HDL CHOLESTEROL AND INTRAVENOUS FAT TOLERANCE IN DIALYSIS PATIENTS

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Summary

Serum cholesterol, triglyceride, HDL cholesterol and HDL triglyceride concentrations were determined in 27 dialysis patients and the same number of control subjects. Fat tolerance tests were performed in all dialysis patients and repeated 15 minutes after 100U/kg of heparin given intravenously in haemodialysis patients. Dialysis patients had higher serum triglyceride, lower HDL cholesterol, higher HDL triglyceride concentration, and lower fractional clearance rates of Intralipid than the control subjects.

Introduction

Hypertriglyceridaemia has long been recognised in chronic renal failure [1]. Nevertheless, its pathogenesis remains controversial [2, 3]. Recently, low concentrations of high-density lipoprotein (HDL) cholesterol have been observed in dialysis patients [4]. This is of great interest since HDL cholesterol has been convincingly demonstrated in epidemiological studies [5] to be a 'protective' factor against risks of coronary heart disease and there are claims that dialysis patients have a high incidence of ischaemic heart disease [6]. In the following study we examined the inter-relationship between HDL cholesterol, fractional clearance rates of an artificial chylomicron preparation (Intralipid), and serum triglyceride concentrations in patients on maintenance dialysis in the hope of gaining further insight into the pathogenesis of uraemic hypertriglyceridaemia.

Patients and methods

Twenty seven (17 haemodialysis and 10 peritoneal dialysis) patients were studied. Informed consent was obtained. Blood was taken after 12 hours’ fasting and at least 24 hours after the last dialysis. A fat tolerance test was performed in all patients using a bolus injection (1ml/kg) of 10% Intralipid [7] and repeated in
the haemodialysis patients 15 minutes after an intravenous dose of heparin (100 U/kg). Blood was taken for nephelometry every five minutes for 30 minutes after the injection of Intralipid. The light scattering index (LSI) on each plasma sample was measured on Autoanalyser fluoronephelometer III. The natural log transformed values of LSI minus blank were plotted against time in minutes. Fractional clearance rates of Intralipid before and after heparin administration were obtained from the slopes of the regression lines between loge LSI-blank and time and designated K2 and K'2 respectively. Serum cholesterol [8] and triglyceride [9] concentrations were measured by enzymatic methods on the Autoanalyser. Likewise, concentrations of HDL cholesterol and HDL triglyceride were determined enzymatically in the supernatant after precipitation of low-density lipoproteins and very low-density lipoproteins (VLDL) with sodium phosphotungstate and magnesium chloride [10].

Twenty seven subjects with normal renal function were used as controls. The fat tolerance test was performed in 17 control subjects and repeated after heparin in only 12 of them.

Results

The clinical and biochemical parameters for both dialysis patients and control subjects were recorded in Table I. Although the mean age of the control subjects was slightly lower than that of dialysis patients, the difference did not reach statistical significance. Dialysis patients had higher serum triglyceride, higher HDL

<table>
<thead>
<tr>
<th>TABLE I. Difference in some parameters of lipid metabolism between dialysis patients and control subjects</th>
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<tbody>
<tr>
<td><strong>Dialysis patients</strong></td>
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<tr>
<td>Number of subjects</td>
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<td>Male : Female</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Serum cholesterol (mmol/L)</td>
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<td>Serum triglyceride (mmol/L)</td>
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<td>HDL cholesterol (mmol/L)</td>
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<td>HDL triglyceride (mmol/L)</td>
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<td>K2 (%/min)</td>
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<td>K'2 (%/min)</td>
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All values in mean ± SD
Statistical significance determined by Student t test
* Significantly inversely correlated with serum triglyceride (r = -0.39 p < 0.05)
** Significantly inversely correlated with serum triglyceride (r = -0.47 p < 0.02)
† Significantly inversely correlated with serum triglyceride (r = -0.66 p < 0.01)
† † Significantly inversely correlated with serum triglyceride (r = -0.69 p < 0.01)

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triglyceride and lower HDL cholesterol concentrations than the control subjects, although the mean cholesterol concentrations of the two groups did not differ significantly. Both K2 and K'2 were significantly reduced in dialysis patient. Significant correlations were demonstrated between HDL cholesterol (p < 0.05), K2 (p < 0.02), K'2 (p < 0.01) and serum triglyceride concentrations for the dialysis patients.

Figure 1 illustrates the inverse correlation between K2 and K'2 and serum triglyceride concentrations in 17 haemodialysis patients. It is apparent that the inverse correlation between K'2 and serum triglyceride concentrations is much stronger. It is of particular interest that an arbitrarily chosen K'2 of 4%/min

Figure 1. Correlation between K2 and K'2 and serum triglyceride concentrations in haemodialysis patients. The abscissa represents both K2 and K'2 in %/min. Open circles and black dots represent correlations between fasting serum triglycerides and K'2 and K2 respectively. The vertical broken line represents an arbitrarily chosen K'2 at 4%/min. The horizontal broken line represents the arbitrarily defined serum triglyceride concentrations of 2.1mmol/L above which triglyceride concentrations were considered abnormal. The difference between K'2 and K2 was greater in normo-triglyceridaemic that in hypertriglyceridaemic patients
Figure 2. Correlation between K2 and K’2 and serum HDL cholesterol concentrations in haemodialysis patients. The ordinate represents both K2 and K’2 in %/min. Open circles and black dots represent correlations between fasting serum HDL cholesterol concentrations and K’2 and K2 respectively.

separates the hyper- from the normo-triglyceridaemic haemodialysis patients with practically no overlap, hypertriglyceridaemia in this instance being defined as serum triglyceride concentrations \( \geq 2 \text{mmol/L} \).

