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Severe defect in clearing postprandial chylomicron remnants in dialysis patients

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Severe defect in clearing postprandial chylomicron remnants in dialysis patients. Lipid abnormalities have been suggested as a major cause of the accelerated atherosclerosis and the high incidence of coronary heart disease in chronic renal failure patients. In the present work the postprandial lipoprotein metabolism was studied in chronic dialysis patients with or without fasting hypertriglyceridemia using the vitamin A loading test. This method investigates specifically postprandial lipoprotein metabolism. The determination of vitamin A ester level retinyl palmitate (RP) differentiates the circulating plasma chylomicron and chylomicron remnant fractions from the endogenous VLDL and IDL. Subjects with normal renal function with or without fasting hypertriglyceridemia served as control groups. Dialysis patients have significantly higher level of chylomicron remnants for a more prolonged period of time than controls, irrespective of their fasting triglyceride levels. The area below retinyl palmitate chylomicron remnants curve was 26308 ± 12422 μg/liter · hr in the normolipidemic dialysis patients, significantly higher than (6393 ± 2098 μg/liter · hr; $P < 0.0001$) in the normolipidemic controls. The retinyl palmitate chylomicron remnants curve of the hypertriglyceridemic dialysis patients was 21021 ± 4560 μg/liter · hr, which was higher than 12969 ± 2215 μg/liter · hr ($P < 0.0001$) in the hypertriglyceridemic controls. Moreover, the hypertriglyceridemic dialysis patients had an additional defect in the lipolysis metabolic step, that is, accumulation of chylomicrons in circulation. These findings show a severe defect in postprandial lipoprotein metabolism in chronic renal failure patients. The prolonged exposure of the vascular wall to high chylomicron remnant concentrations might be an important pathogenetic factor in the accelerated atherosclerosis seen in chronic dialysis patients.

Chronic dialysis patients have a high incidence of coronary heart disease and accelerated atherosclerosis [1–4]. The renal and internal iliac arteries of uremic patients have been found to have accelerated atherosclerotic and vascular aging changes as compared with vessels from control populations [5, 6]. Cardiovascular death is a leading cause of mortality in dialysis patients [7]. Although many factors undoubtedly contribute to accelerated atherosclerosis, lipid abnormalities have been suggested as a major cause, and hyperlipidemia is associated with increased cardiovascular mortality [8–10]. The association between the two is now well accepted, and many recent studies have focused on the nature and significance of lipid abnormalities in patients with renal disease [11–14].

The lipid abnormalities in chronic renal failure are hypertriglyceridemic (hyper TG), high VLDL levels, triglyceride enrichment of LDL and HDL, and reduced HDL cholesterol [4, 15–17]. However, the degree of hypertriglyceridemic reported in chronic renal failure (CRF) is only moderate, and according to epidemiologic surveys of normal populations such hyper TG would lead to only a marginal increase in the risk of coronary heart disease [18]. It is therefore possible that other lipoproteins with greater atherogenic potential than VLDL are found in these patients and are responsible for the accelerated atherosclerosis. Chylomicron remnants, intestinal-derived lipoproteins and VLDL remnants (IDL) are known to be very atherogenic lipid particles causing premature peripheral vascular disease and coronary heart disease in patients with type III hyperlipidemia [19, 20]. Recent studies have suggested that the presence of fasting chylomicron remnants (cmr) in patients with CRF may contribute to the increased incidence of coronary heart disease [21–25]. However, these studies were based on indirect evidence only, because of difficulties in differentiating between intestinal-derived lipoproteins and endogenous VLDL and in investigating their metabolism [26].

It is also not known whether such a metabolic defect occurs only in hyper TG renal failure dialysis patients or even in normotriglyceridemic patients.

A new method for investigating the metabolism of postprandial lipoproteins in humans has been introduced [27]. It consists of the determination of Vit A ester levels in plasma following the feeding of a vitamin A (Vit A) fat meal. The Vit A is absorbed, becomes esterified in the intestinal absorbtive cells, and is secreted with chylomicrons. The retinyl ester, mainly retinyl palmitate (RP), circulates with the chylomicron and cmr and is finally taken up with the remnant particles by liver cells. Therefore, the appearance and disappearance of RP in plasma lipoproteins and their remnants reflect the postprandial circulating lipoprotein metabolic steps [28]. In previous studies using the Vit A fat method we have shown that this is a sensitive and highly specific method, and have directly demonstrated the accumulation of chylomicron remnants in type III hyperlipidemia [29–32].

