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ABNORMAL LIPOPROTEIN METABOLISM IN INCIPIENT RENAL FAILURE

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Summary

In 22 patients with various degrees of renal failure, an inverse relationship was found between hepatic triglyceride lipase activity and serum creatinine. Even at a creatinine <4mg/dl, low cholesterol/triglyceride ratio of HDL_2, low apoprotein AI and AII in the HDL_2 and HDL_3 fractions and low HDL_3 cholesterol were found. Total cholesterol and triglycerides were unchanged. The findings suggest early lipoprotein abnormalities despite no change of total lipids in incipient renal failure.

Introduction

Hyperlipoproteinaemia is a known consequence of terminal renal failure [1]. It is mainly due to impaired catabolism of lipoprotein particles, one major cause of which is selective diminution of hepatic triglyceride lipase (HTGL) activity [2]. The mechanism by which HTGL activity is reduced has not been defined. Therefore it seemed of interest to examine HTGL activity and lipoprotein subclass compositions at various degrees of renal function in patients with early renal insufficiency.

Patients and methods

Twenty-two patients were examined (13 male, 9 female, age 42±13 years). Underlying renal disease was chronic glomerulonephritis (n=11), suspected on clinical grounds in four, biopsy confirmed in eight (6 IgA glomerulonephritis; 2 sclerosing glomerulonephritis); chronic interstitial nephritis 2 (biopsy confirmed); analgesic nephropathy 2; Alport's syndrome, nephrocalcinosis, polycystic disease, obstructive uropathy, nephronophthisis and hypertensive nephropathy 1 case each. Median serum creatinine was 4.5mg/dl (range 1.5–8.4). Patients were excluded who were on medications liable to cause lipid abnormalities,

i.e. beta blockers, diuretics, hormonal contraceptives; patients with nephrotic syndrome, diabetes or impaired glucose tolerance; elevated TSH; liver disease or body weight excess and recent changes of body weight. Patients were on their usual self-selected diet and studied on an outpatient basis in the morning after an overnight fast.

As controls we used 450 healthy probands (240 male, 210 female; age range 45–49 years), who had participated in a community health programme which included a detailed lipid analysis.

Blood was collected in EDTA tubes prior to and 15 minutes after an intravenous bolus of 100U/kg body weight heparin. Cholesterol and triglycerides were measured using commercially available kits (Boehringer Mannheim). Lipoproteins were analysed in 10ml plasma by sequential ultracentrifugation according to the Lipid Research Clinic Program [3]. HDL_2 and HDL_3 were always tested for apoprotein B and found free of this apoprotein. Five to seven per cent of the protein moiety of HDL_3 was represented by albumin. Apoproteins AI, AII, CI, CII, $CIII_0$, $CIII_1$ and $CIII_2$ were separated and quantified by isoelectric focusing (IEF) on ultra thin flat bed gels. Apoprotein AI and apoprotein AII were also quantified by immunodiffusion (Immuno AG, Vienna). Apoprotein B was quantified by immunodiffusion on NOR partigen plates (Behring Werke, Marburg). The activities of HTGL and lipoprotein lipase were measured by immunoassay with goat antibodies against HTGL as described earlier [4].

Results

Lipases

As shown in Figure 1, HTGL activity (U) was significantly correlated ($r=0.546$; $p<0.01$) with log serum creatinine (mg/dl). HTGL activity (normal range 15–30U) was normal in patients (n=9) with early renal failure (creatinine <4mg/dl) 23.6±10.1U, but was significantly ($p<0.05$) decreased in patients (n=13) with more advanced renal failure (creatinine >4mg/dl) 16.0±7.2U. In contrast, lipoprotein lipase activity (normal range 6–15U) was unchanged in either early (8.0±1.5U) or more advanced renal failure (8.6±4.0).

Lipoprotein composition

As shown in Table I, total plasma cholesterol was similar in controls and patients with early renal failure, but lower ($p<0.02$) in more advanced renal failure. There were no significant differences of total serum triglyceride.

HDL cholesterol was unchanged in patients with early and decreased ($p<0.05$) in patients with more advanced renal failure. This was due to a reduction of HDL_3 cholesterol, since HDL_2 cholesterol was unchanged. Abnormal HDL_2 composition, despite no change of HDL_2 cholesterol, is suggested by decreased HDL_2 cholesterol/triglyceride ratio in both early and more advanced renal failure. This was paralleled by a similar decrease in the cholesterol/triglyceride ratio of total HDL.

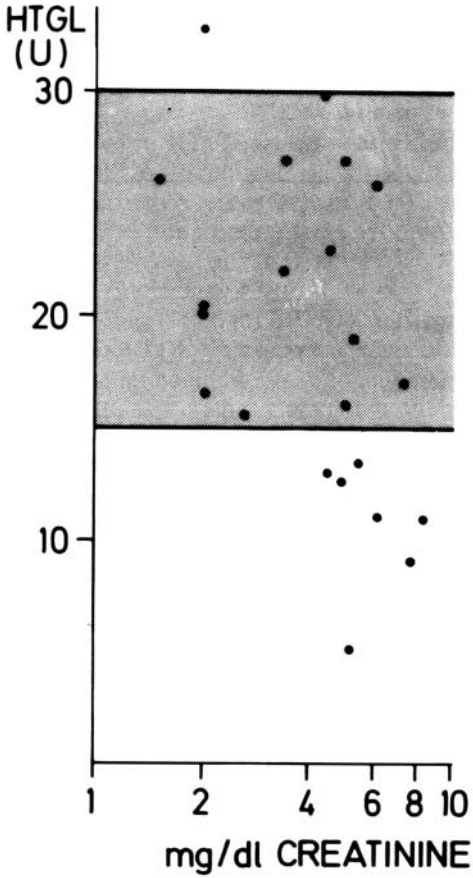

Figure 1. Correlation between HTGL and serum creatinine (stippled area: normal range)

While LDL-cholesterol was not significantly different, the LDL cholesterol/triglyceride ratio was decreased in more advanced renal failure.

