Pediatr Nephrol (1998) 12:660–665

Pediatric Nephrology

Dialysis

Original article

Metabolic effects of erythropoietin in patients on peritoneal dialysis

Robert H. K. Mak

Division of Nephrology, Department of Pediatrics, Oregon Health Sciences University, Portland, Oregon, USA

Received September 23, 1997; received in revised form January 20, 1998; accepted January 22, 1998

Abstract. Insulin and lipid metabolism were studied in seven patients (19±1 years) with end-stage renal disease on continuous cycling peritoneal dialsysis (CCPD) before and after 6 months of therapy with human recombinant erythropoietin (EPO) to correct anemia. Hematocrit increased from 22.2±1.8% to 34.8±1.8% ($P<0.001$) following EPO treatment. Serum ferritin ($P<0.05$) and serum iron ($P<0.01$) decreased significantly after anemia correction. There were no significant differences in the height, weight, anthropometric measures, or intakes of protein and total calories in the patients before and after the 6 months of EPO therapy. There were no differences in serum biochemical parameters, including 1,25-dihydroxyvitamin D_3 and parathyroid hormone in these patients before and after 6 months of EPO therapy. Residual renal function and Kt/V_{urea} were also not different before and after 6 months of EPO therapy. The hyperinsulinemic euglycemic clamp technique was used to measure insulin sensitivity. Before EPO, insulin sensitivity was low in patients on CCPD (238±19 mg/m^2 per min) compared with controls (320±30; $P<0.01$). After 6 months of EPO therapy, insulin sensitivity increased by 28% (305±26, $P<0.01$ vs. pre-EPO values), so that these values were no longer different from control values. The hyperglycemic clamp technique was used to measure insulin secretion. Before EPO, both early- and late-phase insulin secretion were elevated in patients on CCPD compared with controls ($P<0.01$ in both cases). These indices of insulin secretion decreased significantly ($P<0.01$) following 6 months of EPO. Before EPO, plasma triglycerides, total cholesterol, low-density lipoprotein, cholesterol, and apolipoprotein B were elevated in patients compared with controls. These lipid concentrations decreased significantly following 6 months of EPO. Thus, treatment of anemia by EPO is associated with improvements in insulin and lipid abnormalities in uremic patients on CCPD.

Correspondence to: R.H.K. Mak, Department of Pediatrics, Mailcode NRC5, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201-3098, USA

Key words: Erythropoietin - Anemia – Uremia – Insulin resistance – Hyperinsulinemia – Hyperlipidemia – Peritoneal dialysis

Introduction

Insulin resistance, as evidenced by reduced peripheral sensitivity to insulin action, is common in patients with end-stage renal disease (ESRD) [1, 2]. Hyperinsulinemia, as evidenced by increased fasting serum insulin concentrations with normal fasting glucose values as well as increased insulin levels in response to oral or intravenous glucose, has also been reported in these patients [3]. The etiology and significance of insulin abnormalities in ESRD, however, remain unclear. Insulin abnormalities may contribute to hyperlipidemia by impairing lipoprotein lipase activity in patients with ESRD [4]. These metabolic complications may represent important risk factors for accelerated atherosclerosis in these patients [5].

Anemia contributes markedly to morbidity in patients with uremia and may be an important factor in the pathogenesis of metabolic complications. Children with chronic anemia, such as thalassemia major, develop insulin resistance and hyperinsulinemia [6]. These insulin abnormalities in thalassemic children are thought to be secondary to iron toxicity from repeated transfusions [6] and are identical to those described in patients with ESRD, who are often anemic and iron overloaded. There is recent evidence that treatment of anemia with human recombinant erythropoietin (EPO) can correct insulin resistance and hyperinsulinemia in patients on hemodialysis, and that the underlying mechanism involves effects of anemia correction rather than those of iron toxicity [7, 8]. The present study examines the effects of EPO therapy on insulin and lipid metabolism in patients on continuous cycling peritoneal dialysis (CCPD).

