The Pattern of Serum Triglyceride Fatty Acids in Laennec's Cirrhosis

J. F. SULLIVAN, MD, M. KELLY, MD, and N. SUCHY, BS

The pattern of fatty acids in fasting serum triglycerides has been examined in 15 patients with Laennec's cirrhosis. Levels of triglycerides over 170 mg/100 ml were found in 9 of the 15. In each cirrhotic patient, regardless of the triglyceride level, a relative decrease in linoleic acid was found. The data suggest a relative deficiency of this dietary derived fatty acid which may play a role in abnormalities of serum and hepatic triglycerides found in alcoholic cirrhotics.

ELEVATION of the fasting serum triglyceride level has been described in both normal and alcoholic subjects following the prolonged ingestion of alcohol.[1] In patients with Laennec's cirrhosis and pancreatitis, fasting triglyceride levels are also elevated without the ingestion of alcohol.[2] The descriptions of these hyperlipemias have indicated increases in triglycerides, β-lipoproteins, cholesterol, and phospholipids.[3–6] Serum free-fatty-acid levels after alcohol ingestion have been variously reported as decreased,[6] unchanged,[7] or dependent on serum alcohol levels.[5] Increased hepatic fatty acid and triglyceride synthesis[8] and decreased lipoprotein lipase activity[4, 9, 12] have been incriminated as contributing to the hyperlipemia.

While the fatty acid distribution within the triglyceride portion has been studied in normals and in noncirrhotic hypertriglyceridemia patients,[10] relatively little study has been given to this partitioning in cirrhotic patients either with or without hypertriglyceridemia. The present study, initiated to investigate this problem, describes the triglyceride fatty acid composition 12 hr after ingestion of the last prior meal in patients with alcohol liver disease not complicated by pancreatitis and compares this with the triglyceride content and fatty acid composition encountered in control subjects. A positive correlation of hypertriglyceridemia with elevated fasting blood sugar was noted as well as a distinct difference is the linoleic component of the triglyceride fatty acids.

MATERIALS AND METHODS

A total of 15 patients were studied during hospitalization for treatment of hepatic disease secondary to alcoholism. Varying degrees of hepatic cirrhosis

From the Medical Service, Creighton University School of Medicine, and Veterans Administration Hospital, Omaha, Neb.

Supported in part by a Grant from Hartford Foundation.

Address for reprint requests: Dr. Sullivan, V. A. Hospital, 4101 Woolworth Ave, Omaha, Neb 68105.

were demonstrated in each at autopsy or by liver biopsy. At 8 AM following a 12-hr fast, blood specimens were drawn for serum lipid and other analysis. Blood was drawn between the fourth asd sixth day of hospitalization. Total serum triglycerides were determined by the method of Van Handel and Zilversmit,[11] cholesterol and blood sugar by autoanalyzer. The serum lipids were separated by thin layer chromatography. The triglyceride fraction was saponified, esterified, and the fatty acid pattern determined by gas-liquid chromatography. Serum amylase and hepatic function tests were determined by routine laboratory procedures. Serum triglyceride content and TRG fatty acid patterns were determined after a comparable fast in 34 healthy male medical students and house officers, and these constitute our control values. Fasting values above 160 mg/100 ml, serum triglyceride have been considered as hypertriglyceridemia on the basis of the values found in previous studies.[12]

RESULTS

The serum triglyceride level, fasting blood sugar, and degree of hepatic dysfunction of the 15 cirrhotic patients is shown in Table 1. Serum amylase and lipase were normal in all, presumably ruling out pancreatitis. Hypertriglyceridemia of mild degree ranging between 170 and 314 mg/100 ml occurred in 9 of the 15. In the patients with serum albumin greater than 3.0 g/100 ml, 6 of 7 had elevated triglycerides, a distinctly higher incidence than in those with serum albumin lower than 3.0 g/100 ml where only 3 of 7 had hypertriglyceridemia. The general clinical condition of the cirrhotics with low serum

