

Lipids in Biliary Lithogenesis

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Abstract

Serum and biliary lipoproteins, total cholesterol (Tc) and triglycerides (TG) were measured in patients with gallstones and in those without gallstones. Serum and biliary LDLc, TG and Tc were significantly higher ($P < 0.001$) in cases having gall stones than those without stones while HDLc were low ($P < 0.001$) in those with stones. No difference was found in very low density lipoproteins (VLDLc) in the two groups. Present data showed that there is a statistically significant correlation of serum and biliary lipoproteins specifically LDLc and HDLc ($r = +.67$ and $r = +.56$). This report shows that serum HDLc (67.42%) and LDLc (70.28%) play a more critical role in comparison to total cholesterol (59.43%) and triglyceride (57.15%) levels in the formation of gallstone (JPMA 47:253, 1997).

Introduction

Gallstones (OS) are formed when there is a characteristic precipitation of excess cholesterol as a result of production of lithogenous bile. Although, the source of biliary cholesterol has not been established, it has been suggested that serum cholesterol primarily free cholesterol from HDL is the preferential source in man¹. A positive correlation between the total biliary acids and serum high density lipoproteins (HDLc) in patients with a rapid nucleation time ($P = 0.0128$) supports that HDLc is devoted primarily to bile acid synthesis². While much information is available on total cholesterol, triglyceride, bile acids in serum, little or no information exists on lipoproteins in bile. We, therefore, conducted a study on lipoproteins in bile and serum of patients with gallstones and those without gallstones to establish a correlation between biliary and serum lipoproteins. We also, investigated the relationship of serum and biliary lipoproteins with the production of lithogenous bile (supersaturated with cholesterol) if any.

Materials and Methods

Subjects

The present study was conducted on a group of patients (age range 12-50 years), some of whom had gallbladder disease with stones ($n = 50$) and others (controls) who were admitted for other reasons as given in the table below:

The study was approved by the Ethical Committee of the S.V.B.P. Hospital, L.L.R.M. Medical College, Meerut. At the time of the investigation, none of the patients were on any medicine or had any history of diabetes mellitus and hepatic disease or any other disease which may influence lipids metabolism.

1. Controls (n=26)
(without gallbladder,
stones)

Patients admitted for:
(a) Laprotomy, (b) Minor surgical
problems like cystoscopy for
non malignant disorder etc.,
(c) With no hepatobiliary disease
(d) With normal Liver Function
Test (LFT).

2. Patients of Cholelithiasis (50): Showing clinical symptomatology,
signs and confirmed radiological
evidences of gall bladder stones
like x-ray, IVP.

Experimental Design

In all cases, blood samples were collected by veini puncture, after an overnight fast. Serum was separated by centrifugation and was stored in refrigerator at 4 degree centigrade until analysed.

Collection of Bile

Bile was collected from gallbladder by needle aspiration on the operation table at the time of operation. The gallbladder was emptied by needle aspiration so as to exclude unrepresentative sampling due to stratification of bile. In all cases except controls, aspiration was followed by Cholecystectomy.

Analysis of serum and biliary lipids

The lipoproteins were determined by ultracentrifugation and precipitation as described by Wilson and Spige?. Total cholesterol estimation was done by the method described by Zak et al⁴ and triglycerides were estimated by that of Van Handel and Zilversmit⁵.

Statistics

Statistical calculations of data were done using the students t- test for unpaired samples.

Results

Serum and biliary LDLc, TC and TG levels in patients with gallstones showed significant elevation (P<0.001) when compared to control (Table I).

Table I. Serum and biliary levels of lipoproteins, triglyceride and total cholesterol in patients of gallstone and controls.

Serum and biliary lipid profile (mg/dl)		Controls (Mean±SD)	Patients of GS (Mean±SD)	P value
Cholesterol	Serum	224.69±29.25	262.89±39.17	<0.001
	Bile	399.88±87.52	706.93±100.20	<0.001
HDLc	Serum	65.28±12.53	42.69±10.02	<0.001
	Bile	91.17±18.13	177.30±29.38	<0.001
LDLc	Serum	121.80±22.44	180.83±24.86	<0.001
	Bile	261.54±52.31	478.15±121.12	<0.001
VLDLc	Serum	37.12±8.77	39.47±8.85	NS P>0.05
	Bile	47.18±11.07	50.49±12.76	NS P>0.05
TG	Serum	124.06±24.65	157.01±25.65	<0.001
	Bile	193.94±35.58	291.94±51.66	<0.001

Serum and biliary HDLc were significantly low (P<0.001) in the patients with gallstones. VLDLc in serum and bile was not significant (P>0.05). It is apparent from Table II,

Table II. Percentage incidence of serum triglyceride, total cholesterol, high density lipoprotein and low density lipoproteins in patients of gallstones.