Patients and methods

Patients. Seven young adult patients (aged 17–20 years, mean 19±1 years) with ESRD were studied. The etiology of ESRD included chronic glomerulonephritis (2), reflux nephropathy (2), obstructive uropathy (2), and hypoplasia/dysplasia (1). The patients received CCPD from eight to ten cycles nightly. They were dialyzed on Baxter Pac-X peritoneal dialysis cyclers with a mean cycle volume of 35±5 ml/kg. Peritoneal dialysis adequacy was assessed by calculating fractional urea clearance (Kt/V) from urea clearance of 24-h peritoneal fluid collection [dialysate blood urea nitrogen (BUN)/plasma BUN x 24-h drain volume/volume of area distribution]. The volume of urea distribution was assumed to be equal to total body water and was estimated from nomograms [8]. They had been stabilized on their CCPD prescription for at least 2 months prior to entry into the present study. Their dietary intakes of sodium (2 g/day), potassium (2 g/day), and phosphorus (800 mg) were restricted. Oral medications included calcium carbonate (mean dose 1.1±0.1 g given three times a day with meals), 1,25-dihydroxyvitamin D_3 [1,25$(OH_2)D_3$] (mean dose 0.9±0.1 g given once daily before bedtime to minimize hypercalcemia), sodium bicarbonate, and antihypertensives in the form of nifedipine (long acting). There were no significant changes in these medication dosages throughout the study period. None of the patients were on corticosteroids at the time or had been on corticosteroids 6 months prior to the study. Their daily intake of carbohydrate was more than 200 g and their weights were stable for at least 2 months prior to the studies. Dietary intakes were assessed using a 3-day dietary recall. No patient had a history or family history of diabetes mellitus. They were studied just before starting and 6 months after EPO (Amgen, Thousand Oaks, Calif., USA) therapy to correct anemia. EPO was started at 50 U/kg per dose, given three times a week subcutaneously. The dose was then adjusted to maintain a target hematocrit of 35%. The mean dose of EPO was 158±38 U/kg per week.

All patients tolerated treatment well, with no increase in the incidence or severity of hypertension. Six of the seven patients required oral iron supplementation to prevent iron deficiency. Other than the addition of oral iron, there were no changes in other medications. Controls consisted of seven young healthy subjects (aged 18–22 years, mean 20±1 years) consuming regular weight-maintaining diets and taking no medications. They did not have a history of any significant illness or any family history of diabetes mellitus. The study was approved by the local institutional review board at the Children's Hospital of Los Angeles where the clinical studies were performed. The purpose and potential risks of the study were carefully explained to all patients and subjects, and written informed consent was obtained before their participation.

All studies were started about 9 a.m. after an overnight fast of about 12 h. The patients had their dialysis suspended the night before and drained their peritoneum of dialysate from the long day dwell (only 100–200 ml of dialysate, not a full cycle volume) so that they did not have dextrose (dialysate) in their peritoneum overnight. The patients or controls sat comfortably in a reclining chair and were not allowed to eat or drink apart from water during the studies.

Euglycemic clamps. Insulin sensitivity was measured by the hyperinsulinemic euglycemic clamp technique [9]. One intravenous line was inserted in a vein on the dorsum of the hand, kept patent by a slow intravenous infusion of normal saline, and used for blood sampling. This hand was placed in a heated box (65° C) to arterialize the blood [10]. An indwelling catheter was placed in a vein in the opposite arm for infusion of glucose and insulin. After obtaining at least three fasting serum samples for glucose and insulin concentration, a prime continuous infusion of insulin was given intravenously at 40 mU/m^2 per min of body surface area to acutely raise and maintain the serum insulin concentrations at a plateau of around 100 µU/ml for 120 min. Serum glucose concentration was measured at 5-min intervals and a variable infusion of 20% dextrose was adjusted to maintain the glucose concentration at fasting levels. Serum was also obtained every 10 min for measurement of insulin concentrations. Under steady-state conditions of euglycemia and hyperinsulinemia during the euglycemic clamp study, the rate of glucose infusion provides an index of insulin-stimulated glucose transport, and is used as an index of insulin sensitivity (mg/m^2 per min). Since CCPD is known to improve insulin sensitivity at initiation [11], two studies were performed at a 1-month interval before EPO therapy was started to assess whether their insulin sensitivity had stabilized on CCPD.

Hyperglycemic clamp studies. Insulin secretion was measured by the hyperglycemic clamp technique [9]. Patient preparation was similar to the euglycemic clamp. A priming dose of 20% dextrose was given to acutely raise the blood glucose concentration to 125 mg/dl above fasting glucose concentrations. Constant hyperglycemia at this level was then maintained for 120 min by varying the infusion of 20% dextrose but no insulin. The mean concentration of serum insulin in the first 10 min, at 2-min intervals, is an index of early insulin secretion (µU/ml) in response to hyperglycemia. Thereafter, blood was taken every 5 min for measurement of serum glucose and every 10 min for measurement of serum insulin concentrations. The mean serum insulin concentration, at 10-min intervals from 20 to 120 min, is an index of late insulin secretion (µU/ml) under steady-state conditions of constant hyperglycemia.

