Gonadal Function in Male Patients with Alcoholic and Non-alcoholic Liver Disease

Yukihiro KISHIMOTO, Tetsuo YAMAMOTO, Seiichi KATO,
Tadashi WAKUSHIMA and Chisato HIRAYAMA

Gonadal function in male patients with various liver disease has been evaluated by basal plasma testosterone level and a response of plasma testosterone to human chorionic gonadotropin. Compared with healthy male subjects of similar age, gonadal function was not reduced in chronic hepatitis, but in alcoholic liver disease without cirrhosis and in alcoholic and non-alcoholic cirrhosis. Gonadal dysfunction in patients with chronic hepatitis and cirrhosis was correlated with abnormal liver tests. It may be concluded that gonadal function in chronic liver disease is reduced either by alcohol abuse or disturbances of hepatic function and/or hepatic hemodynamics.

Key Words: Gonadal function, Leydig cell function, Liver cirrhosis, Plasma testosterone

Patients with chronic liver disease, such as cirrhosis of the liver are known to have low levels of circulating testosterone, associated with relatively high levels of estrogen, and of gonadotropins¹⁻⁷. The major mechanism responsible for subnormal circulating testosterone levels in cirrhosis, therefore, seems to be due to the dysfunction of the testis. Recent studies have revealed also that there is abnormal metabolism of endogenous and exogenous testosterone⁸⁻¹⁰. These studies provide supporting evidence that primary gonadal dysfunction exists in male cirrhosis patients. However, since ethanol consumption is known to act to increase the metabolic clearance rate of testosterone and to inhibit Leydig cell function¹¹⁻¹³, low levels of circulating testosterone should be elucidated in regard to etiologies and hepatic dysfunction in cirrhosis patients.

The observation that plasma testosterone levels in normal men rise after the administration of an intra-muscular injection of human chorionic

gonadotropin (hCG) has led to the development of tests of Leydig cell secretory capacity^{14, 15}. Several authors have studied the response of plasma testosterone to hCG in selected patients with liver disease, suggesting that gonadal function is normal or subnormal in male patients with chronic liver disease^{3, 5, 6, 9}. The present investigation was carried out to elucidate gonadal function as basal plasma testosterone level and a response to plasma testosterone to hCG in male patients with various chronic liver diseases in regard to different etiologies and to the degree of hepatic dysfunction, and has revealed that gonadal dysfunction in chronic liver disease is closely related either to alcohol abuse or to the severity of liver disease.

SUBJECTS AND METHODS

Six adult males without clinical evidence of liver disease with a mean age ($\pm$ SD) of 55.8 ± 10.7 years served as controls. All had normal liver and kidney function. The test subjects, having various

From the Second Department of Internal Medicine, Tottori University School of Medicine, Yonago 683, Japan.

Received for publication July 2, 1986.

Reprints request to: Chisato Hirayama, MD. Second Department of Internal Medicine,
Tottori University School of Medicine, Yonago 683, Japan.

liver diseases, were 33 male patients with a mean age of 50.1 ± 10.9 years. They had normal kidney function. Chronic liver disease was proven by biopsy: 6 had chronic hepatitis; 6 had alcoholic liver disease without cirrhosis. The six patients with chronic hepatitis were divided into two groups: 3 had chronic persistent hepatitis and 3 had chronic active hepatitis. The six patients having alcoholic liver disease included 3 with fatty liver and 3 with hepatic fibrosis without cirrhosis. The twenty-one patients with liver cirrhosis were divided into two groups: 12 had alcohol abuse and the remaining 9 were defined as having a non-alcoholic etiology. The patients with alcoholic liver disease and alcoholic cirrhosis had no history of blood transfusions and no HBs antigen. They demonstrated alcohol abuse, ingesting ethanol equivalents of over 90 ml per day over a 5 year period. The patients with chronic hepatitis and non-alcoholic cirrhosis had no history of alcohol abuse, ingesting ethanol equivalent to less than 30 ml per day.

Each subject with liver disease received a complete diagnostic examination including liver tests, a hepatic biopsy, a gastrointestinal endoscopy and an abdominal sonography. The liver tests selected were as follows: serum bilirubin, serum albumin, serum γ globulin, aminotransferases (AST, ALT), alkaline phosphatase (ALP) and indocyanine green (ICG) retention (%/15 min; normal < 10%). After entry all subjects were prescribed bed rest and a standard dietary regimen. None of the patients with liver diseases had special medications such as corticosteroid and/or antiviral agents. The patients with alcohol abuse abstained from drinking.

