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EVALUATION OF SEVERITY OF LIVER DISEASES BY ESTIMATING SERUM HDL CHOLESTEROL LEVELS

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Abstract

The liver plays a key role in the metabolism of lipids serving as the centre for uptake of lipoproteins, formation and exportation to the circulation. The acute liver diseases may cause cell necrosis and cell death resulting in the release of intracellular liver enzymes into the blood. In chronic liver diseases the functional liver parenchymal cells are destroyed and are replaced by fibrous tissue resulting in the decreased metabolic functions of the liver. No sensitive biochemical parameters are now available to estimate degree of impairment of synthetic function of the liver damage. HDL is the smallest of all the lipoproteins and is the densest and has the highest proportion of proteins to lipids. The most abundant apolipoproteins in HDL are Apo A1 and Apo A2. The liver synthesizes lipoproteins such as HDL as complexes of apolipoproteins and phospholipids. Generally albumin is considered as a marker for the synthetic function of the liver. In this study we aimed to show whether HDL cholesterol levels can also be considered as a marker for impaired liver synthetic function resulting due to liver injury in both acute and chronic liver disease patients.

Keywords:

Chronic liver disease; acute liver disease; liver cirrhosis; acute viral hepatitis; High Density Lipoprotein; albumin

Introduction

Liver plays a vital role in lipid metabolism. Patients suffering from liver diseases often show abnormality in levels of plasma and circulating lipoproteins composition depending on the nature and severity of the disease (1-4). Altered levels of plasma cholesterol and triglyceride (TG) levels are often found. Various liver disorders reflect the impaired lipid metabolism including synthesis, transport and catabolism. (5,6). HDL is the smallest and densest among all the lipoproteins containing apolipoproteins A1 and A2 and is mainly synthesized by the liver.(7) High density lipoprotein being a macromolecular complex of lipids and lipoproteins (HDL) helps in cholesterol transport. For steroidogenesis to the

adrenal gland HDL is the key transporter of cholesterol where minimal cholesterol stores are found (8).HDL also participates in the reverse cholesterol transport, through the scavenger receptor BI (SR-BI) which brings bach cholesterol to the liver. Any defect in reverse cholesterol transport can enhance the synthesis of foam cells in the aorta leading to atherosclerosis. The enzyme Lecithin Cholesterol Acyl Transferase (LCAT) plays an important role in the synthesis and metabolism of HDL. Albumin, an effective expander of plasma volume is a protein made by the liver. For many years albumin has been used as a marker in the management of cirrhotic patients (9). Albumin helps in maintaining colloidal osmotic pressure and has antioxidant and anti-inflammatory actions. It is involved in ligand binding and transport of various molecules (10). Low albumin levels can cause fluid accumulation, in the abdomen or in the leg. Apart from albumin there are no other sensitive biochemical markers available at present to indicate the extent of synthetic liver injury. The present study was carried out to consider whether serum HDL cholesterol levels can be used as markers of liver injury in comparison to serum albumin levels in acute and chronic liver disease patients.

Materials and methods

This case control observational study was conducted in the Department of Biochemistry of Kasturba Medical College, Manipal from the study period of January 2017-May 2017. Anticipating 70% sensitivity for HDL cholesterol in discriminating between severity grades of liver cirrhosis a minimum of 74 samples were needed. 76 cases within the age group 12-76 years and 82 controls within the age group 15-80 years were taken. Permission from the Medical Superintendent was taken to view the hospital records of the liver disease patients from the Medical Records Department of Kasturba Hospital, Manipal. Reports of patients with abnormal liver function were retrieved from the Laboratory Information System by the faculty in charge and were handed over to the Principle Investigator along with respective residual samples after proper anonymization. The study was commenced after it was approved by Institutional Ethics Committee. 2ml serum was separated from the venous blood of the liver disease patients after centrifugation. Along with liver function parameters like total bilirubin, direct bilirubin, total protein, albumin, Aspartate Amino transferase (AST), Alkaline Phosphatase (ALP), Alanine Tansaminase (ALT) and lipid parameters including total cholesterol, triglycerides and HDL cholesterol were measured in all the serum samples. The total cholesterol, triglyceride and HDL cholesterol levels were

estimated by CHOD-POD method, autokit (GPO/PAP method) and precipitation end point method (autokit) respectively. Patients with acute liver disease such as fulminant hepatic failure and hepatic encephalopathy and chronic liver disease such as decompensated liver cirrhosis and viral hepatitis were included whereas liver cancer patients were excluded in this study.

Statistical methods such as non parametric Kruskal Wallis test (Median and IQR) for comparison of both acute and chronic liver disease patients and Spearman's rho correlation was used for correlating the various parameters.

