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Effects of erythropoietin therapy on the lipid profile in end-stage renal failure

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Effects of erythropoietin therapy on the lipid profile in end-stage renal failure. To evaluate the effects of erythropoietin (EPO) therapy on the lipid profile in end-stage renal failure, we undertook a prospective study in patients on both hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). One hundred and twelve patients (81 HD, 31 CAPD) were enrolled into the study. Lipid parameters [that is, total cholesterol and the LDL and HDL subfractions, triglycerides, lipoprotein (a), apoproteins A and B], full blood count, iron studies, B12, folate, blood urea, aluminium and serum parathyroid hormone were measured prior to commencement of EPO therapy. Ninety-five patients were reassessed 5.2 ± 0.3 (mean ± SEM) months later and 53 patients underwent a further assessment 13.1 ± 0.6 months after the commencement of EPO, giving an overall follow-up of 10.0 ± 0.6 months in 95 patients. As expected, EPO treatment was associated with an increase in hemoglobin (7.7 ± 0.1 vs. 9.9 ± 0.2 g/dl; $P < 0.001$) and a decrease in ferritin (687 ± 99 vs. 399 ± 69 μg/liter; $P < 0.01$). A significant fall in total cholesterol occurred (5.8 ± 0.1 vs. 5.4 ± 0.2 mmol/liter; $P < 0.05$) in association with a fall in apoprotein B (1.15 ± 0.04 vs. 1.04 ± 0.06; $P < 0.05$) and serum triglycerides (2.26 ± 0.14 vs. 1.99 ± 0.21; $P < 0.05$) during the course of the study. Other lipid parameters did not change, although there was a trend towards improvement. These changes correlated with the increase in Hb ($P < 0.001$ in each case), and the reduction in ferritin for total cholesterol ($P < 0.02$), LDL cholesterol ($P < 0.03$), and to a lesser extent apoprotein B ($P < 0.07$). No difference was observed in patients using maintenance HD or CAPD, and similar trends were observed in male and female patients. Improvements in the lipid profile occurred independently of the time on dialysis prior to the commencement of EPO. We conclude that EPO treatment is associated with alterations in the lipid profile which may suggest a long-term improvement in the vascular morbidity of chronic renal failure. The causes of the improved lipids are not addressed by this study and may be equally due to a direct or secondary benefit of EPO therapy.

Erythropoietin (EPO) deficiency is an undoubted factor in the pathogenesis of uremic anemia, and its widespread use has arguably been the most important development impacting on dialysis patients in recent years. However, the long-term effects of erythropoietin on cardiovascular disease have not yet been assessed. In particular, the effect of EPO on the blood lipid profile has not been well documented.

There are theoretical benefits resulting from the use of EPO on cardiovascular disease in uremia. The resultant increase in hemoglobin causes improved tissue oxygenation, not only to the heart, but also to the vascular endothelium. Increased exercise tolerance is well documented [1] to improve the cardiovascular risk profile in nonuremic patients. An improvement in the known carbohydrate intolerance of uremia has also been demonstrated [2].

Conversely, there are also potentially adverse effects of EPO treatment on cardiovascular risk factors. An increase in hemoglobin leads to an increase in blood viscosity, hypertension may be exacerbated and increased appetite may lead to weight gain [1]. Thus an alteration in metabolic conditions may occur as a result of EPO treatment which may theoretically be beneficial, or conversely, adversely affect the lipid profile. The net effect of these changes is not well documented. The current study prospectively assessed the changes in the blood profile which occurred in association with EPO treatment in patients on long-term dialysis.

Methods

The study included patients from three dialysis units in Sydney, Australia. All patients on hemodialysis, which included both single pass and sorbent dialysis, and patients on CAPD who were commencing erythropoietin treatment were enrolled into the prospective study. Patients prescribed pharmacological lipid lowering agents were excluded from the study from the time these agents were commenced. Dialytic prescription, EPO doses and other drug therapy was at the discretion of the primary care physician. Attempts were made to keep dialytic regimens uniform throughout the study unless clinical considerations dictated otherwise. Hemodialysis patients were dialyzed using cupraphan or cellulose acetate membranes which were not altered during the course of the study. Kinetic modeling was not routinely used to monitor dialysis delivery. Patients on CAPD used standard peritoneal dialysate (Dianeal®, Baxter Healthcare, Round Lake, Illinois, USA). No patient on CAPD required a significant variation in the dialysate glucose content, nor in dialysate volume instilled during the study period. All patients were similarly advised by a dietician regarding a diet appropriate to their dialysis and low in saturated fats.

