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Interrelated changes in gamma-glutamyltransferase activity and HDL-cholesterol level in the sera of patients with alcoholic liver injury.

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Abstract

The levels of HDL-cholesterol and gamma-glutamyltransferase in the sera of 17 patients with alcoholic liver injury were followed after abstinence and compared with those of 11 patients with acute non-alcoholic hepatitis. The activity of gamma-glutamyltransferase decreased in all cases irrespective of the type of liver injuries. The level of HDL-cholesterol also decreased in 11 of 17 cases with alcoholic liver injury. The other alcoholics, in whom HDL-cholesterol level increased or showed no definite change after withdrawal of alcohol, had severe and advanced liver injuries. In non-alcoholic hepatitis, the HDL-cholesterol level increased as normal liver functions were restored except for one case with cholestatic features. It was concluded that alcohol intake can increase HDL-cholesterol level even in the presence of a concomitantly induced hepatic lesion.

KEYWORDS: alcoholic liver injury, HDL-cholesterol, γ -glutamyl-transferase.

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**INTERRELATED CHANGES IN γ -GLUTAMYLTRANSFERASE
ACTIVITY AND HDL-CHOLESTEROL LEVEL IN
THE SERA OF PATIENTS WITH ALCOHOLIC
LIVER INJURY**

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Abstract. The levels of HDL-cholesterol and γ -glutamyltransferase in the sera of 17 patients with alcoholic liver injury were followed after abstinence and compared with those of 11 patients with acute non-alcoholic hepatitis. The activity of γ -glutamyltransferase decreased in all cases irrespective of the type of liver injuries. The level of HDL-cholesterol also decreased in 11 of 17 cases with alcoholic liver injury. The other alcoholics, in whom HDL-cholesterol level increased or showed no definite change after withdrawal of alcohol, had severe and advanced liver injuries. In non-alcoholic hepatitis, the HDL-cholesterol level increased as normal liver functions were restored except for one case with cholestatic features. It was concluded that alcohol intake can increase HDL-cholesterol level even in the presence of a concomitantly induced hepatic lesion.

Key words : alcoholic liver injury, HDL-cholesterol, γ -glutamyltransferase.

Increased activities of serum γ -glutamyltransferase (GGT, (5-glutamyl)-peptide: amino-acid 5-glutamyltransferase, EC 2. 3. 2. 2) in alcoholic liver injuries are well documented (1-3). High levels of serum HDL-cholesterol in alcoholics have also been demonstrated in recent studies (4-6). On the other hand, low levels of HDL-cholesterol have been reported in patients with liver injuries caused by agents other than ethanol (7-9). Recent studies in our laboratory (9) revealed a significant decrease in HDL-cholesterol level in alcoholic liver injury, although the extent of the decrease was much less and more variable than that in non-alcoholic liver injury. This suggested that the level of serum HDL-cholesterol in alcoholic liver injury is determined by two opposing factors: one is the inductive effect of ethanol on HDL and the other is the

injurious effect of ethanol on the liver. If the former effect is predominant, the HDL-cholesterol level would decrease after the withdrawal of alcohol intake, and *vice versa*. The assumption was tested in the present study with alcoholics by following the time-courses of changes in serum HDL-cholesterol level after abstinence. GGT activities were also determined serially in order to ensure a smooth clinical course after cessation of alcohol intake (3). The results were compared with those obtained in a similar study made on acute non-alcoholic hepatitis.

MATERIALS AND METHODS

The subjects studied included 17 male alcoholics with liver injury and 11 patients, 8 males and 3 females, with acute non-alcoholic, mostly viral, hepatitis. Their ages ranged from 22 to 65 years old. The diagnoses were based on the patient's history, physical findings and laboratory data. Some of the results of liver function tests are given in Table 1. The alcoholics had histories of drinking more

TABLE 1. LABORATORY DATA OF ALCOHOLIC AND NON-ALCOHOLIC PATIENTS

Liver function tests	Alcoholic liver injury	Non-alcoholic liver injury
Bilirubin (mg/dl)	1.0-12.4 (2.9)	0.8-16.2 (5.9)
GOT (K. U.)	35-240 (100)	114-2860 (988)
GPT (K. U.)	22-270 (86)	37-5610 (1486)
GOT/GPT ratio	0.5-3.0 (1.4)	0.2- 3.1 (0.8)
HDL-cholesterol (mg/dl)	29.9-91.2 (52.7)	15.3-76.0 (32.7)
GGT (mU/ml)	66-4112 (675)	45-326 (184)