Lipid and lipoprotein profiles. Fasting lipid and lipoprotein values were determined from fresh plasma samples. Lipoprotein fractionation was performed with ultracentrifugation and selective precipitation. Triglycerides and cholesterol from whole plasma and cholesterol from lipoprotein fractions were assayed by enzymatic methods using a centrifugal autoanalyzer. Low-density lipoprotein (LDL)-cholesterol values were derived from the total cholesterol and high-density lipoprotein-cholesterol levels. Apolipoprotein (Apo) A1 and Apo B were determined by nephelometry.

Biochemical measurements. Serum glucose concentration was measured by the glucose oxidase method using a Yellow Springs 23 AM glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio, USA). Serum immunoreactive insulin concentration was measured by double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden). Serum parathyroid hormone (PTH) was measured by an immunoradiometric assay for the intact molecule (Incstar, Stillwater, Minn., USA). Serum 1,25 $(OH)_2$ D_3 was measured by a radioreceptor assay (Incstar). This assay is specific for both 1,25$(OH)_2D_3$ and 1,25$(OH)_2D_2$. Serum total calcium, phosphorus, potassium, creatinine, and BUN were measured by standard methods on a multichannel autoanalyzer. Plasma ferritin was measured by a solid-support radioimmunometric assay (Ramco Laboratories, Houston, Tex., USA). All values are expressed as mean plus or minus standard error of the mean. The data were tested for normality using the chi-squared method. Analysis of variance and Student's *t*-tests were used for analysis of the result. Statistical significance was recognized at the 5% level.

Results

Clinical and biochemical parameters after EPO

All patients tolerated EPO treatment well. In most patients, it took about 3 months for their hemoglobin and hematocrit to stabilize and they were restudied 6 months after starting on EPO, which represented 3 months of stable hemoglobin and hematocrit levels. Their clinical and nutritional data are presented in Table 1. There were no significant changes in weight, mean arterial pressure,

Table 1. Hematological, nutritional, and biochemical data in patients on continuous cycling peritoneal dialysis (CCPD) before and after 6 months of human recombinant erythropoietin (EPO)

	Before EPO	After EPO	*P* value
Hematocrit	22.2±1.8	34.8±1.8	<0.001
Serum ferritin	1,189±168	726±138	<0.05
Serum iron	133±12	85±10	<0.01
Caloric intake (kcal/day)	1,623±212	1,788±323	NS
Protein intake (g/kg per day)	2.4±0.4	2.7±0.4	NS
Weight (kg)	45.6±2.3	47.5±2.0	NS
TSF (mm)	9.4±0.3	9.9±0.2	NS
AMA (mm^2)	2,638±238	2,836±199	NS
Ca (mg/dl)	9.6±0.3	9.9±0.3	NS
PO_4 (mg/dl)	6.0±0.3	6.5±0.3	NS
HCO_3 (mmol/l)	22±1	22±1	NS
Albumin (g/dl)	3.2±0.3	3.5±0.2	NS
BUN (mg/dl)	70±4	72±3	NS
Creatinine (mg/dl)	10.4±0.7	10.6±0.8	NS
Creatinine clearance (ml/min per 1.73 m^2)	3±1	3±1	NS
Kt/V urea (per week)	2.2±0.4	2.0±0.4	NS
PTH (ρg/ml)	338±44	362±31	NS
$1,25(OH)_2D_3$ (ρg/ml)	31±3	30±2	NS

TSF, Triceps skinfold thickness; AMA, arm muscular area; Ca, calcium; PO_4, phosphate; HCO_3, bicarbonate; BUN, blood urea nitrogen; PTH, parathyroid hormone; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3

