Effects of alcohol on plasma lipoproteins and cholesterol and triglyceride metabolism in man

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Abstract To define the effects of moderate alcohol intake on cholesterol and triglyceride metabolism in man, twelve patients were hospitalized on a metabolic ward and were fed defined diets for 10 weeks. Each patient underwent testing of plasma lipid and lipoprotein levels, of cholesterol metabolism (absorption, fecal excretion, bile saturation), and of triglyceride metabolism [turnover of triglycerides in chylomicrons and very low density lipoproteins (VLDL)]. This testing was done twice, first during a 4-week control period and then during a 4-week period in which 630 calories of alcohol were either added to or substituted for baseline calories. This increased the average baseline caloric intake by only 24% (range 20% to 30% depending on the initial caloric intake). Addition of alcohol to the baseline diet did not cause weight gain in lean individuals. Obese individuals' responses were more variable, and 3/6 definitely gained weight when the diet was supplemented with alcohol. In addition, obese subjects appeared to be more susceptible to the hyperlipidemic effects of alcohol; whereas 4/6 obese patients developed increased total triglyceride and VLDL-triglyceride concentrations when alcohol was administered, concentrations increased with alcohol administration in only 1/6 lean individuals. High density lipoprotein (HDL) cholesterol increased in all volunteers. Low density lipoprotein (LDL) levels did not change. Metabolic studies showed increased transport of VLDL-triglycerides in overweight patients but not in normal weight individuals; increased transport of VLDL-triglycerides in the former was associated with delayed clearance of chylomicron triglycerides. Alcohol consumption did not affect lipoprotein lipase or hepatic triglyceride lipase in six patients in whom these enzyme activities were measured. In the amounts of alcohol taken in this study, no changes were observed in absorption, synthesis, or excretion of bile acids, or percent saturation of gallbladder bile with cholesterol.—**Crouse, J. R., and S. M. Grundy.** Effects of alcohol on plasma lipoproteins and cholesterol and triglyceride metabolism in man. *J. Lipid Res.* **25:** 486–496.

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Despite the large quantities of alcohol consumed in many populations, research on the influence of alcohol on plasma lipids and lipoproteins and on lipid metabolism has been largely of a descriptive nature. Previous studies in human subjects have shown that ethanol consumption is often associated with transient increases in concentrations of plasma triglycerides, particularly pronounced in patients with underlying hypertriglyceridemia (1–3); these changes are exaggerated in those consuming large amounts of alcohol (4–7) compared to "social drinkers" (1–3, 8–10). Recently, epidemiologic studies have also correlated alcohol consumption with increased plasma high density lipoproteins (HDL) (10–12). However, relatively little is known about effects of ethanol on metabolism of cholesterol, triglycerides, and lipoproteins in man. Although two previous reports have addressed the short-term effects of acute administration of alcohol on plasma triglyceride metabolism (13, 14), longer-term actions of consumption of moderate doses of alcohol on the metabolism of endogenous and exogenous triglyceride-rich lipoproteins have not been evaluated. Furthermore, effects of alcohol on cholesterol absorption have not been reported, and only one previous paper has evaluated the effects of moderate alcohol consumption on excretion and synthesis of cholesterol and bile acids in man (15). Finally, no information is available on the influence of alcohol on the percent saturation of gallbladder bile with cholesterol. For these reasons we undertook a study of the effects of moderate quantities of alcohol, approximately 20% of total calories, on the metabolism of cholesterol and triglycerides in human volunteers. The studies were carried out on a metabolic ward to insure controlled conditions.

In this study the following questions were addressed. *a*) How do moderate intakes of alcohol (24% of calories) affect plasma concentrations of the lipoprotein fractions? *b*) What are the effects of alcohol on hepatic secretion of triglycerides and on clearance of triglyceride-rich lipoproteins from plasma? *c*) Does alcohol ingestion alter the absorption of cholesterol, the fecal excretion of cholesterol

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Abbreviations: VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; TG, triglyceride; CH, cholesterol; FFA, free fatty acid.

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and bile acids, or the lipid composition of gallbladder bile?

METHODS

Patients

Studies were carried out in twelve men on the Special Diagnostic and Treatment Unit (metabolic ward), Veterans Administration Medical Center, San Diego, California. Their clinical data are given in **Table 1.** Patients were excluded who had a history of either complete abstinence from alcohol, or of past hospitalization to treat complications of alcohol abuse. Patients also were excluded who had evidence of abnormalities of liver function (including BSP test), or who had any metabolic disease such as thyroid dysfunction or diabetes mellitus. Half of the patients (No. 1-6, Table 1) were obese (over 120% of ideal body weight); three had fasting hypertriglyceridemia, and two had clinical manifestations of atherosclerotic disease.

Metabolic ward conditions and diet

All patients remained hospitalized on the metabolic ward for 10 weeks. The first 2 weeks served as an "equilibration" period to allow for adjustment to the liquid-formula diet and to regulate dietary intake to establish weight maintenance. During this period the patients consumed a diet of mixed solid food and liquid formula (16). Fat supplied 40% of total calories, protein 15%, and carbohydrate 45%. Fat was mostly in the form of lard. The ratio of saturated:monounsaturated:polyunsaturated fatty acids was 1.0:1.2:0.2. Daily intakes of cholesterol were low (85-134 mg/day). The second (4-wk) period was the "control" period. Ten of the twelve patients continued the diet of the equilibration period while they underwent the studies described below. These ten then entered the third (4-wk) "test" period of alcohol-feeding during which time the studies were repeated. In this period 630 calories of alcohol (90 g in five divided doses daily) were given daily. In one patient (No. 9) the alcohol was substituted for liquid calories. For reasons discussed below, the alcohol was added to the isocaloric diet in the remaining nine patients. Two of the twelve patients (Nos. 4 and 10) entered the alcohol test period before the control period.