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Assessments were made prior to the commencement of EPO, at three to six months (follow-up 1) and 12 to 18 months (follow-up 2) after EPO treatment was started. Measurements included hemoglobin and hematocrit; pre-dialysis blood urea; iron status as determined by serum iron and ferritin; serum B12 and folate; as well as factors known to be associated with EPO resistance, that is, serum parathyroid hormone and aluminum levels. The lipoprotein profile was assessed by measuring the following parameters: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apoproteins A1 and B, and lipoprotein (a). All lipid measurements were performed in a single laboratory. Other measurements were standard laboratory procedures and performed in individual laboratories.

Total cholesterol was measured by a spectrophotometric colorimetric end-point determination using the Boehringer Mannheim Enzymic Method run on the Hitachi 705 analyzer. HDL cholesterol was measured using the Seba Diagnostics kit which employs polyethylene glycol as the precipitant. LDL was directly measured by subtracting the HDL cholesterol from the cholesterol content of the lowermost fraction following ultracentrifugation at 100,000 g for 24 hours. Triglycerides were determined by Boehringer Mannheim GPO-PAP method on the Hitachi 705 analyzer. Apoproteins were measured by nephelometry using the Beckman nephelometer, with the apoprotein B assay specific for apoprotein B100. Lipoprotein (a) was measured by radioimmunoassay using a Pharmacia kit.

Due to ethical considerations, a control group of patients with a similar degree of anemia not treated with EPO was not available for comparison on a prospective basis. Thus, in order to determine whether increased time on dialysis *per se* was associated with alterations in the lipid profile, patients in whom EPO was commenced within one year of the commencement of dialysis were compared with those who had been on maintenance dialysis for greater than one year.

Statistical analysis

Statistical analyses were made using Statview II® software. Longitudinal changes in measured parameters were compared using paired *t*-tests. Comparisons between two groups were made using unpaired *t*-tests or chi-squared statistics. Analysis of variance was used to detect differences between three groups, and the protected Fisher test for least significant difference was used to determine which pairs of groups differed when the *F* test was significant. Correlations were sought between the changes in lipoproteins, that is, total serum cholesterol, triglycerides, HDL and LDL cholesterol, apoproteins A1 and B and lipoprotein (a), and the changes in hematological and biochemical parameters using univariate and multivariate analysis. A *P* value less than 0.05 was considered a significant difference.

Results

A total of 112 patients (57 males and 55 females) were entered into the study. The ages reflected the populations of the hospitals involved in the study and ranged from 18 to 85 years (59.9 ± 1.4 years; mean ± SEM). Males and female patients were similarly aged being 59.2 ± 2.1 versus 60.9 ± 1.9 years respectively. Eighty-one patients were on maintenance hemodialysis, with 32 patients on single pass and 49 on sorbent dialysis. No difference was observed between patients who used either form of hemodialysis, and no center effect was evident. Thus the hemodialysis group was regarded as uniform. Thirty-one patients were on continuous ambulatory peritoneal dialysis (CAPD).

The primary causes of end-stage renal failure were: primary glomerulonephritis 36.6%; analgesic nephropathy 21.4%; diabetes mellitus 8%; unclassified 7.5%; chronic interstitial nephritis 4.5%; renovascular 3.6%, hypertension 3.6%; reflux nephropathy 3.6%; polycystic kidneys 2.7%; multiple myeloma 2.7%, amyloid 2.7%, other 3.1%. This reflects the study population at the study centers, but differs from the Australian experience in general, where analgesic nephropathy accounts for 11% and diabetic nephropathy for 14% of the end-stage renal failure population [3].

Those on hemodialysis and CAPD were aged similarly, being 59.5 ± 1.75 versus 61.2 ± 2.4 years, respectively, and had been on dialysis for a similar length of time 30.5 ± 4.6 versus 28.7 ± 6.7 months.

Patients were followed from 3 to 18 months from commencement of the study. During this period 22 patients died, 5 underwent renal transplantation and 4 commenced pharmacological lipid lowering agents. The causes of death were: cerebrovascular accident 4, myocardial infarction 5, withdrawal from dialysis 4, malignancy 3, infection 3, pancreatitis 1, accidental 1, and cardiac tamponade 1. The excess death rate is accounted for by the high representation of patients with analgesic nephropathy and the elderly in the study population.