Lipid content	Group A		Group B	
	Patients with normal range		Patients with abnormal range	
	No.	%	No.	%
Triglyceride	21	42.85	29	57.15
Cholesterol	20	40.57	30	59.43
HDLc	16	32.57	34	67.42
LDLc	15	29.75	35	70.28

that percentage of gallstone patients with abnormal lipoprotein content was much higher than that of patients with normal lipoprotein contents. In contrast, serum cholesterol which was found to be diagnostic only in 59.43% of the cases, the percentage incidence of abnormal HDLc and LDLc level was as high as 67.42% and 70.28% respectively. The correlation coefficients of serum and biliary LDLc and HDLc indicate that there exists a good correlation between HDLc and LDLc ($r=+.67$ and $r=+.56$).

Discussion

The importance of increased serum concentration of cholesterol and triglyceride (TG) with Cholelithiasis has been stressed in various publications⁶⁻⁸. The present data revealed a positive correlation of serum cholesterol and TO levels with the incidence of gallstone. A 59.4% hypercholesterolemia and 57.1% hypertriglyceridaemia was observed in this study (Table II): Though, serum cholesterol and serum triglyceride may be contributing towards the genesis of cholelithiasis, a few contradictions⁹⁻¹⁰ report that a considerable percentage of patients have gallstones without these factors. As demonstrated in Framingham¹¹ subjects, the possibility of shared factors as the basis of the cholesterol related gallstone disease and coronary heart disease association, it is clear that these two diseases have in common a variety of risk factors -most notably, age, obesity, blood lipids and diet⁶⁻¹². Therefore, measure of specific lipoprotein blood fractions seem to be more meaningful than total serum cholesterol values as intervening variable in the gallstone disease and its lithogenic index. The present study indicated increased low density lipoprotein (LDLc) levels in gallstone patients as to controls which, suggests, that as LDLc in serum increases, the development of stones in gallbladder increases. The findings presented herein also reported low (abnormal) levels of high density lipoproteins (HDLc) in the patients of gall stones as compared to controls. This illustrates that patients having decreased serum HDLc levels are more susceptible to develop cholelithiasis. Reduced concentrations of HDLc with gall bladder stones has been reported by other workers^{13,14}. Similarly, Chen et al, also showed significantly decreased HDL1-Ch and HDL2-Ch values of serum in all his experimental groups of cholelithiasis compared with control group¹⁵. He found the disorder of lipoprotein metabolism in the formation of low levels of bile acids as compared with controls. To be more illustrative and informative about the importance of parameters, serum HDLc and serum LDLc at a criterion level in cholelithiasis, patients were divided into two groups; Group A: Comprising of patients with normal serum HDLc (above 50 mg/dl), serum LDLc (below 130 mg/dl), serum cholesterol (below 250 mg/dl) and serum TO (below 150 mg/dl) and Group B: Patients with abnormal serum HDLc levels (below 50 mg/dl), serum TC (above 250 mg/dl) and serum TG (above 150 mg/dl) as shown in Table II. The percentage of patients with abnormal serum LDLc levels and serum HDLc levels was found to be 70.2% and 67.4% whereas, serum cholesterol and serum TO were abnormal in only about half of the cases. Our results reflected greater degree of percent increase in abnormal serum levels of HDLc and LDLc than cholesterol and triglyceride. Thus, it can be said that patients with decreased serum HDLc and increased serum LDLc levels have greater risk for the development of cholelithiasis by producing supersaturated bile with cholesterol. It is hypothesized that this changed pattern of unfavourable specific lipoprotein profile in the serum and bile of these patients may be a good predictive index for the presence of cholesterol-related gallstones. This fact was further strengthened by the findings of Breyfogle and others who correlated gallstone with MI, diabetes and atherosclerosis^{11,16,17}. and assessed the importance of lipid metabolism in the pathogenesis of cholelithiasis.

HDLc probably delivers cholesterol to the liver for excretion¹⁷, it can be reasonably expected that a high concentration of HDLc may overwhelm the ability of liver to excrete cholesterol, shunting more cholesterol away from bile acid pathway and producing bile that is more lithogenic. Hyperlipidaemia is strongly associated with cholelithiasis. According to Ahlbeig¹⁸ and Einarson¹⁹, GS is associated with hyperlipoproteinaemia type IV^{18,19}. In our study evidence of familial factors in GS are very few but 62% of the patients were of cholesterol type and had definite evidence of hyperlipidaemia in one of their parents or children which further strengthens the validity of higher frequency of gallstone found in family members and are likely to be due to genetic factors. Familial hypercholesterolaemia related to cholesterol gallstones has been reported by Linden et al²⁰. It is concluded that familial hyperlipidaemia is the causative factor in the development of cholelithiasis where assessment of specific lipoprotein profile may play an important role in the diagnosis of the patients of cholelithiasis.

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