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Plasma lecithin cholesterol acyl transferase activity, high density lipoprotein cholesterol and cholesterol ester in cholestasis

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Summary

Lecithin cholesterol acyl transferase activity, cholesterol ester and high density lipoprotein cholesterol concentrations were determined in Nigerian subjects suffering from cholestatic jaundice.

Plasma lecithin cholesterol acyl transferase activities in all the study groups were similar. High density lipoprotein cholesterol and cholesterol ester were significantly increased in extrahepatic cholestasis while reduced levels were found in intrahepatic cholestasis. Enhanced cholesterol esterification may occur in extrahepatic cholestasis.

Résumé

Nous avons déterminé l'activité de la transacylase du cholestérol de lécithine, ainsi que les concentrations en ester de cholestérol et en HDL cholestérol, chez des sujets Nigérians atteints d'ictère choléstatique.

Les taux d'activité de la transacylase plasmatique du cholestérol de lécithine sont semblables dans tous les groupes étudiés. Les niveaux de HDL cholestérol et d'ester de cholestérol augmentent de manière significative chez les sujets atteints de cholestase extra-hépatique, mais se trouvent réduits chez ceux atteints de cholestase intra-hépatique. Il est possible que l'estérification du cholestérol soit accrue chez les sujets atteints de cholestase extra-hépatique.

Introduction

Alterations have been observed in various fractions of serum lipids in patients with liver diseases. In obstructive jaundice hyperlipidaemia, due to accumulation of LP-X[1] is a fairly constant finding while plasma lipids tend to fall with parenchymal liver disease[2]. An important role in maintenance of lipoprotein composition has been thought to involve the enzyme, lecithin cholesterol acyl transferase (LCAT). It has been suggested that a low LCAT activity may be responsible for the abnormal lipoprotein patterns in obstructive jaundice[3]. However, there are conflicting reports indicating low, normal or high LCAT activity in this condition[4,5].

There is limited information on the LCAT status in liver diseases in this community where malnutrition related diseases of the liver are very common. Associated effects of undernutrition may further moderate the activity of LCAT in our patients suffering from liver diseases.

We have therefore decided to evaluate the interrelationship between LCAT activity and cholesterol ester in cholestasis.

Material and methods

One hundred patients aged between 12 and 64 years who were attending the Out Patient Clinic of the Gastroenterology Unit of the Department of Medicine, University College Hospital, Ibadan and diagnosed for liver disease were recruited. Clinical features and standard liver functions showed that all patients had liver diseases of varying aetiology. Confirmatory tests using specialised techniques were used to categorise the patients and only 13 had hepatitis (Intrahepatic Cholestatis) and 11 had carcinoma of the head of pancreas (extrahepatic cholestatis). For the purpose of the survey, the diagnosis of hepatitis was based on typical clinical course, serological tests and ultrasonography. The diagnosis of the carcinoma of the head of pancreas was by clinical features, gastrointestinal x-rays, ultrasonography, laparotomy or autopsy. Twenty sex and age matched normal volunteers without any clinical evidence of liver or other diseases served as controls.

Fifteen millilitres of venous blood was collected between 8.00 and 10.00 a.m. from each subject. Ten

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millilitres was dispensed into EDTA bottles (1mg/ml) and plasma separated in each case within 1 hr of collection using a refrigerated centrifuge. Plasma HDL was isolated immediately using the Mn^{++} -heparin precipitation method[6] and the cholesterol fractions estimated after digitonin precipitation of free cholesterol using the method of Searcy and Berquist[7]. LCAT activity was assayed using Anasolv LCAT reagent kit (DAIICI Pure Chemical Ltd. Tokyo, Japan). The remaining 5ml was dispensed into heparinised bottles and plasma separated for liver function tests. Statistical comparisons were made using student *t*-tests.

Results

Plasma HDL

The total plasma HDL cholesterol (HDLC) concentrations showed intra-individual variations in both intrahepatic and extrahepatic cholestatis. Using the control range of values (35- 62mg/100ml) 38% of intrahepatic cholestatis had low HDLC, 31% had normal and 31% had high values. On the other hand for extrahepatic cholestasis, 27% had low HDLC, 9% had normal and 64% had high values. However the mean HDLC in intrahepatic cholestatis was similar to the control value, while the corresponding value in extrahepatic cholestasis was significantly elevated when compared with either control or those presenting with intrahepatic cholestasis. (Table 1)

Cholesterol esters

The mean cholesterol ester (CE) was significantly reduced in intrahepatic cholestasis when compared with either control or extrahepatic cholestatis ($P < 0.001$) respectively. The CE concentrations ranged between 65 and 106mg/100ml in the control subjects. In patients with intrahepatic cholestatic jaundice CE was very low in all patients (100%) with none normal or higher than normal. On the other hand in patients with extrahepatic cholestasis, CE was low in 9%, normal in 55% and high in 36% respectively with a mean higher than normal. (Table 1)

LCAT

The LCAT activity in control subjects showed variable values with a mean value of 740 ± 464 units. Similar within group variations were observed in both groups of patients suffering from liver diseases, with mean values of 774 ± 470 and 844 ± 462 units in intra-and extra-hepatic cholestasis respectively. The mean activity in extrahepatic cholestasis tended to be higher than corresponding values in control and intrahepatic cholestasis respectively, but the differences were not statistically significant. (Table 1).