Ninety-five patients completed at least one follow-up at 5.2 ± 0.3 months, and 53 patients completed a second follow-up 13.1 ± 0.6 months after the initial assessment. Overall, the follow-up in 95 patients was 10.0 ± 0.6 months.

The hematological, biochemical and lipid results for the initial and follow-up assessments are presented in Table 1. As expected the hemoglobin increased significantly in association with decreased serum ferritin. Parathyroid hormone fell at the second assessment, but showed no difference from baseline at the time of the final measurement. No significant difference in dialysis efficiency as measured by pre-dialysis urea was evident during the course of the study. Serum albumin levels increased by a small but significant amount following the introduction of EPO, with the major effect evident at the time of first follow-up. There was a trend for serum albumin to correlate with total serum cholesterol in the initial assessment ($r = 0.2$; $P = 0.06$). However, this association was not present at the final follow-up ($r = 0.01$; $P = 0.96$). No change in B12 or folate occurred as a result of EPO treatment and, although serum aluminum levels tended to increase, no significant change occurred during the course of the study.

Fasting blood sugar levels were similar before and after the instigation of EPO treatment. However, significant reductions occurred in the total cholesterol and triglycerides. This fall in total cholesterol was associated with a fall in apoprotein B. Although LDL cholesterol fell significantly at the second follow-up it was not significantly different from baseline at the final assessment. A similar fall and subsequent return to baseline was also evident in the blood sugar measurements. Otherwise, the majority of any observed change was observed by the first follow-up with little change evident in further follow-ups. Overall, at the initiation of the study the prevalence of hypercholesterolemia was 59% and of hypertriglyceridemia 47%.

Table 1. Changes in measured parameters at baseline and during follow-up in entire study population

Parameter	Baseline (N = 112)	Follow-up 1 (N = 95)	Follow-up 2 (N = 58)
Hemoglogin *g/dl*	7.7 ± 0.13	9.1 ± 0.2[c]	9.9 ± 0.2[cd]
Hematocrit %	23.5 ± 0.4	27.1 ± 0.7[c]	29.6 ± 0.6[cd]
Urea *mmol/liter*	25.6 ± 0.4	25.7 ± 1.2	25.4 ± 1.2
Iron *μmol/liter*	15.9 ± 0.9	14.4 ± 1.3	14.7 ± 1.3
Ferritin *μg/liter*	687 ± 90.1	383 ± 73[b]	399 ± 69[b]
B12 *pmol/liter*	432 ± 42	395 ± 75	421 ± 37
Folate *nmol/liter*	23.8 ± 2.8	17.9 ± 2.7	33.8 ± 11.7
PTH *ng/liter*	240 ± 31.1	113.5 ± 51[a]	175 ± 47.7
Aluminum *μmol/liter*	0.78 ± 0.08	0.86 ± 0.16	1.34 ± 0.19
Albumin *g/dl*	32.1 ± 0.5	33.5 ± 1.1[c]	33.4 ± 0.6[c]
Blood glucose *mmol/liter*	6.65 ± 0.33	6.04 ± 0.44[a]	6.23 ± 0.62
Total cholesterol *mmol/liter*	5.78 ± 0.13	5.40 ± 0.20[a]	5.38 ± 0.2[a]
Triglycerides *mmol/liter*	2.26 ± 0.14	2.07 ± 0.10	1.99 ± 0.21[a]
HDL cholesterol *mmol/liter*	1.14 ± 0.04	1.03 ± 0.06	1.13 ± 0.05
LDL cholesterol *mmol/liter*	3.44 ± 0.11	3.15 ± 0.19[a]	3.30 ± 0.16
Apo A1 *g/liter*	1.165 ± 0.03	1.18 ± 0.04	1.23 ± 0.04
Apo B *g/liter*	1.15 ± 0.04	1.04 ± 0.06[a]	1.04 ± 0.06[a]
Lipoprotein (a) *mg/liter*	806 ± 76	579 ± 90	531 ± 63

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ versus follow-up 1
[d] $P < 0.05$ versus follow-up 2

Table 2. Changes in measured parameters at baseline and at each individual's last follow up in hemodialysis and CAPD patients