The aim of the present work was to study the postprandial lipoprotein metabolism using the Vit A fat loading test in

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end-stage renal failure dialysis patients with or without fasting hyperlipidemia.

Methods

Patients

Twenty-one chronic renal failure adult patients on regular dialysis and 24 subjects with normal renal function participated in the study.

Group 1. Fifteen subjects (7 females and 8 males) with no renal disease and normal renal function, and normal fasting plasma lipids.

Group 2. Nine hypertriglyceridemic patients (3 females and 6 males) with normal renal function.

Group 3. Thirteen patients (5 females and 8 males) with end-stage renal failure. Seven were on maintenance hemodialysis (HD) at least three months, for three times four hours per week, and six on continuous ambulatory peritoneal dialysis (CAPD), who had been at least three months free from peritonitis. All these patients had normal fasting triglyceride levels.

Group 4. Eight patients (3 females and 5 males) with CRF with high fasting TG levels (4 on hemodialysis and 4 on CAPD). None of the patients had liver disease, hypothyroidism, diabetes mellitus, or nephrotic syndrome. The criteria for normal lipids were fasting total cholesterol <240 mg/dl and plasma triglycerides <180 mg/dl. The criteria for hypertriglyceridemia was plasma TG >280 mg/dl.

Sixteen of the dialysis patients had documented myocardial infarction in their medical history.

Vitamin A fat loading test

The test was performed as recently described [31]. After an overnight 12 hour fast, subjects were given a fatty meal plus 60000 U of aqueous vitamin A/m^2 body surface. The fatty meal contained 50 g of fat/m^2 body surface, consisting of 65% calories as fat, 20% as carbohydrate and 15% as protein. It contained 600 mg cholesterol/1000 calories, and the P/S ratio was 0.3. This was given as a milkshake, scrambled eggs, bread and cheese, and was consumed in 10 minutes.

The vitamin A was added to the milkshake. After the meal, the subjects fasted for 10 hours, but drinking water was allowed as desired. Blood samples were drawn before the meal and every hour after the meal. All subjects tolerated the meal well, without diarrhea or other symptoms of intestinal dysfunction.

Laboratory determinations

The blood samples were drawn in sodium EDTA containing test tubes and were immediately centrifuged at 1500 g for 15 minutes. One ml of plasma was stored wrapped in foil at −20°C for total plasma retinyl ester assay. Another sample of 0.5 ml was stored at 4°C for triglyceride determinations. Another 2.5 ml of plasma was transferred into a 1/2 × 2 inch cellulose nitrate tube and overlayered with 2.5 ml sodium chloride solution (d = 1.006 g/ml). Tubes were subjected to preparative ultracentrifugation for 1.6×10^6 g · min with a rotor (SW-55; Beckman Instruments, Inc., Fullerton, California, USA) to float chylomicron particles of Sf >1,000 [31].

The chylomicron containing supernatant (chylomicron fraction), was removed and brought to a total volume of 5 ml with saline. The infranatant (chylomicron remnant fraction) was brought to a volume of 5 ml with saline. Alliquotes of supernatant and infranatant (0.5 ml) were wrapped in foil and assayed for retinyl ester. Additional aliquots were assayed for triglyceride concentration. This procedure appears to separate a predominantly chylomicron population from a predominantly chylomicron remnant population [31, 32].

Retinyl ester determination

Retinyl palmitate was determined in total plasma (TP), plasma chylomicron fraction (CM) and plasma chylomicron remnants fraction (CMR). The assays were carried out in subdued light with HPLC grade solvents. Retinyl acetate was added to the samples as an internal standard. The samples were then mixed with ethanol 4 ml, hexane 5 ml and water 4 ml with vortexing between each addition. Two phases were formed and 4 ml of the upper (hexane) phase was removed and evaporated under nitrogen [33]. The residue was dissolved in a small volume of benzene, and an aliquote was injected into an HPLC 5 μm ODS-18 radial compression column. One hundred percent methanol was used as a mobile phase at a flow rate of 2 ml/min.

The effluent was monitored at 340 nm and the peak of retinyl palmitate (RP) was identified by comparison to the retention time of purified standard (Sigma Chemical Co., St. Louis, Missouri, USA). In agreement with previous reports [30] it was found that 75 to 80% of total plasma retinyl esters were accounted for by retinyl palmitate. In addition the distribution of retinyl esters remained constant throughout the study.