Mean values are given in parentheses.

than 100g of ethanol as "Sake", beer or whisky over 10 years. Two of them had ascites and in 10, the liver was palpable, extending 1 to 5 cm below the right costal margin. Spider angiomas and/or liver palms were noted in 5. All the alcoholics studied had been drinking alcohol until 1 to 7 days before the initial examination of GGT and HDL-cholesterol levels. Those abnormalities were markedly improved after hospitalization and cessation of alcohol intake. Based on these data, this group was referred to as alcoholic liver injury, although 2 of them were positive for HBs-Ag and hence were analyzed separately.

Serum concentrations of HDL-cholesterol were determined by the precipitation method of Kostner (10) with dextran sulfate and magnesium chloride. This was coupled with an enzymatic assay for cholesterol using a T-Choles test kit (Enzymatic, International Reagent Corp., Kobe) (11, 12). Activities of serum GGT were determined at 37°C with an Iatron kit (Sanko Junyaku Co. Ltd., Tokyo) according to the method of Orłowsky and Meister (13).

RESULTS

Time-courses of the alteration in serum HDL-cholesterol concentration were classified into 3 types: ascending, indefinite and descending types. The criteria for this classification were based on maximum changes of more than 5 mg/dl HDL-cholesterol as compared with the initial level using the values observed while the GGT activity was decreasing to a certain level, in most of the cases to the normal range. Fig. 1 illustrates a representative case of the ascending type and Fig. 2 of the descending type. When no consistent alteration

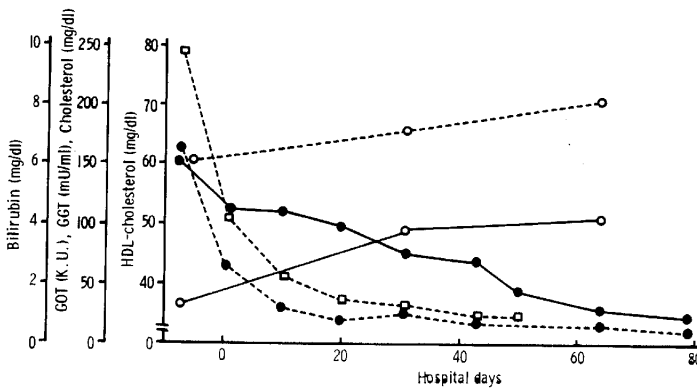


Fig. 1. Time-courses of changes in HDL-cholesterol and other liver function tests in a case of acute non-alcoholic hepatitis (ascending type of HDL-cholesterol change). ●—●, GOT; ●---●, GGT; ○—○, HDL-cholesterol; ○---○, total cholesterol and □---□, bilirubin.

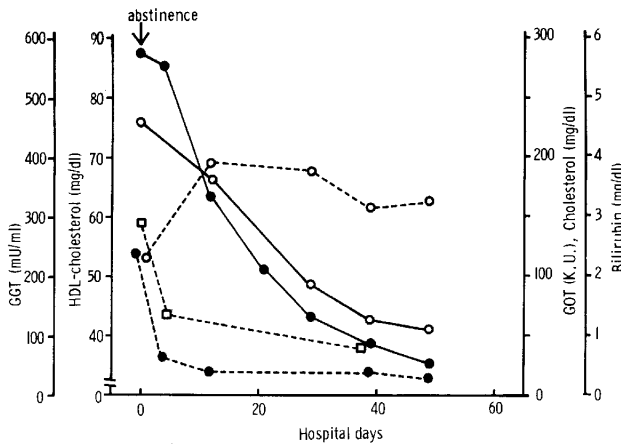


Fig. 2. Time-courses of changes in HDL-cholesterol and other liver function tests in a case of alcoholic liver injury (descending type of HDL-cholesterol change). The patient had been drinking about 135 g of alcohol daily as "Sake" for 20 years until the day before admission. HDL-cholesterol level was higher than normal initially and decreased with recovery of other liver function tests. Symbols, see the legend to Fig. 1.

in HDL-cholesterol level was found, the cases were grouped into the indefinite type such as depicted in Fig. 3.