TABLE 1. LABORATORY EVALUATION OF CIRRHOTIC PATIENTS

Cirrhotic patient (No.)	*Total triglyceride*	*Cholesterol*	*Fasting blood sugar*	*Bilirubin*	*Amylase*	*Albumin*	*Blood urea nitrogen*
Normal value	<160	150–250	<100	< 1.2	80–180	3.5–5.5	10–20
1	98	121	110	15.0	59	2.7	45
2	98	152		12.0	136	2.7	140
3	105	140	288	1.8	N	2.9	29
4	120	200	89	3.0	N	2.8	7
5	139	233	100	1.0	113	3.4	14
6	160	189	150	6.0	35	2.9	—
7	170	250	92	1.0	N	—	N
8	176	144	160	11.0	N	2.8	23
9	191	129	64	1.0	114	3.5	0
10	212	109	226	10.4	31	3.0	40
11	242	—	113	1.0	165	3.77	91
12	282	163	116	9.0	N	3.0	
13	284	246	115	1.0	137	3.5	6
14	309	110	108	20.5	184	2.1	48
15	314	584		9.0	130	3.8	7

All values are stated in mg/100 ml, except amylase which is in Somogyi units.

TABLE 2. COMPARISON OF CONTROL SERUM TRIGLYCERIDE FATTY ACIDS* WITH CIRRHOTIC

No. of patients	*Groups*	*16:0* (%)	*16:1*	*18:0*	*18:1*	*18:2*	*20:0 18:3 22:0*	*20:4*	*24:0*
19	Normal lipemia controls	29.6	4.6	7.4	35.7	14.1	3.6	2.8	2.1
	Mean TG 110 ± 28	± 5.4	± 1.1	± 1.8	± 6.5	± 4.8	± 1.0	± 1.3	± 1.4
15	Hyperlipemia controls	26.4	4.3	6.0	38.1	18.8	3.1	1.9	1.3
	Mean TG 215 ± 47	± 4.4	± 1.6	± 1.2	± 3.1	± 4.8	± 1.1	± .8	± 1.1
34	All controls	28.2	4.5	6.8	36.7	16.2	3.4	2.4	1.8
	Mean TG 157 ± 64	± 5.3	± 1.7	± 1.7	± 5.3	± 5.3	± 1.4	± 1.2	± 1.3
15	Patients	30.0	6.8	7.2	42.2	8.2	2.3	1.4	1.4
	Mean TG 193 ± 77	± 2.1	± 1.4	± 1.8	± 4.3	± 2.6	± 1.1	± 0.4	± 1.1
	p values†	NS	<.001	NS	<.001	<.001	<.01	<.01	NS

* Mean ± standard deviation.

† *p* values for all controls group vs patients.

albumin indicated a more severe degree of hepatic failure. Hypertriglyceridemia was associated with elevation of the fasting blood sugar in five instances, while elevated fasting blood sugar without triglyceride elevation occurred in only 2 patients. However, these apparent correlations between serum TRG, blood sugar, and low albumin is not certain due to the small numbers of patients. Elevation of bilirubin above 3 mg/100 ml occurred in nine of the cirrhotics but was independent of the triglyceride level. Five of the cirrhotic patients had BUN elevation ranging between 45 asd 140. Three had elevated triglycerides, and two did not. Total cholesterol levels did not correlate with TRG levels in the entire group of cirrhotics, nor did they correlate with serum albumin values.

In Table 2, a separate comparison is made between the cirrhotic patients and the controls, with fasting triglyceride levels above and below 160 mg/100 ml. The fatty acid triglyceride composition in the control subjects is similar to values previously described.[10, 13] Differences in the 18:2, 16:1, and 18:1 fractions between controls and cirrhotics are clearly most significant, 18:2, linoleic acid having a mean value of 8.22% in the cirrhotics as opposed to 16.2% is the normals. Although the percentage contribution of 16:0, 16:1, 18:0, and 18:1 was increased in the cirrhotics over the normals, only the 18:1 made a significant contribution. Inasmuch as the values are percentages of the total triglyceride fatty acids, the increases noted presumably are secondary to the lowering of the linoleic fraction. It is of interest that the 18:2 component of the triglyceride fatty acids is significantly higher ($p < .01$) in the controls with elevated triglyceride levels than in the controls with normal triglycerides. This suggests the increased triglyceride is of dietary origin.