Lipid and lipoprotein determinations

Cholesterol and triglycerides were measured enzymatically using the reagents cholesterol 236991 and triglycerides 126012 (Boehringer Mannheim, Inc., Indianopolis, Indiana, USA). HDL cholesterol was determined after precipitation of plasma with dextran sulfate-magnesium.

Statistical analysis

Data are presented as mean ± SD, using the unpaired Student's *t*-test with Bonferroni's correction to compare control and chronic renal failure groups within the categories of normolipidemic or hypertriglyceridemic groups.

The amounts of retinyl palmitate in total plasma, plasma chylomicron fraction and plasma chylomicron remnant fraction were quantified by the ratio method [34] using retinyl acetate as a reference [31].

Two way analysis of variance with repeated measurements was used to assess significant differences between groups. (The Statview MAC II program was used for statistical analysis).

Results

The fasting plasma lipids and lipoprotein levels in the studied groups are given in Table 1. Both normal and high fasting triglyceridemic dialysis groups had significantly lower mean HDL-cholesterol than the normal controls. Total plasma, plasma chylomicron fraction and plasma chylomicron remnant fraction, retinyl palmitate concentration after vitamin A fat loading test are given in Figure 1, and Table 2.

Control subjects with normal renal function

Normolipidemic subjects. Total plasma retinyl palmitate was detectable one hour after the Vit A fat meal, increased rapidly

Table 1. Fasting plasma lipids and lipoproteins, age, sex and body surface area (BSA) in the studied groups

Group	Age	Sex F	Sex M	BSA m^2	Plasma lipids and lipoproteins *mg/dl* TC	TG	LDL-C	HDL-C
Normolipidemic controls (N = 15)	58 (5)	8	7	1.75 (0.12)	210 (22)	101[a] (21)	144 (12)	50[a] (5.2)
Hyper TG controls (N = 9)	59 (11)	6	3	1.77 (0.14)	259 (34)	528[a] (105)	135 (14)	33 (3)
Normolipidemic CRF (N = 13)	63 (10)	8	5	1.75 (0.11)	200 (33)	157 (31)	133 (30)	36 (6)
Hyper TG CRF (N = 8)	58 (9)	5	3	1.81 (0.12)	223 (26)	346 (41)	141 (24)	35 (4.2)

Numbers are mean ± (SD).
[a] $P < 0.05$ vs. the respective chronic renal failure group (unpaired t-test)

between one and four hours, remained high until six hours, declined rapidly between six and 10 hours to reach about 25% of peak levels. The plasma chylomicron and plasma chylomicron remnant fractions appeared to behave differently. The plasma chylomicron fraction RP levels closely paralleled those of total plasma RP. The plasma chylomicron remnant fraction RP levels were lower than chylomicron RP levels, increasing to peak levels between three and six hours, remaining unchanged until eight hours and then slowly decreased. At nine to ten hours their concentration exceeded the chylomicron RP concentrations.

Hyperlipidemic subjects. Plasma, chylomicron and chylomicron remnants RP concentrations were abnormal compared with the normolipidemic control persons. The RP of the two lipoprotein fractions were several-fold higher then in the normal group. The most impressive differences were found in the total plasma and plasma chylomicron fraction RP peak levels and areas below RP curves, demonstrating a high accumulation and a very slow disappearence of chylomicron RP.

Chronic renal failure dialysis patients

Normolipidemic patients. Both hemodialysis and continuous ambulatory peritoneal dialysis patients had similar responses to the Vit A fat loading test and were taken as a group.

The normolipidemic dialysis patients had a twofold higher total plasma RP peak level compared with the respective control group, 8834 ± 3042 μg/liter and 4206 ± 1923 μg/liter, $P < 0.0003$. The RP peak appeared at six hours and declined slowly to 60% of its peak at 10 hours.

The very high total plasma RP levels were caused mainly by the accumulation of RP in the plasma chylomicron remnants fraction.

The RP in the chylomicron remnants fraction had a peak mean value of 4942 ± 1984 μg/liter significantly higher then in the normal kidney function normolipidemic group 1420 ± 630 μg/liter, $P < 0.0023$.

The plasma chylomicron remnants fraction peak was found at six hours and remained almost unchanged at 10 hours.