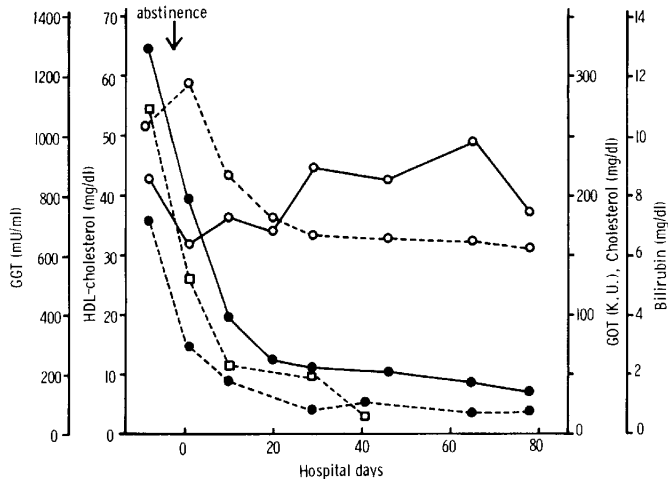


Fig. 3. Time-courses of changes in HDL-cholesterol level and other liver function tests in a case of alcoholic liver injury (indefinite type of HDL-cholesterol change). The patient drank about 175 g of alcohol daily as "Sake" for 30 years and had been sober for 2 days before admission. GGT activities and other liver function tests improved after hospitalization, whereas the level of HDL-cholesterol decreased initially and recovered afterwards. Symbols, see the legend to Fig. 1.

The distribution of the number of cases of alcoholic liver injury and non-alcoholic hepatitis among the 3 types of HDL-cholesterol alteration is presented in Table 2, together with the incidence of abnormal results of other liver function tests. In alcoholic liver injury, approximately two thirds of the cases were of the descending type, while in non-alcoholic hepatitis, most of the cases were of the ascending type. The alcoholics who showed the ascending type of HDL-cholesterol change all consumed more than 150 g of alcohol daily and were characterized by initially lower HDL-cholesterol, cholinesterase and K_{ICG} values and higher ZTT or γ -globulin levels compared with those who showed the descending type of HDL-cholesterol alteration. Incidentally, 2 HBs-Ag positive cases among 5 alcoholics were found in the ascending type. In other words, the patients with alcoholic liver injury of the ascending type had more advanced and severe hepatic injuries. One case of non-alcoholic hepatitis with the descending type of HDL-cholesterol change had intrahepatic cholestasis.

A case of alcoholic liver injury, in whom HDL-cholesterol and GGT levels were determined before and after admission, is presented in Fig. 4. The patient had been sober for 2 years until October 1979, when alcohol consumption was

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TABLE 2. INCIDENCE OF ABNORMAL LIVER FUNCTION TESTS AND OTHER PARAMETERS ON ADMISSION IN THREE TYPES OF HDL-CHOLESTEROL ALTERATION

Liver function tests and other parameters	Time-courses of HDL-cholesterol alteration				
	Alcoholic liver injury			Non-alcoholic hepatitis	
	Ascending type	Indefinite type	Descending type	Ascending type	Descending type
Alcohol intake over 150 g/day	5/5	1/1	3/11	1/10	0/1
GGT activity over 200 mU/ml	4/5	1/1	9/11	4/10	1/1
HDL-cholesterol under 45 mg/dl	4/5	1/1	1/11	10/10	0/1
Total cholesterol under 150 mg/dl	3/5	0/1	3/11	3/10	1/1
Bilirubin level over 2.0 mg/dl	2/5	1/1	4/11	9/10	1/1
GOT activity over 50 K. U.	3/5	1/1	7/11	10/10	1/1
GPT activity over 50 K. U.	2/5	0/1	7/11	9/10	1/1
Cholinesterase under 0.5 Δ ph	4/5	0/1	1/11	0/10	0/1
ZTT over 15 U.	4/5	1/1	1/11	0/10	0/1
γ -globulin over 30%	4/5	1/1	1/11	0/10	0/1
K _{ICG} under 0.10	3/4	1/1	0/8	0/3	0/0
Positive HBs-Ag	2/5	0/1	0/7	5/10	1/1

resumed. The levels of GGT and HDL-cholesterol rose markedly as the results of liver function tests worsened at this time. These abnormalities improved rapidly after hospitalization and total abstinence.

