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Glycocholic acid in chronic active hepatitis and mild liver diseases

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Summary. Serum levels of fasting glycocholic acid were measured in various noncirrhotic liver diseases. Forty-five patients were evaluated, 15 with chronic active hepatitis and 30 with mild liver diseases including chronic persistent hepatitis, steatosis, and minimal changes. There were increased levels of glycocholic acid in 53.3% of chronic active hepatitis cases and in 10% of mile liver disease cases ($P=0.003$), and the levels reached by patients with chronic active hepatitis were higher than those in patients with mild liver disease ($P<0.0001$). The latter did not show significant differences in their serum levels or in the percentage of abnormal results with respect to control group. There were weak, although significant, correlations between glycocholic acid and transaminases, alkaline phosphatase, gamma-glutamyltranspeptidase, albumin, and gammaglobulin. In the present study, the specificity of glycocholic acid was high in the detection of chronic active hepatitis patients at different cut-off levels. Glycocholic acid appeared to reflect histological severity in this group of noncirrhotic liver diseases and might have practical applications in the management of these patients.

Key words: Bile acids – Liver diseases – Hepatitis – Hepatitis, chronic active – Liver tests

The rate of intestinal absorption and liver uptake from portal blood determines the level of peripheral bile acid, and if intestinal dysfunction is absent, serum levels depend on liver clearance [18]. It has been known for many years that serum bile acids are increased in liver diseases [14]. However, until sensitive and specific radioimmunoassays were developed, technical problems in their measurement and the existence of other, cheaper, commonly used liver function tests had limited their clinical use. Determination of serum bile acids has been found useful in the evaluation of numerous liver diseases [2–4, 8, 11, 16], and their serum levels have been related to histological damage, severity, and prognosis of the liver disease [1, 5, 6, 10, 15]. Of the biliary acids routinely measured by radioimmunoassay, glycocholic acid (GCA) has been found to be the most sensitive in liver diseases [1].

This prospective study was undertaken to investigate the behavior of fasting GCA serum levels in untreated, noncirrhotic liver disease patients at the time of diagnosis through a complete clinical and laboratory evaluation. The usefulness of GCA in predicting the severity of the histology was also investigated in order to improve the management of these patients.

Materials and methods

This study included 45 consecutive nonbiopsied patients who were electively admitted for biopsy between March 1990 and November 1991 because of chronic alterations in liver test results persisting for more than 6 months, and who were diagnosed as having chronic active hepatitis (CAH) or mild liver disease (MLD) after biopsy. Of the 45 patients 15 had CAH and 30 MLD. Among the latter, 15 had chronic persistent hepatitis, 6 had steatosis, and the remaining 9 had minimal changes in liver biopsy. There were 28 males (8 CAH, 20 MLD) and 17 females (7 CAH, 10 MLD). Ages ranged between 16 and 76 years (mean 41.4 years), with a similar distribution among the two groups. The etiology of the liver disease was considered to be viral in 24 patients, alcoholic in 5, and other/unknown in 16.

The study complied with the recommendations of the Declaration of Helsinki. Blood was collected simultaneously for all the laboratory determinations after a fasting period of 12 h. GCA was measured by radioimmunoassay using a commercially available kit (Abbott Laboratories, North Chicago, Illinois). The upper limit of normality was established at 1.4 μmol/l, which corresponded to the mean +2 standard deviations of a control group that comprised 90 healthy, hepatitis B surface anti-

Abbreviations: GCA = glycocholic acid; CAH = chronic active hepatitis; MLD = mild liver diseases

gen negative individuals aged 19 to 63 years (mean 38.6 years).

A preliminary test revealed a nonnormal distribution of GCA, and nonparametric statistical tests were therefore used. Spearman's rank correlation coefficient was used to test relationships between continuous variables. The Kruskal-Wallis test was used to compare GCA levels in several groups and the Mann-Whitney U test to compare the levels between two groups. A $P<0.05$ level for a two-tailed test was used to evaluate statistical significance.

Table 1. Serum levels of glycocholic acid in patients and controls

	n	Increased		Mean	SD	Range	Median
		n	%				
CAH	15	8	53.3	3.44	4.44	0.5–16.6	1.5
MLD	30	3	10.0	0.70	0.90	0.06–4.5	0.5
Controls	90	6	6.7	0.62	0.41	0.1–2.4	0.5

Table 2. Correlations between glycocholic acid and laboratory tests

Test	r	P
Hematocrit	−0.02	NS
Mean corpuscular volume	−0.15	NS
Prothrombin activity (%)	−0.259	NS
Aspartate aminotransferase	0.298	0.04
Alanine aminotransferase	0.294	0.04
Alkaline phosphatase	0.361	0.01
Gamma-glutamyltranspeptidase	0.429	0.002
Total bilirubin	−0.127	NS
Direct bilirubin	−0.104	NS
Cholesterol	−0.196	NS
Total protein	0.171	NS
Albumin	−0.405	0.004
Gammaglobulin	0.427	0.002
IgG	0.364	0.01
IgA	−0.127	NS
IgM	0.261	NS

Results

Eleven patients (24.4%) had increased levels of GCA. Eight of these had CAH and three MLD. No MLD patient had GCA values higher than 4.5 μmol/l. Table 1 shows the GCA values and the descriptive statistics in each group. There were no differences in GCA levels with respect to patients' sex or age. Table 2 shows the correlations found between GCA and laboratory tests. It can be seen that although there were some significant correlations, no one test showed a strong association with GCA.