In the first patient (No. 9) substitution of alcohol for an equal portion of weight maintenance calories resulted in a fall in weight. In view of this response and a previous report that excess calories as alcohol do not cause weight gain (17), all subsequent patients were given alcohol in addition to weight maintenance calories. For seven of the eleven remaining individuals these additional alcohol calories did not cause weight gain. When weight gain was noted during alcohol feeding in three subjects (as described under Results, below), formula calories were adjusted to maintain constant weight.

Clinical monitoring

The patients were followed carefully on the metabolic ward by physicians and nurses throughout the study. They were restricted to the metabolic ward throughout the first 2 weeks of alcohol feeding, and at no time in the study were they allowed to leave the hospital. Routine blood testing upon admission included complete blood count, fasting blood glucose, bilirubin, serum protein, albumin, routine liver function tests including BSP, and hepatitis B antigens. Urinalysis was performed on all patients. Measurements were repeated at the end of each period.

TABLE 1. Clinical data

Patient No.	Age	Wt.	IBW[a]	% IBW	Baseline Lipids CH	Baseline Lipids TG	Fasting Plasma Glucose	Alkaline Phosphatase	SGOT	BSP
	yrs	*kg*	*kg*		*mg/dl*		*mg/dl*	*U/l*[b]	*U/l*[c]	%
1	32	105	73	144	207	376	95	75	20	4
2	22	95	73	131	171	214	82	80	21	4
3	59	102	78	131	202	174	86	51	15	4
4	60	79	64	123	180	96	98	71	17	3
5	56	87	72	121	214	175	93	55	11	3
6	62	83	69	120	278	801	92	43	14	4
7	60	85	72	118	179	109	94	72	13	2
8	39	75	65	116	186	166	73	68	17	5
9	47	78	70	112	171	199	92	68	18	3
10	35	74	69	106	220	360	81	100	15	4
11	52	63	73	86	167	134	87	76	12	3
12	49	56	66	84	200	220	49	78	26	4

[a] Abbreviations: IBW, ideal body weight; CH, total plasma cholesterol; TG, total plasma triglyceride.
[b] Normal range = 30-115 U/l.
[c] Normal range = 0-40 U/l.

Studies of cholesterol metabolism

During control and alcohol test periods patients were studied for the effects of alcohol on excretion of neutral steroids and bile acids and on absorption and synthesis of cholesterol. Absorption of cholesterol was assessed by a recently described technique from this laboratory (18). The determination depends on daily oral administration of [^{14}C]cholesterol and [^{3}H]β-sitosterol for 10 days. A comparison of the ratio of $^{14}C/^{3}H$ in feces and diet affords an index of percent cholesterol excreted, and absorption is calculated as (100% − % excreted). Measurements of excretion of neutral steroids and bile acids were carried out by routine sterol balance procedures developed for this purpose and involved lipid extraction of feces, separation of lipids by thin-layer chromatography, and analysis by gas–liquid chromatography (19, 20). Chromium (III) oxide (Cr_2O_3) and β-sitosterol were administered daily, and their recovery in feces served to correct for variations in fecal flow and sterol degradation, respectively (21, 22).

Plasma lipids and lipoproteins

Plasma lipids and lipoproteins were measured from three to ten times during control and alcohol feeding periods by routine Lipid Research Clinic (LRC) procedures. Blood was drawn from fasting patients into tubes containing EDTA and plasma was separated by centrifugation at 2500 rpm for 20 min at 4°C. An aliquot was taken for measurement of cholesterol (CH) and triglycerides (TG), and VLDL were floated by ultracentrifugation at d 1.006 g/ml for 14 hr. VLDL was isolated by tube slicing. LDL was then precipitated with heparin-manganese from the VLDL infranate; the heparin-manganese supernate contained HDL. Cholesterol and triglycerides were measured in plasma, HDL, and the d 1.006 g/ml infranate by Auto Analyzer II (23–25). VLDL-CH and VLDL-TG were obtained by difference between CH and TG in total plasma and the VLDL infranate; LDL-CH and VLDL-TG were estimated as the difference between VLDL infranate and HDL-CH and VLDL-TG.

VLDL-TG metabolism

Measurements of VLDL-TG transport were obtained during the last week of control and ethanol feeding periods in all twelve patients. During the test period ethanol was administered at the usual dose in addition to the usual formula administered for these studies. The methodology for these tests has recently been published (16). In brief, patients are placed on a fat free diet for 36 hr before the study while baseline carbohydrate and protein are continued as frequent (every 3 hr) small feedings of liquid formula. [2-^{3}H]Glycerol is then administered intravenously and plasma is sampled for 48 hr. Specific activity of VLDL-TG glycerol is determined and calculation of plasma VLDL-TG transport is carried out by multicompartmental analysis as previously described (16).