The mean value of the area under the chylomicron remnants RP curves was 26308 ± 12422 μg/liter/hr, fourfold higher than in the normal renal function normolipidemic controls 6393 ± 2098 μg/liter/hr, $P < 0.0003$.

Hyperlipidemic dialysis patients

The dialysis patients with high fasting triglycerides had abnormal chylomicron clearance as found in the hypertriglyceridemic patients with normal kidney function. In addition the dialysis patients had a severe defect in the clearance of the chylomicron remnants. The peak plasma chylomicron remnant fraction was twofold higher than the normal kidney function hyperlipidemic patients.

The chylomicron/chylomicron remnant ratio was 3 in the hypertriglyceride normal kidney function group and 1.2 in the respective dialysis group. In normolipidemic normal kidney function patients this ratio is 2.1.

Total plasma triglyceride after Vitamin A fat loading test

The results of each group of subjects are given in Figure 2 and Table 2.

In the two hypertriglyceridemic groups there was a severe defect in the triglyceride clearance after the fatty meal. In the hypertriglyceridemic normal kidney function subjects, peak levels and areas below triglyceride curves were 896 ± 151 mg/dl and 8442 ± 1092 mg/dl · hr, respectively. In the hypertriglyceridemic patients on dialysis the peak levels and area under the curve were 767 ± 174 mg/dl and 4708 ± 764 mg/dl · hr.

In the normolipidemic dialysis patients the triglyceride peak levels and the area under triglyceride curves were only slightly increased, 355 ± 88 mg/dl and 2116 ± 546 mg/dl · hr compared with 246 ± 76 mg/dl and 1516 ± 374 mg/dl · hr, respectively, in the normolipidemic control persons.

Discussion

The degree of hypertriglyceridemia in patients with chronic renal failure on dialysis does not correlate well with the increased risk of coronary heart disease [18]. Some studies have suggested that accumulation of other lipids or lipoproteins, including circulating chylomicron remnants may play a role in the increased development of atherosclerosis in these patients [21–25].

Chylomicrons are synthesized in the intestine following fat ingestion. They contain APO B-48, APO A-I, APO A-IV. After secretion they acquire C apolipoproteins and APO E, transferred from HDL. After hydrolysis by lipoprotein lipase, these particles are referred to as chylomicron remnants. The particles are then taken up by the hepatic APO E receptors (exogenous pathway). The VLDL with its main protein APO B-100 assembled in the endoplasmatic reticulum of hepatocytes once in the circulation are hydrolyzed to remnant particles IDL and to LDL particles and cleared by LDL receptors (endogenous pathway).