	Baseline (N = 112)		Final follow-up (N = 95)	
Parameter	Hemodialysis	CAPD	Hemodialysis	CAPD
Hemoglogin *g/dl*	7.8 ± 0.16	7.4 ± 0.20	9.9 ± 0.2	9.8 ± 0.4
Hematocrit %	23.9 ± 0.5	22.3 ± 0.7	29.7 ± 0.73	29.2 ± 1.4
Urea *mmol/liter*	25.9 ± 0.8	24.7 ± 1.6	26.7 ± 1.0	21.6 ± 2.9
Iron *μmol/liter*	16.4 ± 1.1	14.3 ± 1.7	15.3 ± 1.7	13.1 ± 1.8
Ferritin *μg/liter*	701 ± 114	650 ± 138	365 ± 82	483 ± 132
B12 *pmol/liter*	385 ± 40	521 ± 94	447 ± 44	354 ± 69
Folate *nmol/liter*	23.5 ± 3.8	24.5 ± 3.5	41.5 ± 16.3	15.4 ± 45
PTH *ng/liter*	248 ± 37	221 ± 58	150 ± 60	231 ± 79
Aluminum *μmol/liter*	0.89 ± 0.1	0.54 ± 0.06[a]	1.49 ± 0.20	0.36 ± 0.16[a]
Blood glucose *mmol/liter*	6.2 ± 0.3	7.6 ± 0.8[a]	5.3 ± 0.3	8.7 ± 1.9[b]
Total cholesterol *mmol/liter*	5.71 ± 0.16	5.89 ± 0.26	5.38 ± 0.22	5.47 ± 0.31
Triglycerides *mmol/liter*	2.20 ± 0.16	2.4 ± 0.27	2.02 ± 0.28	1.91 ± 0.22
HDL cholesterol *mmol/liter*	1.16 ± 0.05	1.09 ± 0.06	1.14 ± 0.06	1.09 ± 0.06
LDL cholesterol *mmol/liter*	3.48 ± 0.14	3.32 ± 0.21	3.33 ± 0.18	3.23 ± 0.34
Apo A1 *g/liter*	1.18 ± 0.03	1.13 ± 0.04	1.28 ± 0.05	1.20 ± 0.05
Apo B *g/liter*	1.12 ± 0.04	1.23 ± 0.09	1.04 ± 0.06	1.04 ± 0.13
Lipoprotein (a) *mg/liter*	731 ± 76	936 ± 157	516 ± 164	599 ± 32

[a] $P < 0.05$, [b] $P < 0.01$ versus hemodialysis

This high prevalence was significantly reduced to 42% ($P < 0.001$) and 42% ($P < 0.05$), respectively, following the introduction of EPO.

Lipoprotein (a) levels were elevated in all patient groups. They were somewhat higher in patients on CAPD compared with hemodialysis but the difference did not reach statistical significance. A trend existed for a reduction in lipoprotein (a) subsequent to the introduction of EPO ($P = 0.16$), but at the final assessment it was similar to baseline. No correlation was observed between Lp(a) and age, weight, hemoglobin, the hematinic factors or predialysis urea. Although no correlation was observed with total cholesterol ($P = 0.17$) or its subfractions, LDL cholesterol ($P = 0.26$) and HDL cholesterol ($P = 0.12$), there was a positive correlation with apoprotein A ($P < 0.05$). Thus, females tended to have a higher Lp(a) level compared with males, but the overall difference was not significant (Table 3). No correlation was observed with apoprotein B ($P = 0.15$) nor serum triglycerides ($P = 0.14$).

The differences in measured parameters between patients on hemodialysis versus those on CAPD are detailed in Table 2, and between male and female patients in Table 3. The baseline results were as expected in that hemodialysis patients had a lower blood sugar level and a higher serum aluminum compared with patients on CAPD, and females had a higher cholesterol which was accounted for by the HDL subfraction and its associated apoprotein, apoprotein A. No difference in the effect of EPO was seen in these subgroup compared to the study population as a whole.

The changes in measured parameters between patients who had been on dialysis for less than one year (N = 53; time on dialysis 4 ± 0.6 months) and the patients who had been on dialysis for greater than one year (N = 59; time on dialysis 52.1 ± 5.2 months) are shown in Table 4. These subgroups had a similar degree of anemia at the commencement of the study and a similar hematological response to EPO therapy. Initial iron stores were lower in patients who had been on dialysis for a shorter period of time, reflecting the transfusion requirements of the dialysis patients prior to the introduction of EPO treatment. The percent reduction in serum ferritin following EPO treatment was similar. Somewhat suprisingly, the PTH levels were similar in the groups and, although aluminum levels tended to be lower in the patients on hemodialysis for a shorter period, the differences failed to reach statistical significance. No difference in total cholesterol, cholesterol subfractions or triglycerides was observed either at baseline or at follow-up. Apoprotein A levels were similar at baseline, however, were higher in patients on dialysis for a shorter period at final follow-up. Apoprotein B levels were similar at each time point and lipoprotein (a) levels were similar in all groups.