Chylomicron-TG metabolism

Clearance rates of chylomicron-TG were measured as described previously in this laboratory (26). For this method, safflower oil is infused into the duodenum at a constant rate (200 mg/kg per hr). Prior to infusion and after a 5-hr equilibration period, chylomicrons are separated from other lipoproteins by preparative ultracentrifugation through saline (1.6×10^6 *g-min* in a Beckman SW-41 rotor). During fat administration, plasma levels of chylomicron-TG rise and plateau by 5 hr. At this time, removal rates of chylomicron-TG should equal the input (200 mg/kg per hr). This assumes complete absorption of fat. From the removal rate and the increment in chylomicron-TG, the residence time of triglycerides in the chylomicron fraction can be calculated as the reciprocal of the fractional catabolic rate (FCR), where FCR = input of triglyceride ÷ plasma pool of chylomicron TG (mg). The residence time of chylomicron-TG can be expressed in units of minutes.

Postheparin lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) activities

Postheparin plasma was obtained from fasting patients during control and alcohol administration periods. Analyses were made on blood drawn 15 min after intravenous injection of 60 IU/kg sodium heparin (Riker Labs., Inc.). Samples were cooled immediately on ice and centrifuged at 4°C for 30 min at 480 *g*. The plasma was removed and recentrifuged at 750 *g*, again at 4°C. Samples were then immediately assayed or stored at −70°C up to 3 months before assay. LPL and HTGL activities were determined as described by Baginsky and Brown (27).

Biliary lipid composition

Samples of gallbladder bile were obtained repetitively during control and alcohol feeding periods. Gallbladder bile, obtained after stimulation of gallbladder contraction with fat, was analyzed for cholesterol, bile acids, and phospholipids as described previously (28). The lipid composition was expressed as percent saturation with cholesterol according to the criteria of Carey and Small, assuming a gallbladder concentration of 10% solids (29).

RESULTS

Clinical effects of alcohol

The dose of alcohol used in this study caused no untoward effects in any of the patients. The patients ap-

peared to be less active during the period of alcohol ingestion than during the control period, but none became overtly intoxicated. In none of the patients did liver function tests become abnormal during alcohol feeding.

Effects of alcohol on body weight

One aim of this study was to maintain a constancy of weight throughout all periods. In general, this aim was achieved: nine patients either gained or lost less than 1.5 kg (**Table 2**). Seven patients (Nos. 1, 2, 7, 8, 10, 11, 12) actually lost small amounts of weight when alcohol was added to weight maintenance calories; the mean weight loss for these seven was 0.85 kg (range = −0.1 to −1.9 kg). On the other hand, four obese patients (Nos. 3, 4, 5, 6) gained weight when alcohol was added to weight maintenance calories. Despite reduction of non-alcohol calories during the "test" period by 300 cal/day in patient 3 and by 380 cal/day in patient 6, these two patients gained 1.3 and 1.8 kg, respectively, during feeding of alcohol. One obese patient (No. 4) received alcohol in the first period, and on discontinuation of alcohol, his weight began to decline; consequently, his non-alcohol calories were increased by 200 cal/day and his weight remained constant thereafter.

Patient 9 was the first patient studied. After the control period, and upon substitution of alcohol for non-alcohol calories, he experienced a weight loss of 2.6 kg throughout the period. His was the greatest weight change experienced by any of the patients, and on the basis of his change, alcohol was added to baseline calories rather than substituted for them in the remaining volunteers.

TABLE 2. Weight changes during alcohol administration

Patient No.	Weight		Alcohol Minus Control
	Control	Alcohol	
	kg	*kg*	*kg*
1	105.2 ± 1.22 (24)[a]	103.8 ± 0.59 (25)	−1.4
2	95.4 ± 2.7 (26)	94.3 ± 0.34 (33)	−1.1
3[b]	101.7 ± 0.38 (31)	103.0 ± 0.60 (27)	+1.3
4[b]	79.4 ± 0.60 (27)	80.2 ± 0.52 (25)	+0.8
5[b]	86.9 ± 0.55 (35)	87.1 ± 0.50 (31)	+0.2
6[b]	82.7 ± 0.47 (25)	84.5 ± 0.67 (29)	+1.8
7	84.8 ± 0.74 (34)	84.3 ± 0.41 (34)	−0.5
8	75.2 ± 0.75 (32)	74.6 ± 0.77 (29)	−0.6
9[c]	77.8 ± 0.61 (20)	75.2 ± 0.55 (34)	−2.6
10	73.0 ± 0.49 (37)	73.6 ± 0.44 (31)	−0.3
11	62.6 ± 0.78 (34)	60.7 ± 0.42 (26)	−1.9
12	55.6 ± 0.50 (28)	55.5 ± 0.63 (28)	−0.1

[a] Mean ± SD (n).
[b] Non-alcohol calories were reduced during the alcohol test period or increased during the control period (when that followed the alcohol test period) in four patients to prevent excess weight gain or loss. Reductions were: from 3100 to 2800 calories/day in patient No. 3; from 2800 to 2600 calories/day in patient No. 5; and from 2330 to 1950 in patient No. 6. In patient No. 4 calories were increased from 2400 calories/day during the alcohol test period to 2600 during the (following) control period.
[c] Alcohol calories were initially substituted for rather than added to formula calories in patient No. 9. Calories in this patient were reduced from 2730 calories/day to 2091 calories/day when alcohol (90 g daily = 630 calories) was started.