Results

Table 1: Liver function tests in controls and patients with both acute and chronic liver disease

Liver Function Test Parameters	Controls (n=82) Median, IQR	Acute liver disease patients (n=32) Median, IQR	Chronic liver disease patients (n=44) Median, IQR	P Value*
Total bilirubin (mg/dl)	0.9 (0.7,0.1)	4.8 (3.2,9.9)	6.1 (4.2,10.7)	<0.001 (<.001)*bc
Direct bilirubin (mg/dl)	0.4 (0.3,0.6)	2.6 (1.8,5.7)	3.7 (2.1, 7.6)	<0.001 (<0.001)*bc
Total protein (g/dl)	7.2 (6.9,7.4)	6.8 (6.3,7.5)	6.5 (5.6,7.3)	0.001 (a=0.065,b=<0.001)*ab
Albumin (g/dl)	4.2 (4,4.5)	3.7 (3.2,4.2)	2.6 (2.1,2.9)	<0.001 (<0.001)*abc
AST (U/L)	25 (19,30)	110 (70,191)	77 (54,118)	<0.001 <0.001)*bc
ALT (U/L)	180 (170,190)	98 (36,143)	139 (87,168)	<0.001 (a=0.001,b=<0.001,c=<0.001)*abc
ALP (U/L)	67 (55,75)	221 (130,362)	151 (115,191)	<0.001 (<0.001)*abc

P*- Spearman's rho significant correlation, Kruskal Wallis test
a= acute vs chronic, b= chronic vs control, c= acute vs control)

Table 2: Serum albumin, total cholesterol, triglyceride and HDL cholesterol levels in controls and patients with both acute and chronic liver disease

Total Number of Parameters	Controls (n=82) Median, IQR	Acute liver disease patients (n=32) Median, IQR	Chronic liver disease patients (n=44) Median, IQR	P Value*
Serum albumin (g/dl)	4.2 (4,4.5)	3.7 (3.2,4.2)	2.6 (2.1,2.9)	<0.001 (<0.001)*abc
Total cholesterol (mg/dl)	180 (170,190)	156 (116,252)	139 (87,168)	<0.001 (0.028)*a
Triglycerides (mg/dl)	89 (72,110)	138 (89, 249)	116 (81,163)	<0.001 a=0.005,b=<0.001,c=0.008)*abc
HDL cholesterol (mg/dl)	53 (49, 59)	26 (15,36)	21 (14,31)	<0.001 a,b= <0.001*bc

P*- Spearman's rho significant correlation, Kruskal Wallis Test
a= acute vs chronic, b= chronic vs control, c= acute vs control)

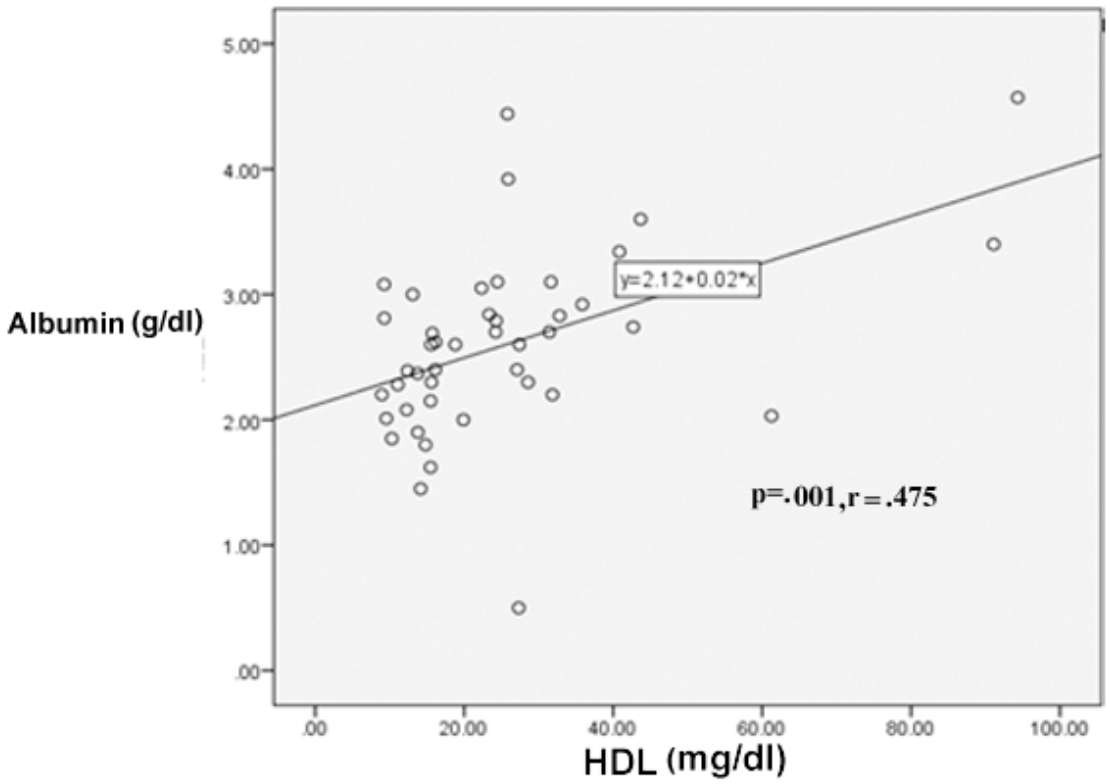

Fig 1: Correlation of albumin with HDL cholesterol levels in chronic liver disease patients

