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ORIGINAL ARTICLE

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Effect of metabolic acidosis on hyperlipidemia in uremia

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Abstract Nine patients (aged 18±1 years) on maintenance hemodialysis with metabolic acidosis and hyperlipidemia were studied before and after 2 weeks of oral sodium bicarbonate ($NaHCO_3$) treatment to correct the acidosis. To control for the effect of additional sodium, they were also studied after 2 weeks of an equivalent amount of oral sodium chloride (NaCl). Oral $NaHCO_3$ treatment led to significant increases in venous pH, serum bicarbonate, and serum 1,25-dihydroxyvitamin D_3 concentrations, but no significant change in total and ionized calcium, phosphate, sodium, potassium, creatinine, blood urea nitrogen, and intact parathyroid hormone concentrations. Oral NaCl did not change any of the biochemical parameters. Before treatment of acidosis, these uremic patients had high serum triglycerides, low serum high-density lipoprotein (HDL) cholesterol, but normal total cholesterol compared with controls. Following 2 weeks of $NaHCO_3$ treatment, there was a significant decrease in the serum concentrations of triglycerides ($P<0.01$). HDL and total cholesterol did not change. There were no changes in triglycerides, HDL or total cholesterol from baseline values following 2 weeks of NaCl. Thus treatment of metabolic acidosis ameliorated hypertriglyceridemia but had no effect on HDL and total cholesterol in patients with uremia on hemodialysis. The underlying mechanism may involve 1,25-dihydroxyvitamin D3.

Key words Triglycerides · Cholesterol · High-density lipoprotein cholesterol · Hemodialysis · Acidosis

Introduction

Abnormalities in lipid metabolism are well documented in patients with uremia and may be a major cause of accelerated atherosclerosis [1–6]. These abnormalities characterize uremia in general and occur regardless of the underlying cause of renal disease [3]. Hypertriglyceridemia is the most-common abnormality in patients on maintenance hemodialysis (HD), with a prevalence of 50%–75% [1–6]. High-density lipoprotein (HDL) cholesterol values are low; total cholesterol concentrations are normal to subnormal in patients on HD [1–6]. The underlying mechanism of these lipid abnormalities in uremia is not well understood. In this study we examined the effect of metabolic acidosis on lipid metabolism in uremic patients on HD.

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Patients and methods

Nine patients (aged 18±1 years) on HD with metabolic acidosis were entered into a controlled study examining the effect of correction of acidosis on lipid metabolism. Their underlying diagnoses included renal dysplasia, obstructive uropathy, reflux nephropathy, prune-belly syndrome, and unknown etiology. They had been stabilized on maintenance HD for at least 6 months prior to the study. The patients were dialyzed with CA 90 dialyzers with mean blood flows of 182±15 ml/min. There was no change in their dialysis prescription during the study. Their blood pressures were controlled on medications and stabilized for at least 2 months before the study. None of the patients had clinical signs of malnutrition or obesity. Their body weights were within 10% of the ideal weight for their height. These nine patients had moderate metabolic acidosis (bicarbonate HCO_3) 15±2 mEq/dl) (Table 1) detected on entry into the study. They underwent the initial metabolic studies whilst being acidotic. Five were then treated first with oral sodium bicarbonate ($NaHCO_3$) (3 mEq/kg per day) for 2 weeks, restudied, and then treated with an equivalent amount of sodium chloride (NaCl) for another 2 weeks and studied at a third time point. The other four patients were first treated with NaCl and then with $NaHCO_3$, and were studied in the same way. Other medications included dihydrotachysterol, calcium carbonate, antihypertensives in the form of long-acting nifedipine, water-soluble vitamins (Nephrovite, R and D Laboratories, Marina Del Rey, Calif., USA) and intravenous erythropoietin during HD sessions. All the medications (other than $NaHCO_3$ or NaCl) were continued and there were no dosage changes during the study.

The patients carbohydrate intake was 4.21±0.20 g/kg per day and their body weights were stable for at least 2 months prior to the studies. Their dietary intakes of sodium (2 g/day excluding $NaHCO_3$ or NaCl), potassium (2 g/day), and phosphorus (800 mg)

were restricted, but the intake of protein was not. Dietary calorie, protein, phosphorus, and sodium takes were monitored by 3-day diet diary during the different study periods. None of the patients had diabetes mellitus nor was there a family history of diabetes mellitus. Controls consisted of seven healthy subjects (aged 19±1 years) consuming regular weight-maintaining diets and taking no medications. There was no family history of diabetes mellitus in the controls. All patients and controls were free from infection at the time of the studies. The clinical studies were performed at Childrens' Hospital of Los Angeles and were approved by the local institutional review board. 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.