Prior to the commencement of EPO, patients with a higher hemoglobin had a lower serum cholesterol ($r = 0.22$; $P < 0.05$). Univariate analysis demonstrated that the improvement in each of the lipid parameters correlated with an increase in hemoglobin (total serum cholesterol $r = 0.59$; LDL cholesterol $r = 0.51$; serum triglycerides $r = 0.46$; $P < 0.001$ in each case). A correlation was also observed between the reduction in serum

Table 3. Changes in measured parameters at baseline and at each individual's last follow-up in male versus female patients

Parameter	Baseline (N = 112)		Final follow-up (N = 95)	
	Male	Female	Male	Female
Hemoglogin *g/dl*	7.8 ± 0.16	7.7 ± 1.9	10.1 ± 0.4	9.6 ± 0.3
Hematocrit %	23.3 ± 0.51	23.6 ± 0.7	30.4 ± 1.1	29.9 ± 0.9
Urea *mmol/liter*	27.1 ± 1.2	24.2 ± 1.1	25.6 ± 1.3	25.6 ± 1.4
Iron *μmol/liter*	15.4 ± 1.2	16.3 ± 1.4	17.5 ± 2.2	15.7 ± 3.4
Ferritin *μg/liter*	659 ± 128	715 ± 129	411 ± 86	367 ± 60
B12 *pmol/liter*	448 ± 63	415 ± 58	420 ± 67	413 ± 71
Folate *nmol/liter*	20.6 ± 2.0	28.7 ± 5.8	19.7 ± 2.2	37.2 ± 9.4
PTH *ng/liter*	227 ± 44	254 ± 46	186 ± 82	145 ± 32
Aluminum *μmol/liter*	0.69 ± 0.10	0.88 ± 0.12	1.11 ± 0.09	0.93 ± 0.28
Blood glucose *mmol/liter*	6.9 ± 0.5	6.4 ± 0.4	6.5 ± 0.6	6.1 ± 0.6
Total cholesterol *mmol/liter*	5.69 ± 0.21	6.02 ± 0.17[a]	5.54 ± 0.41	5.27 ± 0.38
Triglycerides *mmol/liter*	2.21 ± 0.20	2.31 ± 0.19	2.18 ± 0.49	1.78 ± 0.23
HDL cholesterol *mmol/liter*	1.00 ± 0.04	1.26 ± 0.07[b]	1.02 ± 0.06	1.14 ± 0.07
LDL cholesterol *mmol/liter*	3.26 ± 0.17	3.61 ± 0.15	3.13 ± 0.26	3.35 ± 0.18
Apo A1 *g/liter*	1.09 ± 0.03	1.25 ± 0.04[c]	1.20 ± 0.07	1.32 ± 0.07
Apo B *g/liter*	1.11 ± 0.05	1.19 ± 0.09	1.01 ± 0.10	1.09 ± 0.10
Lipoprotein (a) *mg/liter*	636 ± 91	880 ± 156	492 ± 194	626 ± 132

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ versus females

Table 4. Changes in measured parameters at baseline and at each individual's last follow-up in patients on dialysis for greater than 12 months versus those on dialysis for less than 12 months