Figure 2 shows the relation between K2 and K’2 and HDL cholesterol concentrations in 17 haemodialysis patient. It is clear that there is a significant positive correlation between HDL cholesterol concentrations and K’2 but not K2.

Discussion

The findings of increased serum triglyceride and reduced HDL cholesterol concentrations in our dialysis patients accord with those reported by other workers [1-4]. Triglycerides are transported in the plasma in the form of chylomicrons and VLDL, both of which are catabolised by lipoprotein lipase (LPL). Since 1942 heparin has been known to be capable of releasing LPL into plasma [11]. It is paradoxical, therefore, that haemodialysis patients remain hypertriglyceridaemic despite regularly receiving large doses of heparin intravenously. Our results have
provided further insight into the much debated pathogenesis of hypertriglyceridaemia in dialysis patients. We have shown that even after an intravenous dose of heparin known to produce maximal release of lipolytic enzymes [12] the fractional clearance rates of Intralipid remain low in patients on haemodialysis.

Indeed, the mean $K^2$ of the hypertriglyceridaemic haemodialysis patients was significantly lower than the mean $K^2$ of control subjects before heparin ($3.02 \pm 0.75$ vs $5.41 \pm 2.30$ mean $\pm$ SD, $p < 0.05$). $K^2$ correlates well with fractional turnover of endogenous triglycerides [7]. Therefore it is clear that despite intermittent heparinisation, haemodialysis patients had defective triglyceride removal which must contribute to the pathogenesis of their hypertriglyceridaemia, a conclusion reached by other workers using different techniques of investigation [2] and further supported by the significant inverse correlation between serum triglyceride concentrations and both $K^2$ and $K^2'$. Also of interest is the observation that the arbitrarily chosen $K^2$ of 4%/min separating hyper- from normo-triglyceridaemic haemodialysis patients with little overlap, was close to the mean $K^2$ of the control subjects. The suggestion that low $K^2$ and $K^2'$ in dialysis patients were entirely attributable to their expanded plasma triglyceride pools is unconvincing for, even in normo-triglyceridaemic patients, $K^2$ and $K^2'$ were significantly reduced. Furthermore, $K^2$ and serum triglyceride concentrations do not always change reciprocally [7]. It is true to say, however, that reduced triglyceride removal may not suffice to produce hypertriglyceridaemia since some dialysis patients remain normo-triglyceridaemic.

Intralipid does not contain apo protein-CII (apo-CII), the activator of LPL [13]. Presumably, it acquires apo-CII in vivo from HDL prior to its degradation, for HDL is an important reservoir of apo-CII [14]. We suggest that the low HDL cholesterol concentrations in dialysis patients reflected low activator concentrations and were not the mere results of displacement of cholesterol from HDL by triglycerides in hypertriglyceridaemic plasma for, even though HDL triglyceride concentrations were raised in dialysis patients, no reciprocal relationship existed between them and HDL cholesterol concentrations. The positive correlation between HDL cholesterol concentrations and $K^2$ but not $K^2'$ probably reflected the rate-limiting effect of activator concentrations in the presence of increased concentrations of lipolytic enzymes. On the other hand, it may be argued that the correlation is fortuitous and not causal, since both $K^2$ and HDL cholesterol were inversely correlated with serum triglyceride concentrations. Although activator concentrations in subjects with presumably normal renal function have been shown not to be rate-limiting [15], the same has not been demonstrated in dialysis patients [4]. On the contrary, low concentrations of apo-CII in HDL have been reported in ureaemic patients. The ultimate clue to the biochemical basis of reduced fractional clearance rates of Intralipid in dialysis patients, be it increased inhibitor, reduced activator, and/or reduced enzyme (including lipoprotein lipase, hepatic lipase and lecithin-cholesterol-acyl-transferase) concentrations, can only come when all these variables are determined in the same plasma samples.

Acknowledgment

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Open Discussion

WALLS (Leicester) We have just done a very similar study. We looked at both chronic renal failure patients who were non-nephrotic and non-dialysed, a total of 25, and at 32 haemodialysis patients. We found the same negative correlation between serum triglyceride and K₂ values. We did not use the technique you used with heparin to try and separate the groups but found that something like 60% of both the chronic renal failure and the haemodialysis patients had a K₂ value which is lower than the lowest value for any control, so I think this may well add further evidence to support your work.

CHAN This is actually similar to our findings in chronic renal failure before dialysis and we have also studied more peritoneal dialysis patients. They all had this reduced fractional removal of intralipid. But what is interesting from that slide about the post heparin clearance rate against the serum triglyceride is that the arbitrarily chosen value of 4% per minute with separation of normal lipoaemias from the hyperlipoaemics is actually very close to the mean K₂ in the normal subjects before heparin.

WALLS Did you look at fasting blood sugars or plasma insulin levels when you were doing these?

CHAN Yes we did. In fact there is a very good correlation in our patients between the serum triglyceride values and the glucose/insulin ratios as well.