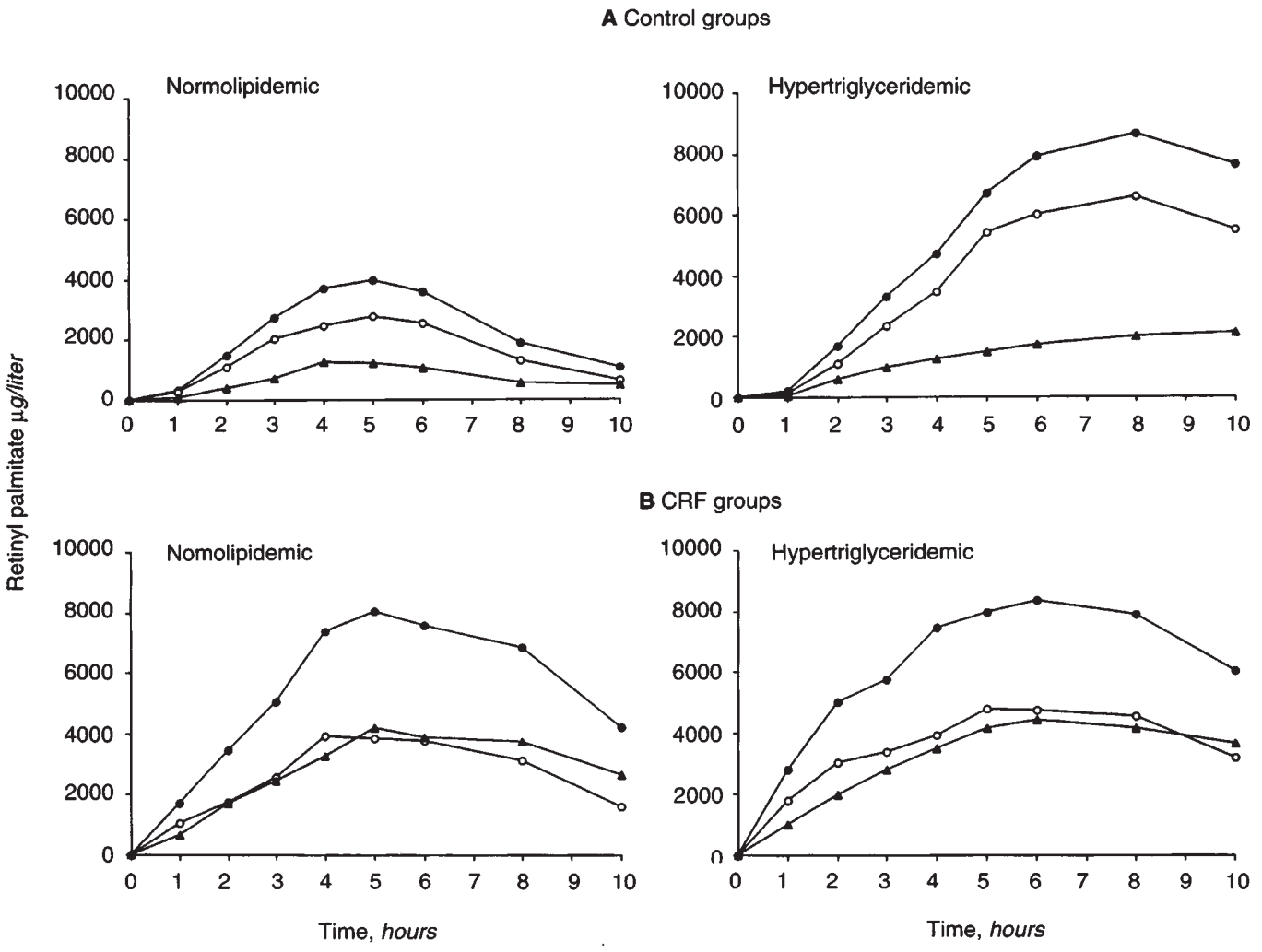

Fig. 1. *Retinyl palmitate (RP) concentration curves in chronic renal failure (CRF) patients and control groups.* Total plasma (●----●), chylomicron fraction (○----○) and chylomicron remnant fraction (▼----▼). RP concentrations were determined for CRF patients with normal fasting lipids (N = 13), and with hypertriglyceridemia (N = 8) and in individuals with normal renal function with normal fasting lipids (N = 15) and with hypertriglyceridemia (N = 9). For each group the levels at each time point were averaged. Two way analysis of variance with repeated measurements between groups: for total plasma RP, F value = 17.315, $P < 0.0001$, for RP chylomicron fraction, F value = 13.593, $P < 0.0001$, for RP chylomicron remnants fraction, F value = 23.38, $P < 0.0001$.

The Vit A fat loading test differentiates between the chylomicrons and chylomicron remnants from VLDL and IDL despite their similar physical and chemical properties. It also follows the metabolic steps of these lipoproteins, and thus is able to detect possible defects in both lipolysis or chylomicron remnant liver uptake [31, 32].

The present findings demonstrate a severe defect in postprandial lipoprotein metabolism in chronic renal failure patients. The main metabolic defect is not in the lipolysis step. This is evidenced by only a slight accumulation of plasma chylomicron fractions. Furthermore, the lipolysis, as shown by the postprandial triglyceride curves in normolipidemic dialysis patients, were similar to those in the normolipidemic nonrenal failure group.

The main defect that causes the accumulation of the postprandial lipoproteins in these patients was the chylomicron remnant uptake by the liver. This results in a threefold accumulation of these lipid particles in the circulation. Thus the arterial wall of these patients on dialysis might be exposed to high postaprandial circulating chylomicron remnants during long periods of time. This metabolic defect occurs in both normolipidemic and hyperlipidemic dialysis patients. Moreover, the chronic renal failure patients with fasting hypertriglyceridemia have the same defect in the hydrolysis as persons with hypertriglyceridemia and normal renal function. This is evidenced by the accumulation of plasma chylomicron fraction and the postprandial total plasma triglycerides curves. A positive correlation exists between the postprandial plasma chylomicron fraction curves and the plasma fasting triglycerides [31]. This reflects competition between the absorbed exogenous fat and the triglyceride's endogenous origin [35]. A similar defect in postprandial lipoprotein metabolism as in the normolipidemic dialysis patients occurs in type III hyperlipidemia. In this condition the removal of chylomicron remnants is not normal,