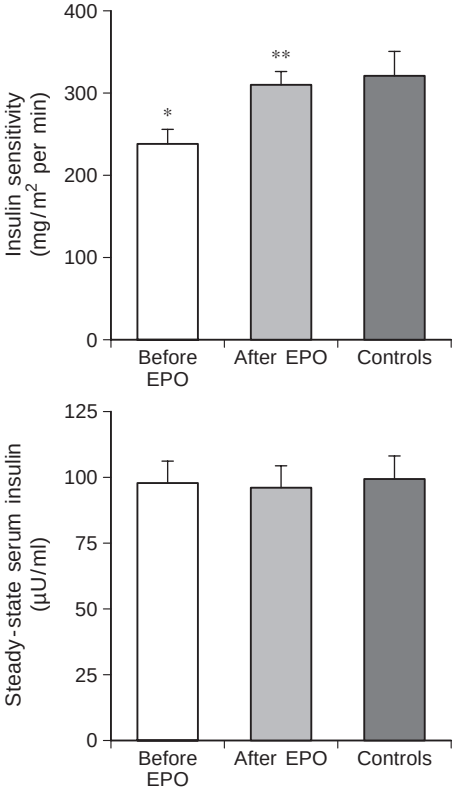

Fig. 1. Insulin sensitivity as measured during the euglycemic clamp in continuous cycling peritoneal dialysis (CCPD) patients before and after 6 months of treatment with human recombinant erythropoietin (*EPO*) and controls. The *lower panel* shows the mean steady-state serum insulin concentrations during the euglycemic clamps. * *P*<0.01 vs. controls; ** *P*<0.01 vs. before EPO

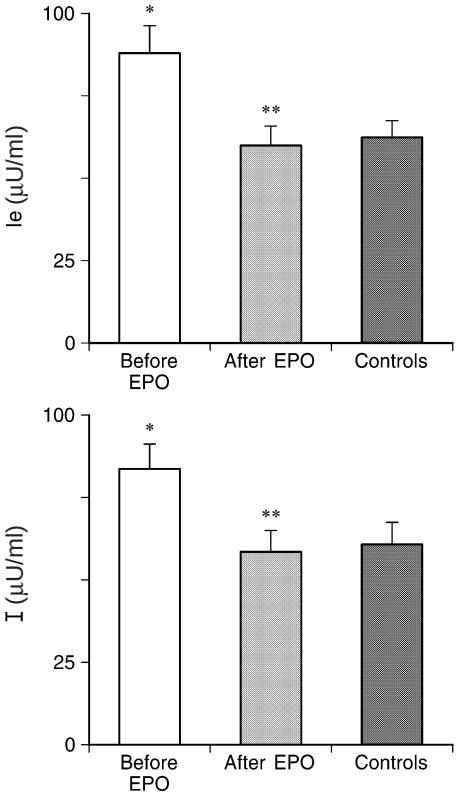

Fig. 2. Insulin secretion as measured during the hyperglycemic clamp in CCPD patients before and after 6 months of treatment with EPO and controls. Early insulin secretion (*Ie*) represents the mean insulin concentrations during the first 10 min of hyperglycemia and late insulin secretion (*I*) represents the mean insulin concentrations during 20–120 min of the hyperglycemic clamp studies. * *P*<0.01 vs. controls; ** *P*<0.01 vs. before EPO

protein intake, caloric intake, triceps skinfold thickness, or arm muscular area. The hematological and biochemical parameters are also presented in Table 1. There were no significant changes in adequacy of dialysis as measured by fractional urea clearance (Kt/V_{urea}) and residual renal function. Weekly Kt/V_{urea} for CCPD was 2.2±0.4 before EPO and 2.0±0.4 after EPO. Residual function measured by urinary creatinine clearance was 3±1 ml/min per 1.73 m^2 before EPO and 3±1 ml/min per 1.73 m^2 after EPO.

Euglycemic clamp studies

Insulin-stimulated glucose metabolism (insulin sensitivity) was stable in patients on CCPD before EPO treatment. The values from the two initial studies were not different. However, the mean insulin sensitivity values in the patients before EPO treatment (238±19 mg/m^2 per min) were low compared with controls (320±30, *P*<0.01). After EPO treatment, insulin sensitivity increased by 28% (305±26, *P*<0.01 vs. pre-EPO values), so that the value was no longer different from control values (Fig. 1). Mean serum glucose and insulin concentrations in the patients during the euglycemic clamp studies before and after EPO treatment were not differ-

Table 2. Fasting plasma lipid profiles in patients on CCPD before and after 6 months of EPO

	Before EPO	After EPO[a]	Controls
Triglycerides (mg/dl)	188±18*	148±16**	130±14
Total cholesterol (mg/dl)	220±22*	172±18**	168±17
LDL-cholesterol (mg/dl)	136±12*	103±11**	99±10
Apo A1 (mg/dl)	103±13	108±12	110±13
Apo B (mg/dl)	128±19*	93±10**	78±8
Apo A1/Apo B	0.8±0.1*	1.2±0.1**	1.4±0.1

LDL, Low density lipoprotein; Apo A1, apolipoprotein A1
* $P<0.01$ versus controls; ** $P<0.01$ versus before EPO values
[a] All "after EPO" values are not different from controls

ent compared with controls. Thus EPO treatment corrected insulin resistance in patients on peritoneal dialysis.