In early renal failure, cholesterol and triglycerides tended to be higher in the IDL and VLDL fractions. In more advanced renal failure, triglycerides in the VLDL fraction were low, resulting in a higher cholesterol/triglyceride ratio.

As shown in Table II, despite unchanged HDL_2 cholesterol (see Table I), markedly lower apoprotein AI and AII concentrations were seen in HDL_2 even in early renal failure with no further decrease in more advanced renal failure. This was paralleled by similar changes in the HDL_3 fraction. No major differences were noted for apoprotein C peptides in the HDL or VLDL fractions. In particular, there were no changes of apoprotein CII/apoprotein CIII ratio, no change of mobility on isoelectric focusing pointing to abnormal dialysation of apoprotein CIII [5] and no staining for apoprotein AIV on isoelectric focusing [6] in any of the patients.

No changes whatsoever were noted for apoprotein B.

TABLE I. Lipoprotein composition in early renal failure

All values mg/dl	Controls (n=450)	Serum creatinine <4mg/dl (n=9)	Serum creatinine >4mg/dl (n=13)
Total cholesterol	222±42.5	240±33.7	200±39.4*
Total triglycerides	177±90.3	183±73.3	173±75.9
HDL-cholesterol	42.9±7.2	39.0±9.0	36.5±7.0†
HDL-triglycerides	13.5±3.5	15.6±4.6	14.9±4.6
HDL-cholesterol/triglycerides	3.18	2.50	2.45
HDL_2-cholesterol	15.6±7.5	16.5±4.1	17.5±5.5
HDL_2-cholesterol/triglycerides	3.18	2.65	2.66
HDL_3-cholesterol	27.3±7.0	22.5±4.6†	19.0±3.5†
LDL-cholesterol	119.3±33.0	129.0±41.0	110.7±40.8
LDL-triglycerides	22.6±9.0	25.8±7.4	30.9±9.4†
LDL-cholesterol/triglycerides	5.28	5.00	3.59
IDL-cholesterol	7.1±4.3	10.4±6.1†	11.6±6.0†
IDL-triglycerides	10.9±6.8	16.7±7.7†	15.8±4.9†
IDL-cholesterol/triglycerides	0.65	0.62	0.73
VLDL-cholesterol	22.9±21.7	26.8±14.0	25.1±13.7
VLDL-triglycerides	105.8±100.3	113.0±63.9	71.8±47.2
VLDL-cholesterol/triglycerides	0.22	0.24	0.53

$\bar{X}$ ± SD

* $p<0.05$ (difference early versus advanced renal failure)

† $p<0.05$ (difference control versus renal failure group)

TABLE II. Apolipoproteins in HDL fractions

All values mg/dl	Controls (n=450)	Serum creatinine <4mg/dl (n=9)	Serum creatinine >4mg/dl (n=13)
HDL_2 – AI	29±8.4	12.0±11.6**	15.0±9.2**
HDL_2 – AII	4.3±1.8	2.0±1.7**	2.9±1.8**
HDL_2 – CI	1.8±1.4	1.2±0.7	1.3±0.5
HDL_2 – CII	1.1±0.8	0.8±0.4	1.0±0.3
HDL_3 – AI	96.0±16	60.1±32.6**	61.9±22.3
HDL_3 – AII	37.0±7.4	9.5±4.7**	10.3±4.0**
HDL_3 – CI	3.1±2.0	1.8±1.0*	1.9±0.9*
HDL_3 – CII	1.8±0.9	1.2±0.3*	1.2±0.3*

* $p<0.05$ controls versus renal failure group

** $p<0.01$

Discussion

In agreement with previous studies on patients with terminal renal failure [2] the present study shows that diminished HTGL activity is present in renal patients even prior to end-stage renal failure. No change of lipoprotein lipase activity was noted. Even when HTGL activity was still in the normal range at serum creatinines <4mg/dl, an abnormal HDL composition was noted, i.e. abnormally low cholesterol/triglyceride ratio in both HDL_2 and HDL_3 fractions. This was accompanied by low apoprotein AI and apoprotein AII concentrations in either HDL fraction.

In patients with serum creatinines >4mg/dl we confirmed previous observations in terminal renal failure of low HDL [7] and particularly low HDL_3. LDL cholesterol, an index of LDL particle mass, was not significantly changed, but abnormal LDL particle composition was indicated by the low LDL cholesterol/triglyceride ratio reflecting accumulation of triglyceride-rich incompletely cleared particles. High IDL cholesterol with a tendency for higher IDL cholesterol/triglyceride ratio pointed to accumulation of incompletely cleared IDL particles. This interpretation is further supported by the finding of low VLDL triglycerides with increased VLDL cholesterol/triglyceride ratio, presumably reflecting delayed particle transit through the VLDL compartment as a result of slow triglyceride removal.

The early lipoprotein abnormalities are in line with the appearance of other facets of the uraemic syndrome at similar levels of glomerular filtration rate, e.g. diminished T-lymphocyte responsiveness and impaired response to hepatitis Bs vaccination [8] or disturbed spermatogenesis [9]. It is difficult to see how this could be due to simple retention of some hypothetical 'toxin' and more complex causes for these early abnormalities are suggested.

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