Inhibition of Postheparin Lipolytic Activity in Uremia and its Relationship to Hypertriglyceridemia[1] (34842)

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Previous studies have established that plasma postheparin lipolytic activity (PHLA) is reduced in patients with chronic renal failure and may contribute to the development of hypertriglyceridemia, a frequent metabolic abnormality in these patients (1, 2).

This hypothesis assumes that PHLA is an indirect estimate of lipoprotein lipase (3) which, if diminished, would delay the removal of triglycerides from plasma and result in hyperlipemia.

The cause of the reduced PHLA is not clear. However, the fact that activity increases after more frequent hemodialysis, suggests the presence of a circulating inhibitor (4).

We have measured the inhibition of normal PHLA activity by fasting uremic plasma from 10 different patients to explore this possibility.

Materials and Methods. Blood was drawn in heparinized tubes from 10 fasting, chronically uremic patients immediately prior to a 6-hr, twice-weekly hemodialysis. All patients had been ingesting normal amounts of carbohydrate and fat. One patient was a diabetic who required insulin. Ten milliliters of blood were drawn into 12 mg EDTA for serum triglyceride determinations (5) and lipoprotein electrophoresis (6). PHLA was determined in plasma obtained 10 min after the intravenous administration of 10 units heparin/kg body weight (Organon, Inc. 1 ml = 1000 USP units) (7). Blood was centrifuged at 4°, and the plasma was used immediately or frozen for periods not greater than 2 weeks, since activity was observed to decline thereafter. Lipolytic activity was determined for each patient in both a preheparin and a postheparin plasma, using both Ediol and rat chylomicrons as substrate. Ediol (Riker Laboratories, Northridge, California) was diluted so that 0.3 ml contained 15 mg triglyceride. Rat chylomicrons were obtained from rats fed 2–3 ml corn oil three times daily by nasogastric tube. The thoracic duct had been cannulated (8) and chyle was collected continuously at 4° in a tube containing 24 mg EDTA and 10 mg each of penicillin and streptomycin. Chylomicrons were isolated by centrifugation for 30 min at 40,000 rpm in a 40.3 rotor in a Spinco L-2 ultracentrifuge at 15°. The chylomicrons in the top 2.1 cm of the cellulose nitrate tubes were then resuspended and washed twice in a sodium chloride solution, d. 1.006. They were stored at 4° and used within 2 weeks at which time they were diluted with NaCl, d. 1.006 to a concentration of 15 mg triglyceride/0.3 ml. If the triglyceride concentration was less than 15 mg/0.3 ml, the chylomicrons were concentrated by overnight dialysis at 4° against Aquacide (Calbiochem, Los Angeles, California).

In order to determine the presence of a PHLA inhibitor in uremic plasma, 0.2 ml of fasting plasma from each uremic patient was incubated with 0.2 ml postheparin plasma (normal PHLA) from a normal control. The reduction in PHLA was then compared with that obtained when normal fasting plasma was substituted for uremic plasma.

Results. As shown in Table I, both in normal subjects and patients with chronic renal disease, Ediol yielded higher PHLA values than when chylomicrons served as substrate, an observation previously reported in normals by Fredrickson *et al.* (7). In addition, it was found that regardless of the type of

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TABLE I. Postheparin Lipolytic Activity (PHLA) in Uremic Patients and Normal Controls, Using Both Ediol and Rat Chylomicrons as Substrate.[a]

PHLA source	Substrate	
	Ediol	Chylomicrons
Uremic patients (10)	0.15 ± 0.07	0.06 ± 0.04
Normal controls (13)	0.40 ± 0.11	0.29 ± 0.10
p	<.001	<.001

[a] PHLA is expressed as μEq fatty acids hydrolyzed/min/ml plasma and is given as the mean and standard deviation. Plasma from each subject (10 uremic patients and 13 normals) was tested with 15 mg triglyceride from both sources of substrate.

substrate employed, patients with chronic renal disease had significantly lower PHLA values than normal subjects. Although PHLA values were low in all 10 patients with renal disease, only 6 showed abnormal lipoprotein electrophoresis patterns and had serum triglyceride levels that exceeded 190 mg per 100 ml, the upper limit in a normal population described by Fredrickson *et al.* (9) [Table II].