Plasma lipids and lipoproteins

The effects of alcohol on plasma cholesterol and triglycerides and on lipoprotein lipids are summarized in **Table 3.** For the whole group, the feeding of alcohol was associated with small but statistically significant increases in both plasma lipids. A similar increase occurred in VLDL-CH and VLDL-TG. Five patients had a statistically significant increase in total triglycerides when tested as individuals; four of these were obese and three of these tended to gain weight during alcohol feeding.

Levels of LDL-CH and LDL-TG were unchanged by alcohol feeding, but concentratins of both HDL-CH and HDL-TG rose significantly with alcohol. All ten patients tested had a numerical increase in HDL-CH, and in seven the rise was statistically significant for the individuals.

Triglyceride metabolism

Transport of VLDL-TG was estimated in all patients (**Table 4**). Four patients (Nos. 2, 3, 4, 6) responded to alcohol feeding with at least a 45% increase in production of VLDL-TG and a resultant rise in VLDL-TG concentrations. All four of these patients were obese; in the remainder of the patients, alcohol feeding had no effect on production of VLDL-TG.

Clearance rates of chylomicron-TG were determined in ten patients before and during feeding of alcohol (Table 4). In four obese patients (Nos. 2, 3, 5, 6) alcohol prolonged the residence time in plasma of chylomicron-TG. Thus, delayed clearance of chylomicron-TG appeared to be related to enhanced production of VLDL-TG. In general, when alcohol did not stimulate production of VLDL-TG, clearance of chylomicron-TG was not retarded.

Measurements of postheparin lipolytic enzymes [hepatic triglyceride lipase (HTGL) and lipoprotein lipase (LPL)] were determined in the fasting state in six patients (Nos. 1, 2, 6, 9, 11, 12). Alcohol feeding had no effect on the activities of these enzymes (**Table 5**). For postheparin LPL, activity in the control period was 13.0 ± 5 μmol FFA/hr per ml, and was 12.0 ± 3 μmol FFA/hr per ml during alcohol administration. Activity of postheparin HTGL was 29.7 ± 16 μmol FFA/hr per ml for the alcohol-feeding period, vs. 31.3 ± 14 μmol FFA/hr per ml for the control. None of these differences was statistically significant.

Cholesterol and bile acid metabolism

The effects of alcohol on fecal excretion of neutral steroids and bile acids are presented in **Table 6.** Excretion of neutral steroids in the control period averaged 495

TABLE 3. Total plasma and lipoprotein cholesterol and triglyceride

Patient No.	Period	(n)[a]	Total CH	Total TG	Very Low Density Lipoprotein CH	Very Low Density Lipoprotein TG	Low Density Lipoprotein CH	Low Density Lipoprotein TG	High Density Lipoprotein Chol	High Density Lipoprotein TG
						mg/dl ± SD				
1	C	(5)	204 ± 28	340 ± 44	53 ± 8	267 ± 36	124 ± 21	50 ± 9	26 ± 7	24 ± 4
	ETOH	(3)	235 ± 10	391 ± 23	62 ± 2	318 ± 19	133 ± 19	42 ± 1	40 ± 4	29 ± 10
	Δ		31	51	9	51	9	−8	14[b]	5
2	C	(8)	184 ± 19	218 ± 39						
	ETOH	(8)	175 ± 17	349 ± 105						
	Δ		−9	131[b]						
3	C	(9)	205 ± 5	179 ± 19	32 ± 5	125 ± 17	130 ± 6	34 ± 2	43 ± 2	20 ± 3
	ETOH	(6)	207 ± 10	222 ± 18	43 ± 5	164 ± 16	117 ± 9	35 ± 3	46 ± 2	24 ± 3
	Δ		2	43[b]	11[b]	39[b]	−13[b]	1	3[b]	4[b]
4	C	(10)	183 ± 10	98 ± 10	14 ± 1	56 ± 6	126 ± 10	27 ± 3	44 ± 3	15 ± 3
	ETOH	(8)	225 ± 15	205 ± 29	39 ± 7	149 ± 25	139 ± 9	36 ± 2	48 ± 3	21 ± 2
	Δ		42[b]	107[b]	25[b]	93[b]	3[b]	9[b]	4[b]	6[b]
5	C	(3)	214 ± 6	175 ± 17	31 ± 5	122 ± 15	148 ± 8	32 ± 2	35 ± 4	22 ± 2
	ETOH	(6)	233 ± 6	285 ± 15	60 ± 4	218 ± 13	135 ± 7	39 ± 4	38 ± 6	27 ± 4
	Δ		19[b]	110[b]	29[b]	97[b]	−13	7[b]	3	5
6	C	(7)	285 ± 23	821 ± 116	163 ± 16	757 ± 110	99 ± 11	42 ± 7	23 ± 3	22 ± 3
	ETOH	(4)	308 ± 6	836 ± 110	176 ± 12	770 ± 111	100 ± 10	39 ± 8	31 ± 1	28 ± 4
	Δ		23	15	13	13	1	−3	8[b]	6[b]
7	C	(10)	179 ± 11	109 ± 19	15 ± 3	65 ± 15	125 ± 10	28 ± 6	38 ± 4	17 ± 6
	ETOH	(8)	183 ± 9	122 ± 11	17 ± 9	76 ± 9	120 ± 8	28 ± 1	45 ± 2	19 ± 2
	Δ		4	13	2	9	−5	0	7[b]	2
8	C	(6)	186 ± 18	166 ± 19	26 ± 6	113 ± 20	122 ± 19	30 ± 2	38 ± 2	23 ± 3
	ETOH	(6)	192 ± 13	175 ± 17	31 ± 5	122 ± 16	118 ± 12	32 ± 4	43 ± 3	22 ± 3
	Δ		6	10	5	9	−4	2	5[b]	−1
9	C	(6)	171 ± 10	186 ± 28						
	ETOH	(6)	171 ± 7	211 ± 35						
	Δ		0	25						
10	C	(6)	219 ± 5	363 ± 25	76 ± 9	276 ± 27	114 ± 12	56 ± 3	28 ± 2	31 ± 6
	ETOH	(7)	220 ± 10	382 ± 31	82 ± 13	285 ± 31	108 ± 9	62 ± 5	30 ± 3	34 ± 4
	Δ		1	46	6	9	−6	6[b]	2	3
11	C	(7)	166 ± 13	132 ± 20	13 ± 7	72 ± 16	111 ± 12	37 ± 3	41 ± 2	23 ± 4
	ETOH	(6)	180 ± 9	137 ± 23	16 ± 9	78 ± 20	119 ± 4	37 ± 4	45 ± 2	22 ± 4
	Δ		14	5	3	6	8	0	4[b]	1
12	C	(9)	216 ± 15	235 ± 28	46 ± 19	215 ± 69	143 ± 11	37 ± 4	32 ± 3	19 ± 3
	ETOH	(8)	229 ± 20	277 ± 45	41 ± 1	219 ± 32	159 ± 12	41 ± 6	35 ± 2	17 ± 3
	Δ		11	42[b]	5	+4	16	4	3	−2
Mean (± SD)	C		201 ± 32	252 ± 195	47 ± 45	222 ± 215	125 ± 14	38 ± 10	35 ± 7	21 ± 4
	ETOH		213 ± 38	300 ± 191	57 ± 47	258 ± 207	125 ± 17	39 ± 9	40 ± 6	24 ± 5
	Δ		12	48	10	36	0	1	5	3
P^c			<0.01	<0.005	<0.05	<0.02	N.S.	N.S.	<0.002	<0.05

