Deranged Metabolism of Lipids in Patients with Chronic Renal Failure: Possible Role of Secondary Hyperparathyroidism

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We wished to investigate the pathophysiology of hypertriglyceridemia in chronic renal failure. Our subjects were 30 patients under hemodialysis for at least five years who had never taken vitamin D analogues or calcitonin preparations. During those five years, triglycerides were high, with no significant changes, although the cholesterol level decreased significantly 10 to 12 months after the first hemodialysis treatment. There was a significant correlation between alkaline phosphatase and triglycerides ($p < 0.025$) in these patients in the same assay. In the two patients with hypertriglyceridemia, serum triglycerides decreased to within the normal range by six months after parathyroidectomy, and remained there 30 months after surgery. These results suggested that secondary hyperparathyroidism may be involved in the pathophysiological mechanism of hypertriglyceridemia seen in chronic renal failure.

Key Words: Abnormal lipid metabolism, Chronic renal failure, Hypertriglyceridemia, Secondary hyperparathyroidism, Parathyroidectomy

Hypertriglyceridemia, accompanied by hypercholesterolemia or not, is a major complication in chronic renal failure.¹⁾ Ponticelli²⁾ reported that hyperlipidemia was found in 72% of 126 hemodialyzed patients; 55% of which were cases of type IV hyperlipoproteinemia. The uremic state promotes atherosclerosis.³⁾ Secondary hyperparathyroidism develops in chronic renal failure, and probably contributes the cause of the metabolic changes in that disease. This study was done to examine the possibility that secondary hyperparathyroidism is involved in the pathophysiological mechanism of deranged lipid metabolism in uremia.

SUBJECTS AND METHODS

Thirty patients with chronic renal failure who had been treated by hemodialysis for five years or more and who had never been given any vitamin D analogues or calcitonin preparation were selected. The cause of the renal failure was chronic

glomerulonephritis in 27 patients, systemic lupus erythematosus in 2 patients and diabetic nephropathy in one patient. The mean period of hemodialysis was 5 years and 2 months, and the mean age at the first hemodialysis treatment was 45.3 ± 12.4 years. Twenty-three of the 30 patients were men and the rest women. Serum levels of electrolytes, lipids, alkaline phosphatase (AP) and parathyroid hormone (PTH) had been measured monthly in these subjects since hemodialysis started. Electrolytes, lipids and AP were assayed in the usual ways and PTH was measured by C-terminal radioimmunoassay. Parathyroidectomy (PTX) was done in five patients (three men and two women) on long-term hemodialysis, and serum lipids were followed closely after surgery.

Data were expressed as mean $\pm$ SD. Statistical analysis was by Student's *t*-test.

RESULTS

In the 30 patients, serum levels of calcium

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and phosphate improved within 3 months of the first hemodialysis treatment, and did not change significantly in the following 5 years of homo-

dialysis (Fig. 1). AP increased significantly 7 to 9 months after hemodialysis started, and tended to increase afterwards (Fig. 2). Serum cholesterol

Fig. 1. Serum levels of calcium and phosphate for 5 years after start of hemodialysis in 30 patients with chronic renal failure, who never received vitamin D analogues or calcitonin preparations. *, **, *** are significantly different from the value before the start of hemodialysis (*; $p < 0.025$, **; $p < 0.01$, ***; $p < 0.005$).

Fig. 2. Level of alkaline phosphatase (AP) for 5 years after start of hemodialysis in the same patients. Δ; $p < 0.1$, *; $p < 0.05$, **; $p < 0.01$, ***; $p < 0.005$.

Fig. 3. Level of cholesterol in serum for 5 years after of hemodialysis. *, $p < 0.05$, **, $p < 0.025$, ***, $p < 0.01$.

Fig. 4. Level of triglycerides in serum for 5 years after start of hemodialysis. There were no significant changes.

decreased significantly 10 to 12 months after hemodialysis started, and decreased gradually later (Fig. 3). Serum triglycerides were high and did not change significantly over the 5 years of hemodialysis; there was a small increase in the first 6 months (Fig. 4). Beta-lipoproteins tended to decrease during the five years, as did cholesterol, and HDL-cholesterol remained at a low level without significant changes.

