μmol/l (18,19). The mechanisms that may contribute to this anemia include shortened red cell survival, decreased EPO production, blood loss because of defective platelet function, and impaired erythropoiesis secondary to inhibitors or toxic metabolites (20). The major explanation, however, is a relative EPO deficiency resulting from an inability of the renal fibroblasts to produce EPO to maintain the red cell mass in response to tissue hypoxia. As the renal function deteriorates, the anemia becomes more marked. The anemia characteristically responds to exogenous EPO administration in the form of recombinant human EPO in the presence of adequate iron replacement (21–23).

Anemia and EPO deficiency are not usually seen during the early stages of renal disease, and they did not occur in the nondiabetic patients with GN described in this study. The exception to this is the nephrotic syndrome, where it is speculated that EPO deficiency results from the severity of proteinuria, leading to reduced EPO production and an excessive loss of EPO in the urine (24–26). None of the patients in this study had nephrotic syndrome.

In some patients, ACE inhibitors may cause a small decrease in serum EPO levels with a nonsignificant reduction in Hb (mean 0.27 g/dl) (28). ACE inhibitors were used in the majority of patients in both groups; however, it is unlikely that their use can therefore account for the anemia in the diabetic patients, and 4 of the 13 anemic DN patients were not using ACE inhibitors.

EPO deficiency and anemia can arise in a number of chronic diseases, including HIV and rheumatoid disease (2,27). Thus, other possible explanations for the failure of adequate EPO production in early DN include cytokine inhibition of EPO production or a failure of the oxygen-sensing mechanism, which triggers the production of EPO synthesis. Cytokine inhibition of the EPO receptor has been proposed as an explanation for the anemia with EPO deficiency that results from rheumatoid disease and other autoimmune diseases. One plausible explanation for inappropriately low EPO in renal disease (based on in vitro work in hepatoma cells) is immunomodulatory cytokine inhibition of EPO formation (29). Type 1 diabetes is closely associated with other autoimmune diseases in which cytokine release might be elevated.

In conclusion, EPO-deficient anemia can be observed prematurely in patients with type 1 diabetes and DN before the onset of advanced renal failure and in the absence of nephrotic syndrome. This is in contrast to other renal diseases of similar severity in which anemia is not normally found. The mechanisms for the failure of appropriate EPO production have not been characterized, but a contributing factor may be renal denervation secondary to diabetic autonomic neuropathy in the presence of damaged EPO-producing fibroblasts in the renal cortex.

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