Biochemical analysis

Serum biochemistry was measured by standard methods on multichannel autoanalyzers. Intact serum parathyroid hormone (PTH) was measured by an immunoradiometric assay (Nichols, San Juan Capistrano, Calif., USA). Serum 1,25-dihydroxyvitamin D_3 [1,25 $(0H)_2D_3$] was measured by a radioreceptor assay (Nichols). This assay is specific for both $1,25(OH)_2D_3$ and $1,25(OH)_2D_2$. It involves a preliminary extraction and purification of serum, followed by quantitation with a radioreceptor assay using a calf thymus receptor and tritiated $1,25(OH)_2D_3$. 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 automated enzymatic methods.

All values are expressed as mean ± standard error of the mean. The data were tested for normality using the chi-squared method. Analysis of variance and Student's *t*-tests for paired and unpaired observations were used for analysis of the results. Statistical significance was recognized at the 5% level.

Results

Serum biochemical data of the nine patients on HD at baseline (whilst acidotic) and during treatment with $NaHCO_3$ and NaCl are presented in Table 1. Oral $NaHCO_3$ treatment led to significant increases in venous pH, serum bicarbonate, and serum 1,25 $(OH)_2D_3$ concentrations, but no significant change in total and ionized calcium, phosphate, sodium, potassium, creatinine, blood urea nitrogen, and intact PTH concentrations. Oral NaCl did not change any of the biochemical parameters. The patients remained moderately anemic despite erythropoietin treatment, and there were no changes in hematocrit values after either $NaHCO_3$ or NaCl treatment. There were also no changes in dietary intake of calories, protein, phosphorus, or sodium during the different treatment periods.

Parameters of lipid metabolism and their changes during the study are also presented in Table 1. Before treatment of acidosis, these uremic patients had high triglycerides, low HDL cholesterol, but normal total cholesterol compared with controls. Following 2 weeks of $NaHCO_3$ treatment, there was a significant decrease in triglycerides ($P<0.01$), although the values did not normalize. HDL cholesterol and total cholesterol did not change. There were no changes in triglycerides, HDL cholesterol, and total cholesterol from baseline values following 2 weeks of NaCl.

Discussion

The patients on maintenance HD in the present study demonstrate abnormalities in lipid metabolism, namely hypertriglyceridemia and decreased HDL cholesterol, which are commonly reported in the literature [1–6]. The amelioration of hypertriglyceridemia in HD patients following correction of metabolic acidosis is a novel finding. The underlying mechanism of these metabolic changes would be most interesting.

Metabolic acidosis is known to alter vitamin D metabolism. Lu et al. [7] showed that acute correction of metabolic acidosis by intravenous $NaHCO_3$ infusion significantly increased serum $1,25(OH)_2D_3$ concentrations, without changes in plasma ionized calcium, potassium, magnesium, phosphorus, and 25-hydroxyvitamin D_3 concentrations in patients with moderate chronic renal failure not on dialysis. The present study confirms these results in patients with end-stage renal disease on maintenance HD. There were no simultaneous changes in oral vitamin D or phosphorus binder dosages, dietary phos-

Table 1 Biochemical parameters in patients on hemodialysis at baseline (whilst acidotic), after sodium bicarbonate (*NaHCO$_3$*) and sodium chloride (*NaCl*) treatment periods, and in control subjects (*Ca* calcium, *PO$_4$* phosphate, *BUN* blood urea nitrogen, *PTH* parathyroid hormone, *1,25(OH)$_2$D$_3$* 1,25-dihydroxyvitamin D_3, *HDL* high-density lipoprotein)