The correlation was significant between AP and triglycerides ($p < 0.025$), between AP and β -lipoproteins ($p < 0.025$) and between AP and phospholipids ($p < 0.025$) in assays done at the

same time in October, 1983 (Table 1).

In the five parathyroidectomized patients, the serum level of PTH decreased to within the normal range immediately after the operation. The findings of renal osteodystrophy improved within one year. The mean values of triglycerides and cholesterol for the six months before and after the operation are shown in Table 2. One patient (case no. 5) had a low level and the others normal levels of cholesterol before surgery. Two of the five patients had high levels of triglycerides at this time. After parathyroidectomy, serum levels of cholesterol decreased to 144 ± 13 mg/dl

Table 1. Correlation between the serum level of PTH, calcium, phosphate, alkaline phosphatase, total protein (TP), triglycerides (TG), cholesterol (CHOL), β -lipoprotein, HDL-cholesterol and phospholipids (PL) in the 30 patients described in the text in assays done at one time.

: $p < 0.025$

	PTH								
PTH									
Ca	$r=0.030$								
P	$r=0.161$	$r=-0.033$							
ALP	$r=0.136$	$r=0.043$	$r=0.282$						
TP	$r=0.102$	$r=0.179$	$r=-0.155$	$r=0.119$					
TG	$r=-0.161$	$r=0.269$	$r=-0.082$	$r=0.389$	$r=0.201$				
CHOL	$r=0.017$	$r=0.281$	$r=0.285$	$r=0.209$	$r=-0.008$	$r=0.581$			
β -Lipo	$r=0.114$	$r=0.251$	$r=-0.076$	$r=0.376$	$r=0.241$	$r=0.942$	$r=0.708$		
HDL-Chol	$r=0.170$	$r=0.030$	$r=0.253$	$r=0.038$	$r=-0.271$	$r=-0.049$	$r=0.231$	$r=-0.115$	
PL	$r=0.063$	$r=0.288$	$r=0.211$	$r=0.396$	$r=0.041$	$r=0.767$	$r=0.899$	$r=0.844$	$r=0.226$

Table 2. Profiles of 5 parathyroidectomized patients. The means of triglycerides and cholesterol in serum for 6 months before and for 6–12 months after surgery. *, **, *** are significantly different to the value before the start of hemodialysis.

*, $p < 0.05$, **, $p < 0.025$, ***, $p < 0.005$.

	sex	ages	HD period	before PTX		after PTX	
				TG	CHOL	TG	CHOL
case 1	male	40 yo.	8yrs 1 mo	104 $\pm$ 11	143 $\pm$ 9	124 $\pm$ 24	136 $\pm$ 7
2	female	46 yo.	7yrs 11mo	226 $\pm$ 47	205 $\pm$ 30	155 $\pm$ 19**	144 $\pm$ 13***
3	female	33 yo.	7yrs 11mo	134 $\pm$ 24	125 $\pm$ 7	150 $\pm$ 22	157 $\pm$ 15
4	male	40 yo.	8yrs 1 mo	184 $\pm$ 51	161 $\pm$ 14	107 $\pm$ 21**	151 $\pm$ 10
5	male	48 yo.	7yrs 9 mo	122 $\pm$ 19	105 $\pm$ 6	128 $\pm$ 19	95 $\pm$ 7*

in the patient (case no. 2), whose mean cholesterol for the six months before the operation, 205 $\pm$ 30 mg/dl, was the highest of the five patients. In the two patients with hypertriglyceridemia (case nos. 2 and 4), the serum triglyceride level entered the normal range, becoming 155 $\pm$ 19 mg/dl or 107 $\pm$ 21 mg/dl after parathyroidectomy; and these values remained normal in the following 30 months (Fig. 5).

DISCUSSION

There was a small incidence, 6.4%, of cholesterol levels higher than 200 mg/dl one year after the first hemodialysis treatment. Incidentally, hypertriglyceridemia was present in 48.2% of the 170 patients under hemodialysis at the same time in our previous study. The finding here was

compatible with Brunzell's report,⁴⁾ as was the finding that mean cholesterol was normal and the triglyceride level was higher than normal after hemodialysis treatment started.