GCA serum levels were not significantly related to urinary bilirubin, urobilinogen, etiology, smoking habits, viral markers, cholelithiasis, hepatomegaly, or splenomegaly. Conversely, significantly higher GCA levels were found in patients whose alcohol intake was less than 40 g/day than in those whose alcohol intake was higher ($P=0.03$), although the prevalence of CAH was slightly higher in nondrinkers than in drinkers (68.7% and 57.1%, respectively). Also, there were negative correlations of only borderline significance between GCA and daily alcohol intake ($P=0.048$) and years of intake ($P=0.04$). Other alcohol markers, i.e., mean corpuscular volume, IgA, and the ratio of aspartate aminotransferase to alanine aminotransferase, did not show correlations with GCA.

Patients with CAH had significantly higher levels of GCA than those with MLD ($P<0.0001$) and than controls ($P<0.001$). Conversely, MLD patients did not show significant differences in their GCA serum levels compared with controls ($P=0.24$).

Table 3 shows the sensitivity, specificity, efficiency, predictive values, and likelihood ratios of GCA in the detection of CAH for different cutoff levels in comparison with other commonly used

Table 3. Usefulness of glycocholic acid and other liver tests to predict chronic active hepatitis as compared with mild liver diseases

	GCA (μmol/l)			Alanine amino-transferase	Alkaline phosphatase	Bilirubin	Albumin
	0.7	1.4	2.8				
Sensitivity	86.7%	53.3%	33.3%	93.3%	26.7%	33.3%	40.0%
Specificity	80.0%	90.0%	96.7%	30.0%	93.3%	66.7%	86.7%
Positive predictive value	68.4%	72.7%	83.3%	40.0%	66.7%	33.3%	60.0%
Negative predictive value	92.3%	79.4%	74.4%	90.0%	71.8%	66.7%	74.3%
Efficiency	82.2%	77.8%	75.6%	51.1%	71.1%	55.6%	71.1%
Likelihood ratio +	4.3	5.3	10.0	1.3	4.0	1.0	3.0
Likelihood ratio −	0.2	0.5	0.7	0.2	0.8	1.0	0.7

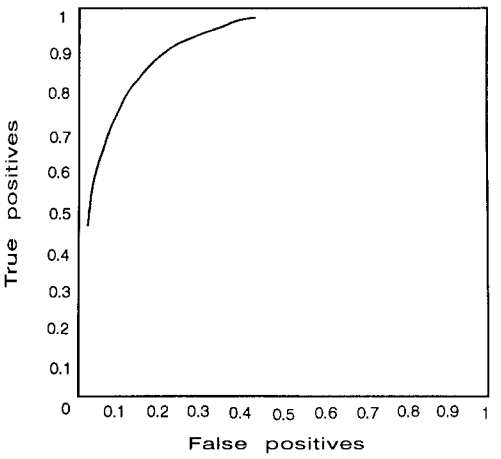

Fig. 1. Receiver-operating characteristic curve of GCA to detect chronic active hepatitis. An "ideal" test is characterized by a curve displaced to the uppermost left of the receiver-operating characteristic space, a test without any power by the major (lower left to upper right) diagonal

liver tests. It can be seen here that GCA was the most efficient of the liver tests. The receiver-operating characteristic curve (Fig. 1) showed the greatest discriminant value of GCA to be 0.75 μmol/l (sensitivity 86.7%, specificity 80.0%).

Discussion

GCA was found to be an useful marker in noncirrhotic liver diseases. Patients with more severe liver disease, i.e., CAH, showed significantly higher GCA levels and a higher percentage of increased values than those with MLD and controls. On the other hand, MLD patients did not show significant differences versus controls in either GCA serum levels or percentage of abnormal values. These results support those of other authors [6, 10] who have also found higher GCA levels in severe liver disease as compared with MLD.

Serum bile acids have been found related to cytolysis and protein synthesis [5], bilirubin [9], and results of cholestatic biochemical tests [1]. In the present study, significant correlations were also found with some liver tests reflecting cytolysis, cholestasis, and impairment of liver function. Perhaps the association observed with a low alcohol intake could be explained by a more aggressive histology of viral origin in these patients. Moderate alcohol consumption produces no change in serum bile acid levels [12]. The etiology of the liver disease is not associated with different GCA serum levels in the patients as a whole nor in the CAH patients.

The fact that bile acid serum levels are increased in patients with liver diseases does not imply that the total bile acid pool size is increased. On the contrary, it may be decreased, as has been shown by isotopic studies [17]. In advanced liver diseases the increase in bile acids has been associated with small intra- or extrahepatic portal-systemic shunts and hepatocellular dysfunction [7, 10, 13].

Although the sensitivity was low at high cutoffs, GCA serum level proved to be a specific marker for the detection of CAH in this study (specificity 90% at the level of the upper normal limit, and higher for higher cutoffs). These findings suggest that determination of fasting GCA serum levels may be useful in the evaluation of these patients as a marker of histological severity, playing an adjunctive role with other liver tests. Specifically, GCA monitoring might be applied to the evaluation of nonbiopsied liver diseases, in the differentiation of active from MLD, in the selection of patients for liver biopsy, and in the follow-up of chronic hepatitis.

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