[a] C, control; ETOH, alcohol feeding period; (n), number of analyses of CH and TG.
[b] $P < 0.05$ (Student's *t*-test).
[c] Paired *t*-test.

± 111 (SD) mg/day and with alcohol 521 ± 159 mg/day. Acidic steroid outputs were 448 ± 249 and 507 ± 505 mg/day for control and alcohol periods, respectively. Cholesterol balance was −836 ± 267 and −919 ± 422 mg/day for the same periods, respectively. None of the differences was statistically significant.

TABLE 4. Metabolism of VLDL-TG and chylomicron-TG

Patient No.	Period[a]	Plasma Volume	VLDL Lipids			VLDL TG Transport			VLDL-TG Residence Time	Chylomicron-TG Residence Time
			CH	TG	CH/TG					
				mg/dl		*mg/hr*	*mg/hr per kg*	*mg/hr per kgIBW*	*min*	*min*
1	C	3604	77	359	0.213	2471	23.7	33.8	218	
	ETOH	3602	90	389	0.233	2676	25.7	36.6	218	
2	C	3532	45	192	0.236	1248	12.9	17.0	226	1.7
	ETOH	3502	57	318	0.179	1793	19.1	24.5	258	25.7
3	C	3738	31	194	0.162	1508	14.8	19.4	200	6.2
	ETOH	3748	40	270	0.149	2408	23.3	31.0	175	16.0
4	C	3006		76		626	8.0	9.5	152	5.3
	ETOH	3036		233		1252	15.5	19.1	235	8.5
5	C	3345	27	142	0.187	817	9.4	11.5	242	17.8
	ETOH	3338	51	249	0.199	1003	11.7	14.2	358	40.9
6	C	3275	145	537	0.270	1477	17.0	21.1	495	12.7
	ETOH	3292	152	729	0.209	2256	26.8	32.2	442	40.7
7	C	3389	21	95	0.220	649	7.6	9.0	200	3.6
	ETOH	3379	27	135	0.203	826	9.8	11.4	230	4.0
8	C	3024	26	130	0.201	877	11.7	13.5	186	8.7
	ETOH	3012	32	168	0.188	688	9.3	10.6	306	9.7
9	C	3165	37	153	0.242	692	9.1	10.2	289	
	ETOH	3145	39	174	0.224	914	12.2	13.3	249	
10	C	3169	82	347	0.238	1474	19.9	21.2	310	5.0
	ETOH	3164	85	342	0.248	1331	18.1	19.2	337	6.3
11	C	2813	28	97	0.291	483	7.7	6.7	235	2.8
	ETOH	2768	15	70	0.214	370	6.0	5.1	218	8.8
12	C	2498	43	308	0.140	1123	20.2	17.1	285	9.4
	ETOH	2462	81	406	0.200	1080	19.7	16.4	385	11.1

[a] C, control; ETOH, alcohol feeding period.

