Increased Concentration of Free Fatty Acids in Liver Disease.*† (26428)

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Plasma free fatty acids (FFA), although quantitatively small, may be an important form of fat transport from adipose tissue to other tissues for oxidative metabolism(2-4). The turnover is rapid(5,6) and plasma concentrations are affected by the nutritional state and certain hormones. Plasma FFA concentrations appear to be primarily regulated by the rate of their release from peripheral adipose tissue and have been correlated with factors affecting peripheral glucose or non-fat calorie utilization(4,7,8). The demonstration of decreased peripheral glucose utilization in cirrhosis(9), in addition to the decreased hepatic oxidation of fat noted in animals on protein deficient diets(10), has suggested that patients with cirrhosis may have abnormal FFA metabolism.

The response of plasma FFA to fasting in patients with acute and chronic liver disease is reported here.

Methods. Plasma FFA was determined by the method of Dole(2), and ketones by the method of Greenberg and Lester(11) as modified by Boshell *et al.*(12). All determinations were made after an 11-16 hour fast except for 3 patients with hepatic coma who were receiving I.V. glucose or oral carbohydrate at regular intervals throughout each 24 hours.

Plasma FFA concentrations were determined in a group of 27 male and 7 female alcoholics hospitalized with cirrhosis. This group comprised 20 patients considered to have chronic cirrhosis by clinical and laboratory evaluation and 14 with active disease, including 6 with jaundice, 3 with jaundice and hepatic coma or pre-coma, and 5 with episodic stupor (a chronic neuropsychiatric disorder associated with stable liver function, increased portal collateral circulation, and intermittent hyperammoniemia). Ascites was present in 7 patients in the chronic group and 7 of those with active disease.

Twenty-eight determinations of FFA concentration were made in 13 male and 15 female subjects without cirrhosis demonstrable by clinical or laboratory means, including 13 ambulatory normals and 15 patients hospitalized for other causes (acute alcoholism, biopsy-proven fatty liver, gastroenteritis, peptic ulcer, chronic bronchitis, pancreatic islet cell adenoma, epilepsy and idiopathic hirsutism).

Blood ketones were determined in 13 of the patients with cirrhosis (4 with jaundice) and in 13 without cirrhosis.

Results. Plasma FAA concentrations after 11-16 hours of fasting are shown in Fig. 1. FAA concentration in 28 subjects without cirrhosis was between 0.27 and 1.27 meq/l, with a mean of 0.73 meq/1 (± 0.04 S.E.M.). No correction was made for obesity or diet previous to the fast. Bierman *et al.*(13) reported plasma FAA concentrations of 0.57 meq/1 for normal fasting non-obese subjects and concentrations of 0.86 meq/1 for normal fasting obese subjects without glycosuria; however, the length of fast was not noted. Dole(2) lists normal overnight fasting FAA concentrations of 0.5-0.9 meq/1 and observed an increase with continued fasting.

Twenty patients with chronic cirrhosis of the alcoholic had FAA concentrations ranging from 0.46-1.13 with a mean of 0.88 meq/1 (±0.04 S.E.M.). The presence of ascites could not be correlated with FAA concentrations. Fourteen patients with active cirrhosis had concentrations ranging from 0.37-1.82 with a mean concentration of 1.27 meq/

* This work was supported in part by U. S. Army Medical Research and Development Command, Dept. of the Army, in part by grants from Nutrition Foundation, Inc., New York, and Merck Sharpe & Dohme, West Point, Pa., to Harvard Univ.

† Presented in part to Am. Soc. for Clin. Invest., May 1959 (1).

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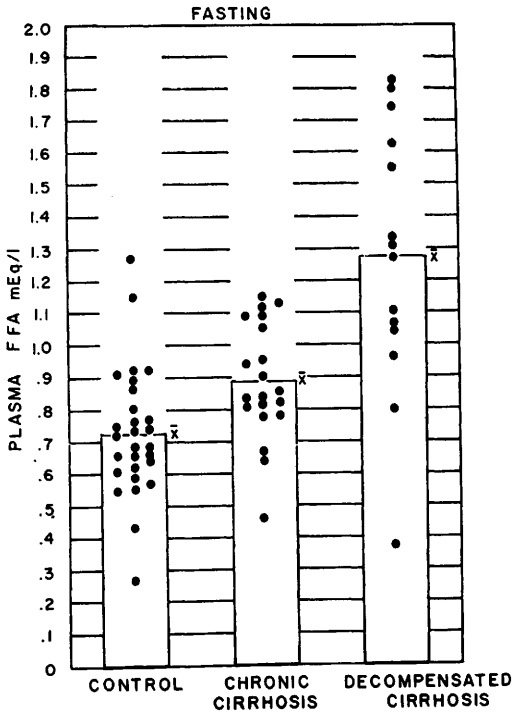

FIG. 1.