Hyperglycemic clamp studies

Mean serum insulin responses to constant hyperglycemia (125 mg/dl above fasting concentrations) are shown in Fig. 2. Insulin responses were higher in patients before EPO treatment compared with controls ($P<0.01$) and these values decreased significantly ($P<0.01$) after EPO treatment, so that they were no longer different from control values. Thus EPO treatment corrected hyperinsulinemia in patients on peritoneal dialysis.

Plasma lipid profiles

Plasma lipid profiles are summarized in Table 2. Before EPO, the patients had high serum concentrations of triglycerides, total cholesterol, LDL-cholesterol, and Apo B compared with controls. These lipid abnormalities all decreased significantly after EPO.

Discussion

Diabetes due to insulin deficiency has been well described in chronic anemic states such as thalassemia major and is thought to be secondary to effects of iron overload [12, 13]. However, other studies have reported increased rather than reduced insulin responses to glucose in thalassemic patients, suggesting that insulin resistance is also present [14]. Merkel et al. [6] studied adolescents with thalassemia who had received a large number of transfusions and were therefore iron toxic, and reported insulin resistance and glucose intolerance. These investigators also studied younger children with thalassemia, who had not received as many transfusions and were therefore less iron toxic, and found that this second group of patients were insulin sensitive and glucose tolerant. The authors concluded that iron toxicity rather than anemia per se was the likely cause of the insulin resistance. However, the ferritin levels in younger children (2,045±278 ng/ml) were still very high (normal levels below 300 ng/ml). The patients in the present study were not very iron toxic to begin with. Their ferritin levels were lower than those in the younger group in the study of Merkel et al. [6] who did not manifest insulin resistance, suggesting that iron toxicity is not a likely cause of their insulin abnormalities. Furthermore, insulin resistance and hyperinsulinemia have been described in patients with chronic renal failure not on dialysis who had not received any transfusions and therefore were unlikely to be iron toxic [15]. Correction of anemia by EPO treatment in the present study led to reversal of insulin resistance in the patients on CCPD. Although there is a concomitant decrease in iron toxicity, this is unlikely to be an important factor contributing to the improvement in insulin sensitivitiy. In a recent study of adult patients on hemodialysis treated with EPO to correct anemia, insulin resistance and hyperinsulinemia were corrected equally in patients with or without iron toxicity [7]. Thus the effect of anemia rather than iron toxicity is likely to be important in the pathogenesis of insulin resistance in uremia.

There are two other studies on the effect of EPO therapy on glucose metabolism in adult patients on hemodialysis. Chagnac et al. [16] performed oral glucose tolerance tests in ten older patients (mean age 60±3 years) on chronic hemodialysis before and after treatment of anemia by EPO for 3–5 months. They did not find any significant difference in areas under the curve both in the glucose and the insulin responses during oral glucose tolerance tests before and after EPO therapy. However, they did not study insulin sensitivity or insulin secretion formally by glucose clamp methodologies. Uremic patients with insulin resistance could maintain glucose tolerance by developing hyperinsulinemia [1, 2]. Borissova et al. [17] studied insulin sensitivity by the euglycemic clamp technique before and after 5 months of EPO treatment in five patients (mean age 42±5 years) with type I diabetes and chronic renal failure on hemodialysis. They found a significant improvement in their insulin sensitivity with simultaneous increase in arterial PO_2 and decrease in plasma lactate concentration. These authors postulated that improving oxygen supply and overcoming tissue hypoxia could account for the improvement in insulin action. There are no previous data on the effect of EPO on adult patients on peritoneal dialysis.

It is possible that the improvement in insulin metabolism in the present study is related to the effects of CCPD. CCPD is known to improve but not correct insulin sensitivity in uremic patients [11]. The improvement usually takes place at the initiation of CCPD. Most patients stabilized on CCPD are however still insulin resistant. The patients in this study have been stabilized on CCPD before initiation of EPO treatment. The two initial studies before EPO therapy showed that insulin sensitivity was stable but still lower than control values.