Absorption of cholesterol was estimated in ten patients. Mean absorption was 44.5 ± 5 (SD) % during the control period and 46.7 ± 7 (SD) % during alcohol feeding (**Table 7**). This difference was not statistically significant.

Lipid composition of gallbladder bile was determined in nine patients. Overall, feeding of alcohol did not alter the composition of bile (**Table 8**). Four patients showed a decrease in saturation of bile with cholesterol; two had an increase; and three were unchanged. Saturation of gallbladder bile averaged 117 ± 27% in the control period and 114 ± 18% during alcohol feeding.

TABLE 5. Postheparin lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) in control and alcohol treatment periods

Patient No.	LPL		HTGL	
	Control	ETOH	Control	ETOH
	μmol FA/hr per ml			
1	16.2	13.6	28.6	35.5
2	16.7	11.2	35.8	37.0
6	8.5	8.2	55.9	50.5
9	19.3	13.3	13.0	13.3
11	10.8	15.3	14.2	15.0
12	6.5	10.1	31.2	36.8
Mean ± SD	13 ± 5	12 ± 3	30 ± 16	31 ± 14

DISCUSSION

Effects of alcohol on body weight

An unexpected finding in the first patient of this study was that substitution of alcohol calories for non-alcohol calories caused a progressive loss of weight. This observation substantiated the claim of Pirola and Lieber (17) that alcohol does not contribute to maintenance of body weight, and led us to alter the experimental design and add, rather than substitute, alcohol for baseline calories. In lean patients the consumption of additional alcohol calories did not produce weight gain. How can this lack of weight gain be explained?

Was the period of alcohol supplementation too short

TABLE 6. Fecal excretion of cholesterol and metabolites during control and alcohol test periods

Patient No.	Period[a]	Days (n)[b]	Cholesterol Intake	Fecal Steroid Excretion: Neutral Steroids	Acidic Steroids	Total Steroids	Cholesterol Balance
			mg/dl		*mg/day ± SD*		*mg/day ± SD*
1	C	32 (6)	120	466 ± 108	267 ± 49	733 ± 128	613 ± 128
	ETOH	11 (3)	134	663 ± 135	396 ± 61	1059 ± 186	925 ± 186
	Δ			−197[c]	−129[c]	−326[c]	−312[c]
2	C	25 (4)	120	520 ± 133	247 ± 129	767 ± 246	647 ± 246
	ETOH	26 (4)	120	400 ± 29	289 ± 65	689 ± 83	569 ± 83
	Δ			120	−42	78	78
3	C	30 (3)	133	451 ± 37	1129 ± 53	1580 ± 71	1447 ± 71
	ETOH	28 (4)	120	498 ± 131	1413 ± 110	1911 ± 230	1791 ± 230
	Δ			−47	−284[c]	−331	−344
4	C	17 (3)	103	643 ± 206	545 ± 94	1188 ± 249	1085 ± 245
	ETOH	13 (3)	103	940 ± 91	751 ± 115	1167 ± 1	1564 ± 1
	Δ			−297	−206	−479	−479
5	C	24 (4)	111	604 ± 70	297 ± 23	902 ± 69	791 ± 69
	ETOH	21 (4)	111	408 ± 40	349 ± 50	757 ± 75	646 ± 75
	Δ			196[c]	−52	145[c]	145[c]
6	C	30 (4)	103	363 ± 108	284 ± 65	647 ± 141	544 ± 141
	ETOH	22 (3)	103	417 ± 69	213 ± 56	630 ± 64	519 ± 64
	Δ			−54	71	17	17
7	C	29 (4)	111	509 ± 66	410 ± 58	919 ± 84	808 ± 84
	ETOH	27 (4)	111	596 ± 44	488 ± 44	1084 ± 10	973 ± 10
	Δ			−87	−78	−165[c]	−165
8	C	26 (4)	103	570 ± 120	516 ± 257	1086 ± 155	983 ± 155
	ETOH	21 (4)	103	468 ± 110	353 ± 85	821 ± 93	718 ± 93
	Δ			102	163	265[c]	265[c]
9	C	30 (6)	100	585 ± 299	293 ± 129	878 ± 330	778 ± 330
	ETOH	22 (4)	90	341 ± 37	267 ± 100	607 ± 125	517 ± 125
	Δ			244	26	271	261
10	C	28 (4)	107	594 ± 119	493 ± 43	1087 ± 151	980 ± 151
	ETOH	26 (3)	107	523 ± 69	499 ± 52	1022 ± 67	915 ± 67
	Δ			71	−6	65	65
11	C	47 (6)	94	320 ± 61	622 ± 132	941 ± 107	847 ± 107
	ETOH	18 (3)	94	579 ± 165	777 ± 243	1356 ± 406	1262 ± 406
	Δ			−259	−155	−415	−415
12	C	19 (4)	85	326 ± 29	270 ± 29	596 ± 16	511 ± 16
	ETOH	20 (4)	85	424 ± 98	293 ± 64	717 ± 35	632 ± 35
	Δ			−98	−23	−121[c]	−121[c]

[a] Period: C, control; ETOH, alcohol 90 g/day, added to or substituted for (one patient, #9) baseline formula calories; Δ, difference, control − alcohol.
[b] (n), Number of determinations. Stools from this period were combined into three to six pools. The quotient is the average number of days per pool.
[c] Alcohol period significantly different from control ($P < 0.05$ or less).