Table 2. Plasma triglyceride (TG), retinyl palmitate (RP), peak levels and area under the curves in the total plasma (TP), chylomicron fraction (CM), chylomicron remnant fraction (CMR) in normolipidemic and hypertriglyceridemic (Hyper TG) patients with chronic renal failure (CRF) and with normal kidney function

	Normolipidemic		Hyper TG	
Groups	Control (N = 15)	CRF (N = 13)	Control (N = 9)	CRF (N = 8)
Peak levels				
Plasma TG	246	355[a]	896	767[a]
mg/dl	(76)	(88)	(151)	(174)
RP *μg/liter*				
TP	4206	8834[a]	9023	8610
	(1923)	(3042)	(1232)	(1612)
CM	3118	4505	6907	5681[a]
	(1421)	(1794)	(1297)	(1587)
CMR	1420	4942[a]	2373	4987[a]
	(630)	(1984)	(452)	(1414)
Area under the curves				
Plasma Tg	1516	2116[a]	8442	4708[a]
mg/dl · hr	(374)	(546)	(1509)	(764)
RP *μg/liter · hr*				
TP	21202	49566[a]	61159	48570
	(6947)	(22401)	(11243)	(8022)
CM	14815	23257	47613	27691[a]
	(5755)	(11791)	(11212)	(7378)
CMR	6393	26308[a]	12696	21021[a]
	(2098)	(12422)	(2215)	(4560)

Data are mean ± (SD).
[a] Significantly different from the respective control group (unpaired Student's t-test with Bonferroni correction)

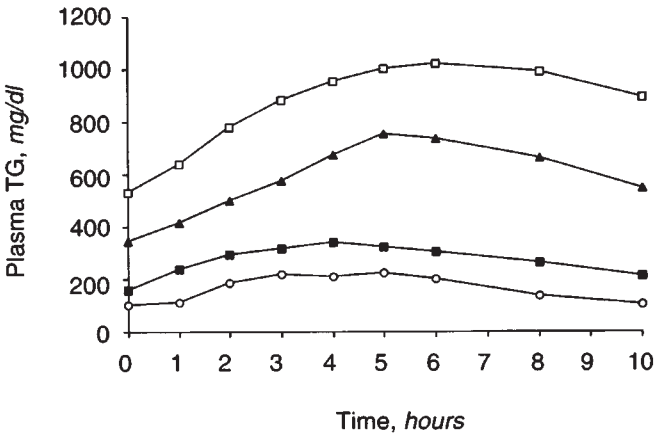

Fig. 2. *Triglyceride concentration (TG) curves in chronic renal failure (CRF) patients and control groups.* Total plasma triglyceride concentrations were determined for CRF patients with normal fasting lipids (■——■) (N = 13), and with hypertriglyceridemia (▼----▼) (N = 8) and for individuals with normal renal function with normal fasting lipids (○----○) (N = 15) and with hypertriglyceridemia (□----□) (N = 9). For each group the levels at each time point were averaged. Two way analysis of variance with repeated measurements between groups: F value = 147.8, $P < 0.0001$.

because of the presence of a form of APO E, APO E2 on the surface of these particles, not recognized by the hepatic receptors [32]. These patients develop early atherosclerotic complications such as peripheral vascular disease and coronary heart disease. The chylomicron remnants accumulate on the endothelial surface of large arteries and their cholesterol becomes incorporated into the artery wall, thus stimulating the formation of atherosclerotic lesions [36, 37].

The exact mechanisms of the defective chylomicron remnant liver uptake in dialysis patients remain to be established. The present study demonstrates that the finding of normal fasting lipids in chronic renal failure patients does not indicate normal lipid metabolism in these patients. The prolonged exposure of vascular wall to high chylomicron remnant concentration may contribute to the accelerated atherosclerosis found in these patients. Therefore preventive steps have to be taken as early as possible. Diets rich in polyunsaturated fatty acids of both vegetable origin (ω-6) and fish oil origin (ω-3) have been shown to increase the removal of triglyceride-rich lipoprotein remnants and to reduce dramatically postprandial lipoprotein levels in plasma [38, 39]. Patients with type III hyperlipidemia also respond well to dietary therapy, and when this is not sufficient the addition of fibric acid derivatives is indicated [40]. Thus our results suggest the necessity of a new and more aggressive dietary attitude in dialysis patients, and the consideration of drug therapy irrespective of their fasting lipid levels.