Malnutrition is common in patients with ESRD [18] and may be an important cause of insulin resistance [19]. Correction of anemia by EPO has been reported to improve appetite [20] and nutritional status [21] of patients with ESRD. Treatment of malnutrition by intravenous nutrition has been shown to improve insulin resistance in

surgical patients [22]. Improved nutrition in patients with ESRD following correction of anemia by EPO may be an important factor in the correction of insulin resistance and glucose intolerance. In the present study, the nutritional parameters (caloric intake, weight, triceps skinfold thickness, arm muscular area) showed some improvement but did not quite reach statistical significance, probably because of the small sample size. A larger study is needed to assess whether changes in nutritional status can account for the improvement in insulin resistance following EPO treatment.

$1,25(OH)_2D_3$ deficiency and secondary hyperparathyroidism have been implicated in the pathogenesis of insulin abnormalities in uremia [23–26]. Furthermore, hyperparathyroidism may also be involved in the pathogenesis of hyperlipidemia in uremia [27]. Before treatment with EPO, the patients in the present study demonstrated mild secondary hyperparathyroidism. These PTH concentrations may represent the optimal concentrations for this subset of patients on CCPD, because of the risk of adynamic bone disease [28]. The serum $1,25(OH)_2D_3$ concentrations were normal at the initiation of EPO. This may be due to the fact that they were measured about 12 h after ingestion of their oral $1,25(OH)_2D_3$ supplements (given at bedtime to minimize hypercalcemia). Since serum PTH and $1,25(OH)_2D_3$ concentrations did not change in the present study, they are unlikely to be responsible for the changes in insulin and lipid metabolism following EPO treatment.

Patients with ESRD generally have low exercise tolerance and this may contribute to their metabolic abnormalities. Goldberg et al. [29] showed that moderate endurance training improved both the exercise tolerance and insulin sensitivity in patients on hemodialysis. The magnitude of the improvement in insulin sensitivity was greater than would be anticipated because of changes in diet or body composition. Furthermore, the return of insulin resistance towards pre-training levels in patients who stopped training suggested that the training effect was primary. Davis et al. [30] showed that exercise training increased insulin sensitivity and responsiveness of muscle glucose uptake and glycolytic utilization in rats with chronic renal failure and controls. Correction of anemia by EPO in hemodialysis patients has been reported to improve exercise tolerance [31]. Although excercise tolerance was not measured in the present study, all patients reported a subjective increase in exercise tolerance and an increase in energy and physical activity. Furthermore, exercise training in patients with hyperlipidemia and coronary artery disease can lead to improvements in plasma triglycerides, total cholesterol, and LDL-cholesterol [32]. Improved exercise tolerance following EPO therapy may very well be an important factor in the improvement in insulin and lipid metabolism in these patients with ESRD.

Hypertriglyceridemia and hyperlipoproteinemia are common in patients with uremia on peritoneal dialysis [33, 34]. The elevated plasma triglycerides, total cholesterol, LDL-cholesterol, and Apo B concentrations in patients in the present study before EPO are compatible with previous reports of type IV hyperlipidemia in patients with ESRD [34]. Pollock et al. [35] studied 112 patients on hemodialysis before and after 6 and 12 months of EPO and found significant decreases in plasma triglycerides, cholesterol, and Apo B following correction of anemia. Mat et al. [36] and Prata et al. [37] studied smaller cohorts of adult patients on hemodialysis and did not report any changes in the lipid profiles after EPO therapy. The patients in the study of Mat et al. [36] were not well characterized and the hematological changes following EPO were not available. The patients in the study of Prata et al. [37] were not very hyperlipidemic to begin with (before EPO, mean triglyceride was 136 and mean cholesterol was 195 mg/dl). Also, the ages of the patients in both studies [36, 37] were not available, so it was difficult to determine whether the lipid levels were elevated with respect to age. Viron et al. [38] reported, in 12 patients with a mean age of over 60 years on dialysis, increases in Apo A1 but no changes in cholesterol and triglycerides after EPO treatment. The pre-treatment cholesterol (189 mg/dl) and triglycerides (146 mg/dl) levels in this last study were not elevated for age. Manitius et al. [39] reported a decrease in plasma total cholesterol, LDL-cholesterol, and free fatty acids in six hemodialysis patients treated with non-hematological doses of EPO as well as a decrease in anaerobic metabolism.