As shown in Table II, fasting uremic plasma inhibited normal PHLA to a greater degree than did normal plasma. However, the magnitude of the inhibition induced by uremic plasma, which varied from case to case, could not be correlated with the plasma triglyceride level, the lipoprotein electrophoretic pattern or the PHLA level in these patients.

Discussion. Hypercholesterolemia and hypertriglyceridemia are well-known complications of the nephrotic syndrome and are thought to be a consequence of increased hepatic lipoprotein synthesis and decreased removal of lipid from the plasma (10). Hypertriglyceridemia is also a common finding in non-nephrotic, chronically azotemic patients, and may persist even after these patients have been on a chronic maintenance hemodialysis program (1). As shown in the present study, the hypertriglyceridemia is characterized by a type IV hyperlipoproteinemia. This could result from (1) an increase in endogenous synthesis of triglyceride, attributed either to a high carbohydrate intake or to an enhanced release of insulin (11–14), (2) a decrease in the rate of removal of triglyceride from plasma, or (3) a combination of these factors.

Previous studies in chronic nephritics with hyperlipemia have established that insulin levels are elevated and can be correlated with increased levels of serum triglyceride (1). However, a reduction in PHLA has also been observed (1, 2), a finding confirmed in the present study.

In addition, we have found that plasma from fasting, uremic subjects contains an inhibitor of PHLA. However, it is unlikely that this inhibition accounts entirely for the low levels of PHLA in uremic serum since the degree of inhibition induced by such serum could not be correlated with its PHLA. This observation taken together with the fact that in half our patients serum triglycerides and lipoprotein electrophoreses were within normal range despite significantly reduced levels of PHLA, suggests that the reduced PHLA is not of great importance in the pathogenesis of uremic hypertriglyceridemia. An increase in endogenous triglyceride synthesis may be a more important factor in producing this form of hyperlipemia.

Summary. The pathogenesis of hypertriglyceridemia associated with renal failure was studied in 10 non-nephrotic uremic patients undergoing twice-weekly hemodialysis. Fasting plasma triglyceride levels, lipoprotein electrophoretic patterns, and postheparin lipolytic activity (PHLA), using both Ediol and rat chylomicrons as substrate, were determined in each patient. Although PHLA activity was reduced in all patients, serum triglyceride levels were elevated to over 190 mg/100 ml in only six. Plasma from the 10 uremic patients usually inhibited PHLA from normal subjects, but often the degree of inhibition was small and did not correlate with the degree of impairment of PHLA. These results suggest that reduced PHLA may be related in part to a circulating plasma inhibitor, but that factors other than plasma clearance of triglyceride are more important in the development of the hyperlipemia seen in chronic uremia.

TABLE II. Abnormalities of Triglyceride Metabolism in 10 Patients with Non-nephrotic Uremia.

Case	Plasma triglyceride (mg/100 ml)	Lipoprotein electrophoresis (type)	PHLA (μEq/min/ml)		Inhibition studies (normal PHLA & uremic plasma) / (normal PHLA & control plasma)	
			Ediol	Chylomicrons	Ediol	Chylomicrons
1	297	IV	0.16	0.04	0.30 / 0.36	0.14 / 0.18
2	297	IV	0.07	0.09	0.24 / 0.36	0.07 / 0.18
3	274	IV	0.11	0.13	0.17 / 0.20	0.08 / 0.14
4	336	IV	0.11	0.07	0.30 / 0.32	0.03 / 0.13
5	231	IV	0.27	0.04	0.18 / 0.20	0.12 / 0.14
6	194	IV	0.15	0.01	0.22 / 0.20	0.004 / 0.14
7	55	Normal	0.00	0.13	0.18 / 0.20	0.09 / 0.14
8	100	Normal	0.10	0.07	0.04 / 0.20	0.12 / 0.14
9	87	Normal	0.13	0.02	0.09 / 0.20	0.03 / 0.14
10	61	Normal	0.16	0.00	0.28 / 0.36	0.13 / 0.18

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