(±0.11 S.E.M.). Abnormally elevated as well as abnormally depressed FAA concentrations were found in the patients with jaundice. All patients with hepatic coma or episodic stupor had FAA concentrations above 0.9 meq/1 (Fig. 1). Comparison of the chronic and active cirrhosis patients (Student's t-test) revealed p value less than 0.001, indicating a high degree of significance of the differences between the mean values; although there is considerable overlap of the concentrations. (Fig. 1).

Blood ketone determinations ranged from 0.9 mg/100 ml to 3.7 mg/100 ml with a mean of 2.10 mg/100 ml (±0.27 S.E.M.) for 13 persons without cirrhosis while 13 patients with cirrhosis had concentrations ranging from 0.9-3.4 with a mean of 1.91 mg/100 ml (±0.36 S.E.M.). Four of these patients had jaundice and the concentration in these patients ranged from 0.9-3.4 with a mean of 1.70 mg/100 ml (Fig. 2). Recant(14), using the Greenberg-Lester method, reported a mean of 2.28 mg/100 ml (±0.47 S.E.M.) for non-hospitalized subjects without liver disease and 2.06 mg/100 ml (±0.47 S.E.M.) for hospitalized controls.. Mean concentration reported by Recant for patients with cirrhosis was 0.9 mg/100 ml (±0.22 S.E.M.) with a range of 0.00-2.08 mg/100 ml which was roughly correlated with severity of cirrhosis.

Discussion. Elevated plasma FFA concentrations have been reported in obesity(13), diabetic acidosis(13), hyperthyroidism(15), following prolonged fasting, after adrenalin and growth hormone injection(2,3,16) and in carbon tetrachloride poisoning in dogs(17). Conditions associated with decreased glucose utilization as well as those associated with loss of fat from fat depots appear to have elevated plasma FFA concentrations. The elevation of fasting FFA concentrations in active cirrhosis reported here is similar to levels described in diabetic ketosis(13) and suggests an abnormality in FFA metabolism and/or transport which may be related to the abnormal carbohydrate metabolism previously reported in acute hepatic failure and hepatic coma(9,18-20).

The lack of elevated blood ketone concentrations in patients with increased FFA concentrations is in accord with the results of Recant(14) who found lowered fasting blood ketone concentrations in patients with cirrhosis, roughly proportional to the severity of cirrhosis, and little or no measurable ketones in many patients with active cirrhosis. This may reflect further abnormalities of intermediary metabolism in cirrhosis (either decreased hepatic ketone production or increased peripheral utilization of fatty acids

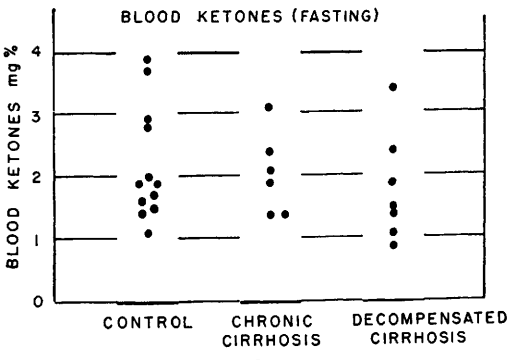

FIG. 2.

and ketone bodies). The hypoketonemic effect of adrenal cortical steroids(21) may be pertinent as cirrhosis patients have a defect in the metabolism of the steroid nucleus(22).

There is strong evidence to suggest that fatty acids in the form of FFA are directly transported from fat depots to other tissues where they may be used as substrate for oxidative metabolism(6). Plasma FFA have a rapid turnover and are transported bound to albumin and low density lipoproteins. As plasma FFA concentration appears to be primarily regulated by peripheral adipose tissue in response to alterations in peripheral nonfat calorie metabolism, the elevated fasting FFA levels and the reported abnormalities of glucose metabolism in cirrhosis would be consistent with a peripheral defect. Nevertheless, the demonstration of intrahepatic abnormalities in lipid synthesis and oxidation in animals fed alcohol or abnormal diets(10. 23) indicates that hepatic uptake and utilization must also be considered. Our results do not reveal an increased FFA concentration in acute alcoholics without cirrhosis or in nutritional fatty liver. The data reported here offer no evidence for determining the cause of the elevated plasma FFA concentrations in acute cirrhosis or hepatic coma. A recent report, while consonant with our observations, has suggested an hepatic defect(24).

Summary. Fasting plasma FFA concentrations were determined in 34 subjects with cirrhosis and 28 without cirrhosis.

Mean fasting FFA concentrations were elevated in subjects with cirrhosis and this was most marked in those subjects with acute hepatic failure or hepatic coma. The increased FFA concentrations were not accompanied by a rise in blood ketone concentrations.

Acknowledgment. The authors are grateful for the technical assistance of Miss Alice N. Ballou and Miss Lois M. Betten.

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Received September 2, 1960. P.S.E.B.M., 1961, v106.