Parameter	Baseline (N = 112)		Final follow-up (N = 95)	
	> 12 months	< 12 months	> 12 months	< 12 months
Hemoglogin *g/dl*	7.8 ± 0.17	7.7 ± 0.20	9.8 ± 0.24	10.0 ± 0.3
Hematocrit %	23.5 ± 0.3	23.6 ± 0.7	29.3 ± 0.10	29.8 ± 0.9
Urea *mmol/liter*	24.7 ± 1.0	27.0 ± 1.2	24.2 ± 1.5	27.2 ± 1.8
Iron *μmol/liter*	19.1 ± 1.2	11.1 ± 0.9	15.3 ± 2.4	14.2 ± 1.5
Ferritin *μg/liter*	856 ± 123	544 ± 72[a]	381 ± 111	293 ± 52
B12 *pmol/liter*	425 ± 54	443 ± 69	410 ± 56	435 ± 48
Folate *nmol/liter*	24.4 ± 4.3	22.9 ± 2.3	35.5 ± 21.8	31.8 ± 5.4
PTH *ng/liter*	257 ± 43	210 ± 39	189 ± 56	127 ± 96
Aluminium *μmol/liter*	0.88 ± 0.1	0.6 ± 0.11	1.63 ± 0.28	0.9 ± 0.14
Blood glucose *mmol/liter*	6.7 ± 0.4	6.7 ± 0.5	6.3 ± 0.8	6.2 ± 0.9
Total cholesterol *mmol/liter*	5.8 ± 0.18	5.8 ± 0.20	5.3 ± 0.29	5.5 ± 0.26
Triglycerides *mmol/liter*	2.4 ± 0.19	2.11 ± 0.23	1.86 ± 0.15	2.1 ± 0.44
HDL cholesterol *mmol/liter*	1.16 ± 0.06	1.13 ± 0.07	1.07 ± 0.06	1.20 ± 0.07
LDL cholesterol *mmol/liter*	3.45 ± 0.15	3.50 ± 0.18	3.22 ± 0.22	3.40 ± 0.23
Apo A1 *g/liter*	1.16 ± 0.03	1.18 ± 0.04	1.17 ± 0.05	1.35 ± 0.06[a]
Apo B *g/liter*	1.12 ± 0.06	1.21 ± 0.06	0.95 ± 0.07	1.14 ± 0.09
Lipoprotein (a) *mg/liter*	732 ± 95	930 ± 32	538 ± 104	501 ± 171

[a] $P < 0.05$, versus patients on dialysis greater than 12 months

ferritin and total cholesterol (r = 0.44; $P < 0.02$), LDL cholesterol (r = 0.44; $P < 0.03$) and to a lesser extent apoprotein B (r = 0.35; $P < 0.07$). Although there was a trend for the fall in ferritin to correlate with the fall in triglycerides (r = 0.28), this failed to reach statistical significance (P = 0.14). Multivariate analysis was unable to demonstrate an effect of a decrease in serum ferritin on lipids independent of the effect of an increase in hemoglobin, although an independent trend existed (P = 0.11 for total cholesterol and P = 0.13 for LDL cholesterol).

Discussion

The present study demonstrates that EPO treatment in patients receiving long-term dialysis therapy is associated with an improvement in the blood lipid profile. This is indicated by significant reductions in total serum cholesterol, serum triglycerides and the apoprotein B100.

Although many studies have addressed the beneficial effects of EPO treatment on cardiac disease, they mainly address the improvement in ventricular function as a result of improved tissue oxygenation [4, 5]. Due to its relatively recent introduction, the long-term benefits of reducing cardiac disease, which is the major cause of death in our dialysis and transplant population, are unknown. Few studies address the effects of EPO on the lipid profile, and these consist of few patients with relatively limited follow-up.

Mat, Stolear and Georges [6] assessed 24 patients before and 9 to 36 months after EPO treatment and found no difference in total cholesterol, HDL cholesterol, triglycerides, apoprotein A1 or apoprotein B. Similarly, Prata et al [7] studied 14 patients before and after EPO treatment and showed no change in the lipid profile. Conversely, Viron et al [8] cautiously proposed that a favorable response in serum lipids may occur as a response to EPO treatment in the dialysis patient, when they documented an increase in the apoprotein A1. Our finding of a decrease in total cholesterol from 5.8 to 5.4 is modest, and no doubt the power of the above studies would not have allowed detection of this difference. Nonetheless, in epidemiological studies, a reduction in serum cholesterol of this magnitude is associated with significant reductions in cardiovascular disease [9, 10]. If one extrapolates from the "normal" population and assumes a 1 to 2% decline in cardiovascular mortality with each 1% decline in cholesterol [10], then a decrease in coronary mortality in the order of 10% could be expected from the results of our study. Furthermore, a significant reduction in apoprotein B was documented, which has been shown to associated with regression of established coronary artery disease [11].

The reasons for this improvement are not elucidated fully by

the present study. It may be that secondary lifestyle changes, which were not assessed, with respect to exercise capacity and diet are responsible for the observed benefits. However, other metabolic effects of EPO may well be more directly responsible for the observed changes. The carbohydrate intolerance of uremia is known to improve following EPO treatment [2], and an improvement in carbohydrate metabolism is known to be associated with decreased serum triglycerides, as was observed in this study. Normalization of several hypothalamic/pituitary hormonal systems has been described after the use of EPO [12, 13], and these may secondarily improve the lipid profile.