to have detected reliably an increase in adipose tissue weight? The ingestion of an extra 630 calories per day for 30 days should have produced an increment of 5.25 pounds (2.39 kg). A weight gain of this magnitude should have been noted, and our inability to detect a change probably cannot explain the lack of weight gain. Therefore we might ask whether there could have been a simultaneous increase in adipose tissue weight and a decrement in body water, so that no net change in body weight occurred. This is a possibility; alcohol is known

TABLE 7. Cholesterol absorption

Patient	Control (I)	Alcohol (II)	Difference (II − I)
	% (n)[a]	% (n)[a]	%
1	45 (3)	53 (3)	+8
2	42 (4)	33 (2)	−9
3	41 (3)	39 (2)	−2
4	40 (4)	44 (4)	+4
6	48 (4)	53 (3)	+5
7	47 (4)	48 (4)	+1
8	36 (3)	49 (3)	+13
10	45 (3)	52 (2)	+7
11	54 (3)	55 (2)	+1
12	47 (4)	41 (3)	−6
Mean ± SD	44.5 ± 5	46.7 ± 7	2.2

[a] %, % Absorption; n, number of determinations.

to induce a transitory diuresis (30, 31), and a net reduction in body water could have occurred. A longer duration of alcohol feeding might be needed to prove the presence or absence of adipose tissue gain. Another possible reason for lack of weight gain is malabsorption of calories. In previous studies of patients with chronic alcoholism, it is difficult to separate the effects of alcohol from those of malnutrition; the latter frequently accompanies alcohol abuse and also is associated with malabsorption (32). The influence of alcohol on absorption of various nutrients is no exception: early work demonstrated that alcohol interfered with absorption of thiamine, folic acid, vitamin B12, and d-xylose (33–35). In another study, in which alcohol provided 46 to 66% of calories, an adequate diet and folic acid supplements prevented malabsorption of d-xylose and fat (36).

Interference with nutrient absorption thus cannot be implicated in the calorie wastage apparently induced by alcohol consumption. This has led investigators to evaluate the possibility that chronic alcohol ingestion leads to a hypermetabolic state not unlike that induced by hyperthyroidism or thyroxine administration (37). In rats, chronic treatment with alcohol increases oxygen consumption, and this effect is thought to result from increased hepatic mitochondrial sodium-potassium ATPase activity. The rise in ATPase activity can account for the rise in oxygen consumption in these animals (37). Thus, further studies on effects of alcohol on energy consumption in man might prove revealing.

Finally, the apparent lack of weight gain during alcohol supplementation seemed to be related to the initial weight. Most patients who failed to gain weight with addition of alcohol were nonobese. Previous investigators have observed that enhancement of caloric intake does not necessarily cause weight gain in nonobese people. The reason for this is unknown. Therefore, we do not know whether alcohol is unique among nutrients in its failure to cause weight gain in nonobese subjects. Pirola and Leiber (17) showed that addition of alcohol calories to a baseline diet was not as effective in causing weight gain as was the addition of an equal amount of carbohydrate calories. However, they added a great deal more ethanol (2000 Kcal per day) than we did. In this study only 63% Kcal of alcohol was administered and this accounted for an increase of, on average, only 24% above baseline calories (range 20–30%). In the present study the weight gain noted in four obese patients given alcohol provides a striking contrast to results in nonobese subjects. Whether obese patients are more likely than nonobese subjects to

TABLE 8. Biliary lipid composition

Patient No.	Control				Ethanol			
	Lipid Composition[a]			Bile Saturation[b]	Lipid Composition[a]			Bile Saturation[b]
	CH	BA	PL		CH	BA	PL	
	moles%			%	moles%			%
1	9.2	67.3	23.6	132 (2)	8.8	66.3	25.0	114 (2)
2	5.9	76.6	17.7	96 (3)	6.7	74.1	19.2	101 (3)
3	8.9	69.5	22.2	114 (4)	9.3	72.2	18.5	152 (3)
4	10.7	70.1	19.2	158 (4)	9.0	71.5	19.5	133 (2)
5	10.0	66.7	23.3	133 (3)	7.6	72.0	20.4	110 (3)
6	9.3	59.7	30.9	112 (1)	8.4	67.0	24.6	109 (5)
7	6.1	7.3	19.6	93 (1)	6.1	76.0	18.1	99 (2)
9	9.6	68.0	22.4	141 (4)	6.5	74.0	19.4	106 (5)
11	4.6	76.7	18.7	73 (2)	5.9	77.3	16.8	99 (1)
Mean ± SD				117 ± 27 (9)				114 ± 18 (9)

[a] Abbreviations: CH, cholesterol; BA, bile acids; PL, phospholipids.
[b] Percent saturation of gallbladder with cholesterol according to Carey and Small (29) assuming 10% solids for (n) samples.

gain weight with a given increment in calories regardless of their source would seem worthy of further study.