In Table 3, the individual and mean TRG fatty acid values are shown for the cirrhotic patients, and these are compared to control subjects. It is evident that the depression of the 18:2 component of the triglyceride fatty acids is present in both the normal and hypertriglyceridemia cirrhotic patients.

DISCUSSION

In this study of 15 patients with varying degrees of Laennec's cirrhosis, several observations were made which confirm earlier studies. The triglyceride levels were elevated in 60% of the cirrhotics studied. This figure is appreciably higher than reported by others and in previous studies from this laboratory. Undoubtedly, this is a result of establishing 160 mg/100 ml of triglyceride as a maximum normal fasting value. While this fasting level is consistent with that of most observed, and has been accepted by us following extensive study of subjects without abnormalities of lipid metabolism,[13] it should be noted that nearly 50% of the controls (male medical students and house officers) in this study exceeded the 160 mg/100 ml level for fasting triglyceride.

TABLE 3. FASTING FA DATA CIRRHOSIS

		FA (%)							
No. of patients	*Total TG*	*16:0*	*16:1*	*18*	*18:1*	*18:2*	*20:0 18:3 22:0*	*20:4*	*24:0*
1	98	29.1	5.7	10.6	30.6	7.3	5.0	1.4	4.3
2	98	29.7	7.0	11.1	38.7	5.7	3.2	1.6	2.8
3	105	29.4	6.1	7.1	42.3	7.6	3.7	2.1	1.5
4	122	27.8	10.4	6.6	41.0	9.1	2.3	1.5	1.3
5	139	31.8	4.6	7.0	44.2	8.1	1.8	1.2	1.3
6	161	26.5	6.0	9.4	43.8	6.6	2.8	2.2	1.8
7	170	34.1	7.1	7.1	39.8	7.2	2.1	1.8	0.9
8	176	31.1	7.4	6.5	46.9	5.0	1.3	0.7	1.3
9	191	30.6	5.4	6.1	45.2	8.5	1.7	1.0	1.4
10	212	28.2	6.1	6.4	39.5	12.7	3.1	1.8	2.2
11	242	28.9	5.5	7.2	34.3	13.9	2.7	1.3	0.4
12	282	28.4	8.3	5.2	50.3	5.4	1.0	1.0	0.4
13	284	33.2	7.8	5.4	40.6	10.1	1.3	1.2	0.3
14	309	31.0	6.9	6.8	47.4	5.2	1.2	0.8	0.8
15	314	30.6	7.1	5.9	43.2	10.0	1.2	1.6	0.5
Mean ± SD for 15 patients	193 ±77	30.0 ± 2.1	6.8 ± 1.4	7.2 ± 1.8	42.2 ± 4.3	8.2 ± 2.6	2.3 ± 1.1	1.4 ± 0.4	1.4 ± 1.1
Mean ± SD for 34 controls	157 ±64	28.2 ± 5.3	4.5 ± 1.7	6.8 ± 1.7	36.7 ± 5.3	16.2 ± 5.3	3.4 ± 1.4	2.4 ± 1.4	1.8 ± 1.3

Bilirubin levels were not related to the degree of lipemia in contradistinction of the study of Phillips.[3]

A tendency toward elevated fasting blood sugar and impaired tolerance to glucose in cirrhotic patients is well known.[14] In this small series, 50% of the patients had elevated blood sugars, and the majority of these also demonstrated hypertriglyceridemia. There was no evidence that pancreatitis, which often accompanies cirrhosis and may result in glucose intolerance, was present in these patients.

The marked diminution of 18:2 fatty acid component, which was present regardless of degree of triglyceridemia is of great interest since this fatty acid must be obtained from dietary sources, and its relatively low value suggests a relative deficiency. Such deficiency is not unexpected in a group of cirrhotics where fat intake may be impaired. Experimental dietary deficiency of essential fatty acids[15] in rats produces increased hepatic triglycerides and phospholipids, but increased plasma free fatty acid content. A greater rate of secretion of triglyceride from the liver and decreased triglyceride content in the low density lipoprotein serum faction occurs.