The association between a reduction in total body iron stores induced by EPO and an improved lipid profile is interesting, as there are several studies which suggest an association between iron accumulation, blood lipid profiles and cardiovascular death. Carbohydrate intolerance in itself is known to improve when total body iron stores are lowered by phlebotomy [14, 15]. Cutler [16] demonstrated a similar improvement in glycemic control when patients with an elevated serum ferritin had a reduction in iron stores when treated with intravenous dexforroxamine. In this small study of 16 patients, 15 had a reduction in total cholesterol after treatment with desferroxamine, although this failed to reach statistical significance probably due to the small size of the study. Many studies have documented the role of iron in accelerating atherogenesis and the relationship between coronary artery disease and liver iron content [17, 18]. The effect of iron in accelerating coronary artery disease is likely to be at least in part due to free radical production, oxidative injury and lipid peroxidation. However, increased iron stores have been demonstrated to aggravate the expression of hyperlipidemia [19]. The current study suggests that a reduction in body iron stores may have a positive effect in improving the lipid profile. However, because of the strong association between an increase in hemoglobin and a reduction in iron stores, an independent effect could not be determined. Indeed, the patients on dialysis for a shorter period of time had a lesser degree of iron overload compared to those on dialysis for a longer period despite a similar lipid profile. Thus, a reduction in iron accumulation may be one of several mechanisms whereby EPO positively affects serum lipids.

The absence of a comparable dialysis population who were randomized not to receive EPO during the same time period was unavoidable due to the ethical implications of witholding EPO from patients in whom a beneficial effect would be reasonably anticipated. Nonetheless, we do not consider that the fall in lipids was likely to be due to factors other than the instigation of EPO treatment. In the hemodialysis patients no alteration in dialysis prescription occurred and no objective evidence of altered dialysis delivery was observed. Similarly, in the CAPD population no alteration in the dialysis regimen, and in particular in the dialysate glucose content, occurred which may have resulted in a improved lipid profile. As EPO is known to stimulate appetite and pre-dialysis blood urea levels were similar, a decrease in nutritional state was unlikely to account for the observed reduction in lipid levels. Although the protein catabolic rate was not routinely monitored in the study population, it is further unlikely that progressive malnutrition accounted for the fall in lipid parameters, as serum albumin rose during the course of the study.

Importantly, patients who commenced EPO shortly after the instigation of dialysis had a similar lipid profile at the baseline assessment to those who had been on dialysis for a mean of 52 months. This suggests that a reduction in lipids with increasing time on dialysis was not observed in the patients under study. This is in agreement with most cross sectional and longitudinal studies of patients on both hemodialysis and CAPD who have shown no improvement in serum lipid and lipoproteins with time on dialysis [20–22]. Indeed, some studies have demonstrated that the lipid and lipoprotein profile of patients on maintenance dialysis may in fact worsen with time [23, 24]. In the current investigation the instigation of EPO was the only parameter altered in overall patient treatment and is therefore likely to be contributing either directly or indirectly to the improvement in the lipid profile. It should be noted that the study comprised few patients with diabetic nephropathy and the results may not generalize to dialysis populations with a higher proportion of diabetic patients.

Lipoprotein (a) has been implicated in the genesis of atherosclerosis [25], and the present study confirms that elevated levels of Lp(a) occur in patients on dialysis [26]. Although no correlation was observed between Lp(a) and LDL cholesterol in the present study, previous investigators have found a fivefold increase in atherogenic risk in patients with elevations in both these lipid parameters [27]. The trend for a reduction in these levels after treatment with EPO points to a further improvement in the patients overall atherogenic risk.

Thus, the study has demonstrated that an improvement in total cholesterol, triglycerides and apoprotein B, which in the method used in the current assay, is largely apoprotein B100 following EPO therapy. If the results of similar changes in lipid profiles from epidemiological studies could be extrapolated to the current study population, a reduction in vascular events and, in particular, coronary artery disease is expected. The reasons for the observed improvement are not explored in the current study and may equally be of primary or secondary benefit. However, the results provide optimism that the high incidence of morbidity and mortality due to vascular events in patients with end-stage renal failure may be reduced with EPO treatment.

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