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References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697–701, 1974
2. Rostand SG, Gretes JC, Kirk KA, Rutsky EA, Andreoli TE: Ischemic heart disease in patients with uremia undergoing maintenance hemodialysis. *Kidney Int* 16:600–611, 1979
3. Ponticelli C, Barbi G, Cantaluppi A, Donati C, Annoni G, Brancaccio D: Lipid abnormalities in maintenance dialysis patients and renal transplant recipients. *Kidney Int* (Suppl 13):S72–S78, 1978
4. Ibels LS, Simons LA, Kind JO, Williams PF, Neale FC, Stewart JH: Studies on the nature and causes of hyperlipidaemia in uraemia, maintenance dialysis and renal transplantation. *Quart J Med* 44:601–614, 1975
5. Vincenti F, Amend WJ, Abele J, Feduska NJ, Salvatierra O Jr: The role of hypertension in hemodialysis-associated atherosclerosis. *Am J Med* 68:363–369, 1980
6. Ibels LS, Alfrey AC, Huffer WE, Craswell PW, Anderson JT, Weil R III: Arterial calcification and pathology in uremic patients undergoing dialysis. *Am J Med* 66:790–796, 1979
7. Haire HM, Sherrard DG, Scardapane D, Curtis FK, Brunzell GD: Smoking, hypertension and mortality in a maintenance dialysis population. *Cardiovasc Med* 7:1163–1168, 1978
8. Ritz E, Augustin J, Bommer J, Gnasso A, Haberbosch W: Should hyperlipemia of renal failure be treated? *Kidney Int* (Suppl 17):S84–S87, 1985
9. Green D, Stone NJ, Krumlovsky FA: Putative atherogenic factors in patients with chronic renal failure. *Prog Cardiovasc Dis* 26:133–144, 1983
10. Hahn R, Oette K, Mondorf H, Finke K, Sieberth HG: Analysis of cardiovascular risk factors in chronic hemodialysis patients with special attention to the hyperlipoproteinemias. *Atherosclerosis* 48:279–288, 1983
11. Cutler RE: Lipid disorders in renal disease: Prevalence, pathogenesis and diagnosis. *Dial Transplant* 17:533–536, 1988
12. Riesen WF, Mordasini R: Hyperlipidemia in renal failure: Phenotypes and pathogenetic mechanisms. *Contrib Nephrol* 41:312–320, 1984
13. Manske CL: Lipid abnormalities and rer l disease. *Kidney* (Natl Kidney Fndt) 20:25–30, 1988