The present study showed amelioration of lipid abnormalities following EPO treatment of anemia in postpubertal patients on CCPD. These lipid changes were accompanied by correction of insulin resistance and hyperinsulinemia. Insulin resistance had been thought to be important in the pathogenesis of the lipid abnormalities in uremia [4]. In younger children with ESRD on dialysis, EPO treatment has been associated with improvements in insulin and lipid metabolism [40]. However, the latter study was limited by the lack of age-appropriate normal controls, because the institutional review board did not allow glucose clamp studies in young healthy children. Whether correction of the atherogenic lipid profiles following EPO treatment will lead to an actual decrease in long-term morbidity in dialysis patients remains to be tested.

Thus correction of anemia by EPO ameliorated insulin and lipid abnormalities in seven uremic patients on CCPD. While these preliminary results are exciting, they should be interpreted with caution because of the small number of patients studied. Future studies involving larger groups of patients, including children, are needed to confirm these results and to individually test whether EPO therapy per se or rather the accompanying improvements in nutrition and exercise tolerance following correction of anemia are responsible for the amelioration of insulin and lipid metabolism. Furthermore, whether correction of these metabolic risk factors for accelerated atherosclerosis will translate into improved morbidity in uremic patients remains to be determined.

Acknowledgements. The author would like to thank Stella Chang M.S. and Joanne Wong M.D. for assistance in the performance of the studies. He would also like to thank the nurses in the dialysis units for their generous support and patience during the studies.