Discussion

The present study confirms the alteration in the concentrations lipids and lipoproteins concentrations in hepatic diseases as observed by the earlier studies (11-14).Chrostek et al revealed in both alcoholic and non alcoholic liver cirrhosis (NALC) there was a mean decline in the concentrations of total cholesterol and HDL cholesterol levels. The triglyceride levels in the non alcoholic liver disease (NALD) patients were observed to be more greater rather than the alcoholic liver disease patients (15). Another study conducted on alcoholic cirrhosis patients by Brier C et al after examining lipoprotein levels in plasma of patients with post alcoholic liver cirrhosis showed increase in triglyceride and decline in total cholesterol, HDL and VLDL levels. (16) In our study in case of total cholesterol, we observed significant decrease in both acute liver disease patients and chronic liver disease patients compared to controls. Chronic liver disease patients had further significant decrease compared to acute

liver disease group (p<.001). This might be due to reduced biosynthesis of cholesterol in liver. Commonly in patients with non alcoholic fatty liver disease (NAFLD) an elevation in the secretion of triglycerides from the liver as VLDL form likely results in elevation in serum triglyceride concentrations (17). Chronic alcoholic toxicity may also contribute to decrease of TG levels (18). Our study showed the triglyceride levels were increased in both acute and chronic liver disease patients compared to controls. This might be due to the active role of microsomal triglyceride transfer protein (MTP) which helps in transferring of lipids to newly formed Apolipoprotein B followed by enzyme induction leading to an adaptive response associated with increase in liver weight of MTP. This results in decline of accumulation of triglyceride in hepatic tissues and improves the exportation of VLDL thereby increasing the levels of serum triglyceride (19) or this might be due to compensatory increase in beta globulin synthesis in hepatic tissues and improvement in the exportation of VLDL. Chrostek et al also revealed that HDL cholesterol decreases in non-alcoholic liver cirrhosis with the extent of severity of liver disease leading to abrupt diminished levels in severe liver damage (score C) than that in mild damage (score A). Decompensated liver cirrhosis is referred to as Class C in which the liver fails to synthesize β-oxidation of fatty acids. In this regard triglyceride synthesis is also hindered. Ramcharran and co-workers [20] have stated that lower lipid levels are associated with more severity liver disease except TG levels that has direct relation with steatosis. Our study showed non significant decrease in HDL cholesterol levels in acute liver disease (group 1) patients when compared to controls (p=.298) whereas significant decline was found in chronic liver disease patients when compared to controls (p=<.001). Moreover, significant decrease in HDL cholesterol levels were found in chronic liver disease patients when compared to acute liver disease patients (p=<.001). In Figure 1 HDL cholesterol levels showed positive significant correlation with albumin levels (p=.001, r=.475) in chronic liver disease patients. No such correlation between albumin and HDL cholesterol levels were observed in the acute liver disease patients. The reason behind the decrease in HDL-cholesterol levels in liver cirrhosis might be due to the decreased synthesis of Apolipoproteins A and B [21]. The impairment of synthesis of HDL can also be due to damage in the synthetic machinery of the liver to synthesize HDL molecule by hepatic lipase and impairment in synthesis of APO A1 which is mainly responsible for the formation of HDL. In our study we found a significant correlation of HDL with albumin levels. Conditions interfering with the production of albumin, elevation in breakdown of proteins, elevation in loss of proteins or expand plasma volume may lead to decline in albumin levels to a greater

or lesser extent. It may happen that a person may have absolutely normal or near to normal albumin levels with liver injury until the condition has worsened and progressed to an advanced stage. For example, albumin levels is usually normal for patients who have not yet progressed to the stage of cirrhosis whereas albumin levels are generally found to be very low in cirrhotic patients. Our study observed significant decrease in serum albumin levels in both acute and chronic liver disease patients compared to the controls. The decrease observed in the acute liver disease patients was significant ($p=.05$) but the decrease was more significant in the chronic liver disease patients compared to controls ($p<.001$). Moreover, the serum albumin levels in chronic liver disease patients were significantly reduced compared to the serum albumin levels observed in acute liver disease patients ($p<.001$). In our case we can finally conclude that decrease in HDL cholesterol levels in both acute and chronic liver disease patients compared to controls suggesting that it may be a more sensitive marker of liver injury than albumin and can be relatively used in the diagnosis, assessment and prognosis of chronic liver disease patients further supporting a role for HDL in the management of liver disease patients.

Limitations

- The results of this study might have been influenced by smaller sample size.
- Periodic estimation of parameters in liver disease patients was done that could have given us a better picture of prognostic values of these markers.
- Liver ultra sonographic findings could have been compared with these markers.

Conclusion

- Positive correlation of HDL with albumin was observed in this study indicating a potential to be used as a marker of liver disease.
- HDL cholesterol indicated impairment in the synthetic function of liver.
- Further studies may be required to evaluate the usefulness of serial estimations of HDL cholesterol levels in prognostication.

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