14. Chan MK, Varghese Z, Moorhead JF: Lipid abnormalities in uremia, dialysis, and transplantation. *Kidney Int* 19:625–637, 1981
15. Bolzano K, Krempler F, Sandhofer F: Hepatic and extrahepatic triglyceride lipase activity in uraemic patients on chronic haemodialysis. *Eur J Clin Invest* 8:289–293, 1978
16. Bagdade J, Casaretto A, Albers J: Effects of chronic uremia, hemodialysis, and renal transplantation on plasma lipids and lipoproteins in man. *J Lab Clin Med* 87:38–48, 1976
17. Brunzell JD, Inbers JJ, Haas LB, Goldberg AP, Agadoa L, Sherrard DJ: Prevalence of serum lipid abnormalities in chronic hemodialysis. *Metabolism* 26:903–910, 1977
18. Hulley SB, Rosenman RH, Bawol RD, Brand RJ: Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N Engl J Med* 302:1383–1389, 1980
19. Mahley RW, Innerarity TL, Rall SC Jr, Weisgraber KH: Lipoproteins of special significance in atherosclerosis. Insights provided by studies of type III hyperlipoproteinemia. *Ann NY Acad Sci* 454:209–221, 1985
20. Krauss RM, Lindgren FT, Williams PT, Kelsey SF, Brensike J, Vranizan K, Detre KM, Levy RI: Intermediate-density lipoproteins and progression of coronary artery disease in hypercholesterolaemic men. *Lancet* ii:62–66, 1987
21. Nestel PJ, Fidge NH, Tan MH : Increased lipoprotein-remnant formation in chronic renal failure. *N Engl J Med* 307:329–333, 1982
22. Ron D, Oren I, Aviram M, Better OS, Brook JG: Accumulation of lipoprotein remnants in patients with chronic renal failure. *Atherosclerosis* 46:67–75, 1983
23. Norbeck HE, Carlson LA: Increased frequency of late pre-beta lipoproteins (LP beta) in isolated serum very low density lipoproteins in uraemia. *Eur J Clin Invest* 10:423–426, 1980
24. Minamisono T, Wada M, Akamatsu A, Okabe M, Handa Y, Morita T, Asagami C, Naito HK, Nakamoto S, Lewis LA, Mise J: Dyslipoproteinemia (a remnant lipoprotein disease) in uremic patients on hemodialysis. *Clin Chim Acta* 84:163–172, 1978
25. Wilson DE, Chan IF, Cheung AK, Dutz W, Buchi KN: Retinyl ester retention in chronic renal failure. Further evidence for a defect in chylomicron remnant metabolism. *Atherosclerosis* 57: 189–197, 1985
26. Redgrave TG: Formation of cholesteryl ester-rich particulate lipid during metabolism of chylomicrons. *J Clin Invest* 49:465–471, 1970
27. Hazzard WR, Bierman EL: Delayed clearance of chylomicron remnants following vitamin-A-containing oral fat loads in broad-beta disease (type III hyperlipoproteinemia). *Metabolism* 25:777–801, 1976
28. Goodman DS, Blomstrand R, Werner B, Huang HS, Shiratori T: The intestinal absorption and metabolism of vitamin A and beta-carotene in man. *J Clin Invest* 45:1615–1623, 1966
29. Wilson DE, Chan IF, Ball M: Plasma lipoprotein retinoids after vitamin A feeding in normal man: Minimal appearance of retinyl esters among low-density lipoproteins. *Metabolism* 32:514–517, 1983
30. Berr F, Kern F Jr: Plasma clearance of chylomicrons labeled with retinyl palmitate in healthy human subjects. *J Lipid Res* 25:805–812, 1984
31. Weintraub MS, Eisenberg S, Breslow JL: Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. *J Clin Invest* 80:1571–1577, 1987
32. Weintraub MS, Eisenberg S, Breslow JL: Different patterns of postprandial lipoprotein metabolism in normal, type IIa, type III, and type IV hyperlipoproteinemic individuals. Effects of treatment with cholestyramine and gemfibrozil. *J Clin Invest* 79:1110–1119, 1987
33. Blomhoff R, Rasmussen M, Nilsson A, Norum KR, Berg T, Blaner WS, Kato M, Mertz JR, Goodman DS, Eriksson U, et al: Hepatic retinol metabolism. Distribution of retinoids, enzymes, and binding proteins in isolated rat liver cells. *J Biol Chem* 260:13560–13565, 1985
34. DeRuyter MG, De Leenheer AP: Simultaneous determination of retinol and retinyl esters in serum or plasma by reversed-phase high-performance liquid chromatography. *Clin Chem* 24:1920–1923, 1978
35. Grundy SM, Mok HY: Chylomicron clearance in normal and hyperlipidemic man. *Metabolism* 25:1225–1239, 1976
36. Morgannoth J, Levy RI, Fredrickson DS: The biochemical clinical and genetic features of type III hyperlipoproteinemia. *Ann Intern Med* 82:158–164, 1975
37. Floren CH, Albers JJ, Beirman EL: Uptake of chylomicron remnants causes cholesterol accumulation in cultured human smooth muscle cells. *Biochim Biophys Acta* 663:336–349, 1981
38. Weintraub MS, Zechner R, Brawn A, Eisenberg S, Breslow JL: Dietary polyunsaturated fats of ω-6 and ω-3 series reduce postprandial lipoproteins levels. *J Clin Invest* 82:1884–1893, 1988
39. Demacker PNH, Reijmen IGM, Katan MB, Stuyt PMJ, Stalenhoef AFH: Increased removal of remnants of triglyceride-rich lipoproteins on a diet rich in polyunsaturated fatty acids. *Eur J Clin Invest* 21:197–203, 1991
40. Brewer HB Jr, Zech LA, Gregg RE, Schwartz D, Schaefer EJ: NIH conference. Type III hyperlipoproteinemia: diagnosis, molecular defects, pathology, and treatment. *Ann Intern Med* 98:623–640, 1983