References

1. Mak RHK (1994) Renal disease, insulin resistance and glucose intolerance. Diabetes Rev 2:19–28
2. Mak RHK, DeFronzo RA (1992) Glucose and insulin metabolism in uremia. Nephron 61:377–382
3. DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J (1981) Insulin resistance in uremia. J Clin Invest 67:563–570
4. Chan MK, Varghese Z, Morrhead JF (1981) Lipid abnormalities in uremia, dialysis and transplantation. Kidney Int 19: 625–637
5. DeFronzo RA, Smith D (1985) Is glucose intolerance harmful for the uremic patient? Kidney Int 28 [Suppl 17]:S88–S96
6. Merkel PA, Simonson DC, Amiel SA, Plewe G, Sherwin RS, Pearson HA, Tamborlane WV (1988) Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. N Engl J Med 318:809–814
7. Mak RHK (1996) Correction of anemia by erythropoietin reverses insulin resistance and hyperinsulinemia in uremia. Am J Physiol 270:F839–F844
8. Friis-Hansen B (1961) Body water compartments in children: changes during growth and related changes in body composition. Pediatrics 28:169–181
9. DeFronzo RA, Tobin J, Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–E223
10. McGuire EAH, Helderman JH, Tobin JD, Andres R, Berman M (1976) Effects of arterial versus venous sampling on analysis of glucose kinetics in man. J Appl Physiol 41:565–573
11. Mak RHK (1996) Insulin resistance in uremia: effect of dialysis modality. Pediatr Res 40:304–308
12. Flynn DM, Fairney A, Jackson D, Clayton BE (1976) Hormonal changes in thalassemia major. Arch Dis Child 54: 345–376
13. Zuppinger K, Molinari B, Hirt A, Imbach P, Gugler E, Tonz D, Zurbrugg RP (1979) Increased risk of diabetes mellitus in beta-thalassemia major due to iron overload. Helv Paediatr Acta 34:197–207
14. Costin F, Kogut MD, Hyman C, Ortega JA (1977) Carbohydrate metabolism and pancreatic islet-cell function in thalassemia major. Diabetes 26:230–240
15. Mak RHK, Haycock GB, Chantler C (1983) Glucose intolerance in children with chronic renal failure. Kidney Int 24 [Suppl 15]:S22–S26
16. Chagnac A, Weinstein T, Zevin D, Korzets A, Hirsh J, Grafter U, Levi J (1994) Effects of erythropoietin on glucose tolerance in hemodialysis patients. Clin Nephrol 42:398–400
17. Borissova AM, Djambazova A, Todorov K, Dakovska L, Tankova T, Kirilov G (1993) Effect of erythropoietin on the metabolic state and peripheral insulin sensitivity in diabetic patients on hemodialysis. Nephrol Dial Transplant 8:93–95
18. Kopple JD (1978) Abnormal amino acid and protein metabolism in uremia. Kidney Int 14:340–348
19. Feldman HA, Singer I (1975) Endocrinology and metabolism in uremia and dialysis: a clinical review. Medicine (Baltimore) 54:345–376
20. Eschback JW, Kelly MR, Haley NR, Abels I, Adamson JW (1989) Correction of anemia in progressive renal failure with recombinant human erythropoietin. N Engl J Med 321: 158–163
21. Barrany P, Peterson E, Ahberg M, Hultman E, Bergstrom J (1991) Nutritional assessment in anemic hemodialysis patients treated with human recombinant erythropoietin. Clin Nephrol 35:270–279
22. Church JM, Hill GL (1988) Impaired glucose metabolism in surgical patients improved by intravenous nutrition: assessment by euglycemic hyperinsulinemic clamp. Metabolism 37:505–509
23. Mak RHK (1992) 1,25 Dihydroxycholecalciferol corrects glucose intolerance in hemodialysis patients. Kidney Int 41: 1049–1054
24. Mak RHK, Turner C, Haycock GB, Chantler C (1983) Secondary hyperparathyroidism and glucose intolerance in children with uremia. Kidney Int 24 [Suppl. 16]:S128–S133
25. Mak RHK, Bettinelli A, Turner C, Haycock GB, Chantler C (1985) The influence of hyperparathyroidism on glucose metabolism in uremia. J Clin Endocrinol Metab 60:229–233
26. Akmal M, Massry SG, Goldstein DA, Fanti P, Weisz A, DeFronzo RA (1985) The role of parathyroid hormone in the glucose intolerance of chronic renal failure. J Clin Invest 1037–1044
27. Massry SG, Akmal M (1989) Lipid abnormalities, renal failure and parathyroid hormone. Am J Med 87:42–44
28. Salusky IB, Goodman WG (1996) The management of renal osteodystrophy. Pediatr Nephrol 10:651–653
29. Goldberg A, Hagberg J, Delmez J, Haynes ME, Harter HR (1980) The metabolic effects of exercise training in hemodialysis patients. Kidney Int 18:754–761
30. Davis TA, Klahr S, Karl IE (1987) Glucose metabolism in muscle of sedentary and exercised rats with azotemia. Am J Physiol 252:F138–F145
31. MacDougall IC, Lewis NP, Sauners MJ, Cochlin DL, Davies DE, Hutton RD, Fox KA, Coles GA, Williams JD (1990) Long term cardiorespiratory effects of amelioration of renal anemia by erythropoietin. Lancet 335:489–493
32. Lavie CJ, Milani R (1994) Effects of cardiac rehabilitation and exercise training on low-density lipoprotein cholesterol in patients with hypertriglyceridemia and coronary artery disease. Am J Cardiol 74:1192–1195
33. Ramos JM, Heaton A, McGurk JG, Ward MK, Kerr DNS (1983) Sequential changes in serum lipid subfractions in patients receiving continuous ambulatory peritoneal dialysis. Nephron 35:20–23
34. Querfeld U, Leboeuf RC, Salusky IB, Nelson P, Laidlaw S, Fine RN (1991) Lipoproteins in children treated with continuous peritoneal dialysis. Pediatr Res 29:155–159
35. Pollock CA, Wyndham R, Collett PV, Elder G, Field MJ, Kalowski S, Lawrence JR, Waugh DA, George CR (1994) Effects of erythropoietin therapy on the lipid profile in end-stage renal failure. Kidney Int 45:897–902
36. Mat O, Stolear JC, Georges B (1992) Blood lipid profile in haemodialysis patients treated with human erythropoietin. Nephron 60:236–237
37. Prata MM, Sousa FT, Barbas JM, Rodrigues MC (1990) Blood lipids in hemodialysis patients treated with erythropoietin. Nephrol Dial Transplant 5:474
38. Viron B, Donsimoni R, Michel C, Al Kayat R, Mignon F (1992) Effect of recombinant human erythropoietin on nutritional status and plasma lipids in uremic patients. Nephron 60:249
39. Manitius J, Szolkiewicz M, Mysliwska J, Zorena K, Mysliwska A, Jakubowski Z, Lysiak-Szydlowska W, Rutkowski B (1995) Influence of ‘non-hematological’ doses of erythropoietin on lipid-carbohydrate metabolism and life quality in hemodialysis patients. Nephron 69:363–364
40. Mak RHK (1996) The effect of human recombinant erythropoietin on carbohydrate, amino acid and lipid metabolism in uremia. J Pediatr 129:97–105