The main cause of hypertriglyceridemia in uremic conditions is probably peripheral impairment of the removal of lipids from blood, probably because of the lowered metabolic turnover of very low density lipoprotein (VLDL) due to the suppression of LPL,^{5,6)} abnormality in the protein composition of lipoproteins,⁷⁾ and decreased hepatic lipase.⁸⁾ Moreover, hormonal disturbances such as hypothyroidism, hypogonadism, or diabetes might influence lipid metabolism in uremia.¹⁾

Glucose metabolism and protein metabolism are involved in uremia and are probably influenced

Fig. 5. Levels of cholesterol and triglycerides in serum after parathyroidectomy as relative values of the mean for 6 months. Upper; cholesterol, lower; triglycerides. *, $p < 0.05$, **, $p < 0.025$, ***, $p < 0.005$.

by secondary hyperparathyroidism. The insulin-mediated peripheral metabolism of glucose is reduced in uremia due to postbinding defects of insulin, because there is no difference in the receptor binding of insulin between controls and uremic patients.⁹ Mak¹⁰ reported that secondary hyperparathyroidism inhibits the increase of insulin secretion that compensates for peripheral insulin resistance, resulting in reduced glucose metabolism in uremia. There is increased catabolism of protein, and essential amino acids are reduced in uremic patients.¹¹ Koppel¹² reported that the high level of PTH in uremia intensifies the increased catabolism of proteins in muscles. These findings suggest that secondary hyperparathyroidism could influence the metabolism of glucose and protein in uremia, and that these results of secondary hyperparathyroidism might affect lipid metabolism in uremia.

In this study, the serum level of AP of skeletal origin increased after the start of hemodialysis. This means that secondary hyperparathyroidism may develop even in patients on hemodialysis. Because serum levels of triglycerides correlated positively to the serum level of AP and that of cholesterol did not, the high level of triglycerides may be sustained over the course of hemodialysis by the progress of secondary hyperparathyroidism in spite of declining cholesterol. The progress of secondary hyperparathyroidism may suppress decreases in triglycerides. However, triglycerides did not have a significant correlation to PTH, which was assayed as C-terminal PTH. C-terminal PTH cannot be substituted fully for intact PTH, and is expressed more variably. Therefore, the level of triglycerides could be influenced by secondary hyperparathyroidism.

In an *in vitro* study,¹³ PTH increased lipolysis in adipocytes. Paloyan¹⁴ showed in dogs that cholesterol was reduced by parathyroidectomy, and that the reduced level was restored by injection of PTH. Cantin¹⁵ also reported that total lipids decreased after parathyroidectomy. Based on these aspects of PTH action, Massry¹⁶ suggested that PTH is a uremic toxin. In this study, although not all of the patients had lowered levels of lipids, in the two patients with hypertriglyceridemia, lipid levels were decreased at 1 month and stayed low over the 30 months after parathyroidectomy. This suggested that in patients with hypertriglyceridemia or hypercholesterolemia, parathyroidectomy may decrease serum lipids. Many authors^{17, 18} have found that parathyroidectomy has clinical benefits for patients treated by hemodialysis, including improvements in anemia, nutritional status and renal osteodystrophy, so we cannot claim that a decline in lipids after this operation is direct evidence of PTH action upon the deranged lipid metabolism in chronic renal failure. However, nutritional status is maintained better after such surgery by the improvement in anemia, so that from the nutritional point of view, the effect of parathyroidectomy may be a negative factor in decreasing lipids. This may be why the lowered levels of lipids seen in Cases 1 and 3 were increased

temporarily after surgery. Therefore, we think the higher level of PTH is important in maintaining high triglyceride levels in the serum of patients with chronic renal failure.

Active vitamin D alters the pathophysiological status of secondary hyperparathyroidism.^{17, 19)} Calcitonin decreases the serum levels of lipids in uremic rats, hypothalamic obese rats and heritable hyperlipemic rabbits,²⁰⁾ and it inhibits lipolysis in rat epididymal fat pads caused by PTH.¹³⁾ For these reasons, we studied only patients who had not taken vitamin D analogues or calcitonin.

The results of this study suggest that secondary hyperparathyroidism may participate in the pathophysiological mechanism of hypertriglyceridemia in patients with chronic renal failure.

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