Table 1: Plasma lipids and LCAT activity in cholestasis ($\bar{X}$ ± S.D)

	Control $n = 20$	Hepatic Intra- $n = 13$	Cholestasis Extra- $n = 11$
HDLC mg/100ml	44.0 ± 6.2	47.0 ± 24.9^a	107.0 ± 86^a
CE mg/100ml	80.0 ± 20.4	30.0 ± 16.2^b	139.0 ± 150.8
LCAT nmol/ml/hr	740 ± 116	774 ± 136	844 ± 146

n = number of subjects
a = compared with control ($P < 0.05$)
b = compaed with control or extrahepatic cholestasis ($P < 0.01$).

Discussion

Total HDL cholesterol was increased in extrahepatic cholestasis with a large proportion of patients (64%) having very high levels. The cholesterol ester was either normal or increased in about 91% of the patients.

In contrast, in intrahepatic cholestasis the mean total HDL was significantly lower than in extrahepatic cholestasis and the cholesterol ester below normal in all patients (100%) (Fig. 1 and 3). LCAT is thought to play a role in lipoprotein metabolism, particularly the catabolism of triglyceride rich particles and reverse cholesterol transport from peripheral tissues to the liver[8-10]. Since LCAT is synthesised in the liver, serum level of this enzyme is said to satisfactorily reflect the intensity of hepatic parenchymatous impairments. However it was significant in our study that the LCAT activities in both intra-and extra-hepatic cholestasis had similar range of values and were not significantly different from the control values (Fig. 2). This could be due to large intra-individual variations of LCAT activity within the different groups. It is also possible that reduction in LCAT activity may be a late manifestation in advanced stages of liver diseases.

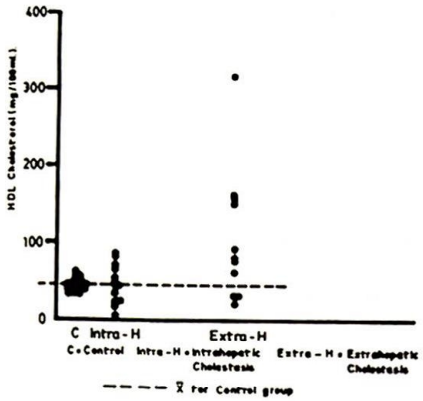

Fig 1: HDL - cholesterol concentration. Distribution in intra- and extra- hepatic cholestasis.

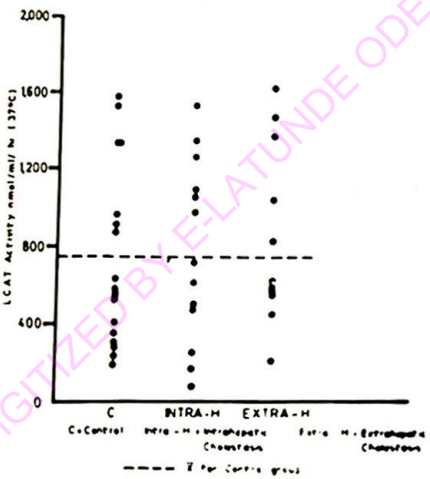

Fig 2: LCAT activity. Distribution in intra- and extra-hepatic cholestasis.

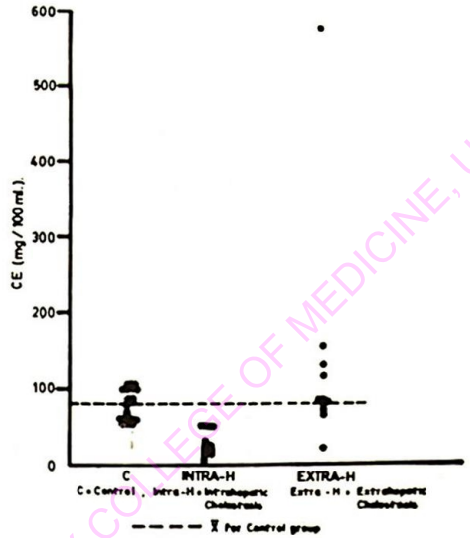

Fig. 3: Cholesterol ester concentration. Distribution in intra- and extra- hepatic cholestasis.

Changes in the properties of lipoproteins are known to be frequently accompanied by reduced LCAT-activity[4,11-12], but it was striking that despite the absence of any significant reduction in plasma LCAT activity in our patients we still found altered lipid levels. Also, our finding does not preclude the presence of LP-X in our subjects but may indicate that other factors apart from the LCAT system may be important determinants of altered lipid profiles in cholestasis.

Although ApoE concentration has not yet been determined in these patients, the seemingly more efficient cholesterol esterification in extrahepatic as compared to normal or intrahepatic cholestasis despite the similarity in LCAT activities, may be an indirect evidence of enhanced HDLC uptake in extra- and not intra-hepatic cholestasis. This proposition will be in line with the earlier report by Owen *et al*[13] that HDLE stimulated cellular cholesterol esterification in certain liver diseases. Further studies are required to confirm the presence of excess apolipoprotein E on HDL particles in extrahepatic cholestasis. This is currently under investigation.

In conclusion the apparent differences in lipid and lipoprotein profiles established between intra- and extra-hepatic cholestasis in this study might not be

due to differences in LCAT activity, and thus other important factors may be involved.

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