Effects of alcohol on plasma lipids and lipoproteins

Very low density lipoproteins and chylomicrons. Alcohol is known to enhance concentrations of hepatic triglycerides. This increase is due to an increased synthesis of triglycerides in the liver (38). The actions of alcohol on plasma triglycerides are more variable and depend upon the dose of alcohol administered, the underlying diet, the genetic predisposition to hypertriglyceridemia, and the duration of administration (1–10). In a previous study (4) for instance, the increase in plasma levels of triglycerides following the administration of very large amounts of alcohol was only transitory. Likewise, administration of smaller amounts of alcohol, such as described in the present study and within the boundaries of social drinking, resulted in a hypertriglyceridemic response in individuals with type 4 hyperlipoproteinemia but not in normal persons (1–3). In our own study the response to alcohol ingestion was also variable and appeared to depend upon both underlying hypertriglyceridemia and initial body weight. Only one of six nonobese individuals developed significant hypertriglyceridemia during the consumption of alcohol, whereas four of six individuals whose body weight exceeded 120% of ideal showed a significant increase in plasma triglycerides over control values (Table 3). Alcohol feeding was continued for 4 weeks, and in all patients, plasma triglyceride had returned to control values at the end of this period of alcohol feeding; this observation therefore seems in agreement with the experience of previous investigators. Experiments carried out during the early phase of alcohol feeding have shown increased synthesis of VLDL-TG in human volunteers (13, 14). To our knowledge, however, synthesis of VLDL-TG after longer-term alcohol feeding has not been studied previously. Our studies of the latter type showed that changes in production of VLDL-TG often occur but not invariably. All six obese patients had a rise in production rates of VLDL-TG after a month of alcohol feeding. In contrast, nonobese subjects generally did not demonstrate this response. Therefore, as with the effects of obesity on both the body weight response and the plasma triglyceride response to alcohol feeding, an increased synthesis of VLDL-TG was confined mainly to obese patients.

The rise in plasma triglycerides in several of the subjects during alcohol feeding was due mainly to a stimulation of VLDL-TG synthesis. Another possibility is that alcohol reduces the clearance of triglyceride-rich lipoproteins. We could demonstrate no effects of alcohol on activities of postheparin LPL or HTGL; in another report, an increase in activities of these enzymes was noted (39). A reduction in clearance rates of chylomicron-TG during alcohol administration occurred in several of our patients. This change however was primarily in obese patients who also had enhanced synthesis of VLDL-TG. Delayed clearance of chylomicron-TG therefore might be explained by competition for removal of excess VLDL-TG (40) and not necessarily by induction of a clearance defect. Competition seems particularly likely in view of the fact that most nonobese subjects had no delay in chylomicron clearance with alcohol feeding. Also, alcohol had no consistent effect on the residence time of VLDL-TG. Although four patients (Nos. 4, 5, 8, and 12) had prolongation of the residence time of VLDL-TG during alcohol administration, the absence of this effect in the remaining patients, together with the absence of any demonstrable effect on activities of post-heparin LPL or HTGL, makes unlikely the induction of a definite defect in clearance for plasma triglycerides by alcohol.

Low density lipoproteins. A previous epidemiologic report noted an inconsistent reciprocal relationship between alcohol intake and plasma LDL-CH (12). This might imply that alcohol per se lowers LDL. In the present study, however, no such effect was seen. For the group as a whole, no changes in levels of LDL-CH were observed.

High density lipoproteins. Several epidemiological studies suggest that alcohol raises plasma HDL-CH (10–12). This effect also has been demonstrated in experimental animals (41). To our knowledge, however, it has not been shown that controlled administration of alcohol raises HDL concentrations in man under metabolic ward conditions. In the current study all of the patients showed a rise in HDL-CH, and the increase for the whole group was statistically significant. Most patients also had a small increase in HDL-TG. Thus, despite the fact that alcohol raised triglycerides, which usually is associated with decrease in HDL-CH, there was instead a definite and paradoxical increase in HDL-CH. The mechanism for this rise in HDL-CH induced by alcohol remains to be determined.

Cholesterol metabolism. Studies in experimental animals suggest that alcohol has a variety of effects on cholesterol metabolism (41), but we know of only one previous study on effects of alcohol on cholesterol metabolism in man; in this study (15), three hypertriglyceridemic and four normolipidemic individuals were investigated during a control period and during a period in which ethanol (about 37% of calories) was substituted for carbohydrate or fat. In these patients there was no consistent effect on synthesis or excretion of cholesterol, except that the proportion of steroid excreted as bile acids increased during alcohol feeding in the three hyperlipidemic subjects.

CONCLUSIONS

In summary, this investigation defines certain differences in the metabolic response to alcohol that appeared

to be related to body weight. Overweight individuals responded to alcohol feeding by increasing their body weight, by transient increases in VLDL-TG levels, and by an increase in VLDL-TG production. Concomitantly, these individuals had a reduction in clearance of chylomicron-TG that was most likely the result of competition for LPL with VLDL-TG rather than a reduction in LPL. These metabolic responses of the obese were not noted in lean individuals who did not gain weight when fed alcohol and in whom metabolism of triglyceride-rich lipoproteins was unaffected. In spite of the rise in TG levels in overweight individuals, alcohol feeding caused a paradoxical increase in levels of HDL-CH in overweight as well as in lean subjects. Alcohol feeding resulted in no changes in levels of LDL-CH, although we cannot rule out the possibility of an increased flux of LDL. Furthermore, we could not detect changes in the metabolism of either cholesterol or bile acids, and alcohol feeding did not cause a tendency for increased saturation of gallbladder bile. This study suggests that the most adverse metabolic effects of alcohol are in obese subjects, who already are at increased risk in other ways.

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