	Baseline (Acidotic)	After $NaHCO_3$	After NaCl	Controls
Arterial pH	7.28±0.01*	7.38±0.01**	7.25±0.01*	7.38±0.01
$HCO_{3\ (mEq/dl)}$	15±2*	24±2**	17±2*	25±1
Na (mEq/dl)	138±4	142±4	141± 5	139±3
Total Ca (mg/dl)	9.6±0.3	9.4±0.2	9.3±0.2	9.8±0.2
Ionized calcium (mg/dl)	4.7±0.2	4.4±0.2	4.6±0.2	4.8±0.1
$PO_{4\ (}$ mg/dl)	6.8±0.3	6.7±0.3	6.8±0.3	4.5±0.3
Albumin (g/dl)	3.8±0.2	3.7± 0.2	3.6±0.2	4.3±0.1
Hematocrit (%)	31±5	29±4	30±4	45±3
BUN (mg/dl)	80±10	78±9	81±10	8±1
Creatinine (mg/dl)	10.4±0.9	10.3±1.0	10.4±0.9	1.0±0.2
PTH (ρg/ml)	738±80*	730±83*	727±78*	32±8
$1,25(OH)_2D_3$ (ρg/ml)	13±2*	21±2*,**	14±2*	40±3
Triglycerides (mg/dl)	200±20*	165±17*,**	193±21*	130±14
HDL cholesterol (mg/dl)	39±5*	42±5*	40±5*	63±7
Total cholesterol (mg/dl)	177±20	180±20	173±21	168±17

* $P<0.01$ compared with control values
** $P<0.01$ compared with baseline acidotic values

phorus intakes, or PTH concentrations, so that the $1,25(OH)_2D_3$ changes were most likely a result of correction of acidosis. $1,25(OH)_2D_3$ concentrations in the patients during the baseline acidotic phase were about one-third of control values, and rose significantly (to about half of control values) after correction of metabolic acidosis, but did not normalize. This may reflect the low renal reserve in these patients in terms of their remaining 1 α-hydroxylase capacity. These results suggest the improvement in lipid abnormalities following correction of acidosis may be related to an increase in circulating $1,25(OH)_2D_3$ concentrations. Lind et al. [8] reported that intravenous calcidol treatment in HD patients reduced serum triglycerides, fasting blood glucose, and hemoglobin A_{1C}, suggesting that active vitamin D metabolites could improve hyperlipidemia and glucose intolerance. Furthermore, Yeksan et al. [9] also reported a significant reduction in triglyceride concentrations without changes in total cholesterol and HDL cholesterol concentrations in HD patients after oral $1,25(OH)_2D_3$ therapy. In these two previous studies, the changes in lipid concentrations following vitamin D therapy in HD patients are very similar to those in the present study. Amelioration of $1,25(OH)_2D_3$ deficiency may indeed be the underlying mechanism for the partial correction of hypertriglyceridemia in the HD patients in the present study. Whether a longer period of $NaHCO_3$ treatment will lead to a full correction of $1,25(OH)_2D_3$ deficiency and/or full correction of hypertriglyceridemia will be most interesting.

There is evidence that PTH may be involved in the pathogenesis of the lipid disturbances in uremia [10]. Akmal et al. [11] demonstrated hypertriglyceridemia and decreased post-heparin lipoprotein lipase activity in uremic dogs and that parathyroidectomy corrected hypertriglyceridemia as well as lipoprotein lipase activity in these animals. Liang et al. [12] demonstrated hypertriglyceridemia in rats with chronic renal failure and that parathyroidectomy partially ameliorated hypertriglyceridemia through upregulation of hepatic lipase and lipoprotein lipase. Suppression of secondary hyperparathyroidism in HD patients by intravenous calcidol treatment led to amelioration of hypertriglyceridemia [8] although a more-recent study showed that amelioration of hypertriglyceridemia by intravenous $1,25(OH)_2D^3$ in HD patients could occur without significant changes in PTH concentrations [13]. PTH concentrations did not change in the patients in the present study. However, this does not rule out the role of PTH. Metabolic acidosis inhibits the renal actions of PTH [14], including the stimulation of renal 1α-hydroxylase [15]. The relief of acidosis may allow such actions to be altered without changes in levels of the hormone. Indeed, the increase in $1,25(OH)_2D_3$ concentrations in the present study is likely to be due to the increased action of PTH on renal 1α-hydroxylase following correction of metabolic acidosis. Whether this applies to the action of PTH on lipid metabolism following correction of acidosis in uremic patients remains to be determined.

In summary, treatment of metabolic acidosis partially corrected hypertriglyceridemia but had no effect on HDL cholesterol in patients with uremia on HD. Further studies are needed to investigate the underlying pathophysiological mechanism, and whether longer periods of acidosis correction are associated with normalization of hypertriglyceridemia, as well as amelioration of other abnormalities in lipoprotein metabolism, in uremic patients.

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