The relative deficiency of linoleic acid may have additional significance due to the fact that 18:2 is a functional component of phospholipid with a consequent role in fat transport. If such a deficiency existed, then it might be manifested not only by a relative deficiency in the serum TRG when these

are elevated, but also in a decrease in the ability to remove TRG from the liver, secondary to impaired phospholipid formation. Thus a combination of fatty liver and hypertriglyceridemia, commonly found in alcoholic cirrhotics, might in part result from a deficiency of essential fatty acid, in which case the relative deficiency of 18:2 might be expected in the serum TRG.

Dietary inadequacy of linoleic acid may also contribute to hypertriglyceridemia by a diversion of fatty acids from oxidative pathways.[10] A further effect of linoleic acid may arise from its spatial configuration as suggested by Spritz,[16] a decrease in linoleate content resulting in a disproportionate increase in other saturated fatty acids.

REFERENCES

1. Lieber, C. S., Jones, D. P., Mendelson, J., and DeCarli, L. M. Fatty liver, hyperlipemia, and hyperuricemia produced by prolonged alcohol consumption, despite adequate dietary intake. *Trans Ass Amer Physicians 76:*289-301, 1963.
2. Sullivan, J. F., Swartz, M. J., and Robertson, P. R. Hyperlipemia in Laennec's cirrhosis. *Amer J Med Sci 246:*109, 1963.
3. Phillips, G. B. Lipid composition of serum in patients with liver disease. *J Clin Invest 39:*1639, 1960.
4. Losowsky, M. S., Jones, D. P., Davidson, C. S., and Lieber, C. S. Studies of alcohol hyperlipemia and its mechanism. *Amer J Med 35:*794, 1963.
5. Schapiro, R. H., Drumney, G. D., Scheig, R., Mendelson, H. H., and Isselbacker, K. J. Abnormalities of lipid transport accompanying prolonged alcohol ingestion in man. *Gastroenterology 44:*849, 1963.
6. Jones, D. P., Losowsky, M. S., Davidson, C. S., and Lieber, C. S. Effects of ethanol on plasma lipids in man. *J Lab Clin Med 62:*675, 1963.
7. Nestel, P. J., and Hirsch, E. Z. Mechanism of alcohol-induced hypertriglyceridemia. *J Lab Clin Med 66:*357, 1965.
8. Lieber, C. S., and Schmid, R. The effect of ethanol on fatty acid metabolism: Stimulation of hepatic fatty acid synthesis in vitro. *J Clin Invest 40:*394, 1961.
9. Datta, D. V. The mechanism of low post heparin plasma lipolytic activity (PHLA) in patients with cirrhosis of the liver. *Proc Soc Exp Biol Med 112:*1006, 1963.
10. Nichaman, M. Z., Sweeley, C. C., and Olson, R. E. Plasma fatty acid in normolipemia and hyperlipemic subjects during fasting and after linoleate feeding. *Amer J Clin Nutr 20:*1057, 1967.
11. Van Handel, E., and Zilversmit, D. B. Micromethod for the direct determination of serum triglycerides. *J Lab Clin Med 50:*152, 1957.
12. Swartz, M. J., Brewster, A. C., and Sullivan, J. F. Fat transport in cirrhosis. *Amer J Med Sci 252:*105, 1966.
13. Luddy, F. E., Barford, R. A., Riemenschneider, R. W., and Evans, J. D. Fatty acid composition of component lipids from human plasma and atheromas. *J Biol Chem 232:*843, 1956.
14. Megyesi, C., Samols, E., and Marks, V. Glucose tolerance and diabetes in chronic liver disease. *Lancet 2:*1051, 1967.
15. Sinclair, A. J., and Collins, F. D. Fatty liver in rats deficient in essential fatty acids. *Biochim Biophys Acta 152:*498, 1968.
16. Spritz, N., and Mishkel, M. A. Effects of dietary fats on plasma lipids and lipoproteins: An hypothesis for the lipid lowering effect of unsaturated fatty acid. *J Clin Invest 48:*78, 1969.