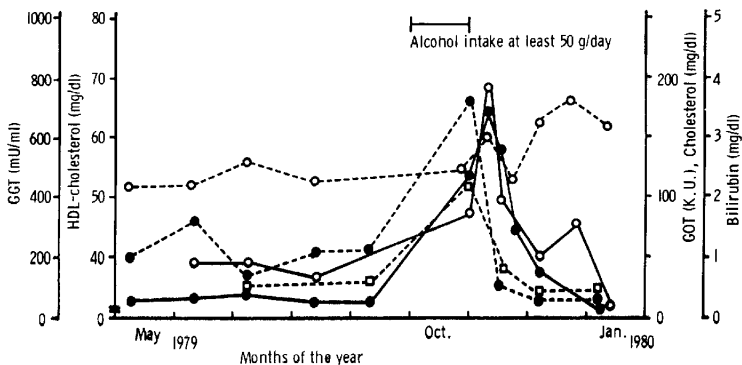


Fig. 4. Laboratory data before and after hospitalization of a case of alcoholic liver injury. Symbols, see the legend to Fig. 1.

Laboratory data of another case of alcoholic liver injury with repeated hospitalization are illustrated in Fig. 5. High levels of HDL-cholesterol and GGT were noted on every admission after alcohol abuse, and both decreased rapidly in a similar manner after abstinence, although the decrease in HDL-cholesterol level in the third hospitalization was not straightforward.

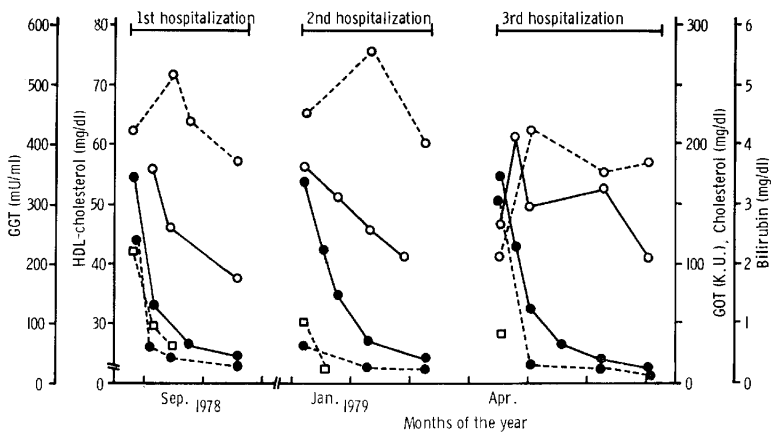


Fig. 5. Laboratory data of a case of alcoholic liver injury with repeated hospitalization. Symbols, see the legend to Fig. 1.

The results of these 2 cases indicated that the alcohol intake increases HDL-cholesterol level even in the presence of concomitantly induced hepatic injury.

DISCUSSION

Low levels of serum HDL-cholesterol are present in acute hepatitis and other liver diseases, and increase with recovery (7, 8). On the other hand, alcohol intake is known to elevate the serum HDL-cholesterol concentration (4-6). When hepatic injury is induced by alcohol abuse, HDL-cholesterol level appears to be generally increased. This was shown in the present study by following the entire courses of HDL-cholesterol alteration in 2 alcoholics.

When the change in HDL-cholesterol level was followed in a large number of alcoholic patients after total abstinence, the level of HDL-cholesterol decreased, as expected, in most of the cases with improvement of liver function tests. Only in a few cases of alcoholics with advanced liver injuries did the HDL-cholesterol level tend to increase more or less with recovery of hepatic functions towards normal. In interpreting this, the implication of underlying hepatic injury associated with HBs-Ag appears to be important. It is assumed in these severe cases that the lowering effect of hepatic injury on HDL-cholesterol level surpassed the increasing effect of alcohol intake. Conversely, the liver of alco-

holics with mild injury appeared to be capable of secreting an increased amount of HDL into the blood stream following induction by the ingested alcohol although the resulting serum HDL-cholesterol level was somewhat lower than the normal but slightly higher than the non-alcoholic hepatitis.

Accordingly, the time-course of HDL-cholesterol alteration after abstinence would serve as a better indicator of assessing the involved hepatic injury. However, it should be noted that the alcoholics with the descending type of HDL-cholesterol alteration had increased GOT activities, bilirubin levels and other abnormal results of liver function tests. Thus, the descending type of HDL-cholesterol change after abstinence could not be taken as a safe guard for alcoholics. In alcoholics with the ascending type of HDL-cholesterol alteration, GGT activity decreased in all cases. Therefore, HDL-cholesterol is a more sensitive marker of hepatic injury than GGT; a low HDL-cholesterol level with a high GGT activity may represent a more severe hepatic injury.

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