Gonadal function was studied principally within one month of entry. After fasting overnight, blood samples were obtained at 7:00 am, and hCG was administered intramuscularly at 3000 IU daily for 3 days. On the 4th day, blood samples were again obtained at 7:00 am. Plasma levels of testosterone were determined by specific radioimmunoassay. Gonadal function was expressed as basal plasma testosterone levels and the increase of plasma testosterone levels by hCG administration.

RESULTS

The clinical, histological and biochemical findings of the 39 subjects studied are shown in Table 1. Because control subjects had been selected roughly age matched to cirrhosis patients, patients with chronic hepatitis and alcoholic liver disease belong to a slightly younger age group than the control subjects. As shown in Table 2, mean ($\pm$ SD) basal testosterone level was 11.0 ± 0.77 ng/ml in control subjects, and did not change in patients with chronic hepatitis but was lower in alcoholic liver disease and also lower in cirrhosis. In cirrhosis patients, the basal testosterone level was not different between the alcoholic and non-alcoholic patients. The response to hCG expressed as Δ testosterone was 8.30 ± 0.85 in control subjects. The response did not change in chronic hepatitis but was reduced significantly in alcoholic liver disease and in liver cirrhosis. In the latter there was no difference in alcoholic and non-alcoholic patients.

Alcohol is known to cause Leydig cell dysfunction, so that alcohol abstinence may restore Leydig cell function. Fig. 1 shows the relationship between basal and Δ testosterone levels and the period of abstinence from alcohol in 12 patients with alcoholic cirrhosis. As expected, there was gradual recovery of testicular function with abstinence. To evaluate further the relationship of testicular function to liver function and liver blood flow, the relationship of basal and Δ testosterone levels to serum levels of bilirubin, albumin, and ICG retention was examined in control subjects and patients with chronic hepa-

Fig. 1. Changes of gonadal function in alcoholic cirrhosis by abstinence from alcohol.

Table 1. Clinical findings in male subjects studied

	No.	Age (year)	Positive HBsAg	Bilirubin (mg/dl)	Albumin (g/dl)	ICG (%/15 min)
Control	6	55.8 ± 10.7	0/6	0.4 ± 0.1	4.3 ± 0.4	(-)
Chronic hepatitis	6	40.0 ± 7.1 *	4/6	0.7 ± 0.4	4.2 ± 0.4	17.5 ± 6.6 (n=4)
Alcoholic liver disease	6	46.5 ± 13.9	0/6	0.5 ± 0.2	4.6 ± 0.4	11.8 ± 3.5 (n=4)
Liver cirrhosis	21	54.0 ± 9.0	3/21	1.0 ± 0.5 *	3.5 ± 0.5 **	32.7 ± 11.5 (n=9)
alcoholic	12	50.8 ± 6.7	0/12	0.9 ± 0.6	3.6 ± 0.6 *	34.2 ± 15.7 (n=5)
non-alcoholic	9	58.3 ± 10.1	3/9	1.0 ± 0.4 **	3.5 ± 0.5 **	30.8 ± 4.1 (n=4)

*p < 0.05, **p < 0.01, as compared with control.

Table 2. Plasma testosterone level before and after hCG stimulation

	No.	Plasma testosterone (ng/ml)		
		before	after	Δ
Control	6	11.0 ± 0.8	19.1 ± 1.1	8.3 ± 0.9
Chronic hepatitis	6	13.8 ± 3.0	22.1 ± 2.8 **	8.5 ± 3.9
Alcoholic liver disease	6	8.5 ± 5.6	13.3 ± 6.1	4.6 ± 3.4 *
Liver cirrhosis	21	8.0 ± 3.6	12.1 ± 5.1 **	4.0 ± 1.9 **
alcoholic	12	8.4 ± 2.9 *	12.8 ± 4.6 **	4.5 ± 2.1 **
non-alcoholic	9	9.0 ± 4.5	11.0 ± 5.9 **	3.5 ± 1.7 **

*p < 0.05, **p < 0.01, as compared with control.

titis and cirrhosis. As seen in Fig. 2, there was a significant relationship of testicular function to serum levels of bilirubin, albumin and ICG retention in cirrhosis patients. The result indicates that gonadal dysfunction in patients with chronic liver disease is related to hepatic function and hepatic hemodynamics.

DISCUSSION

Hypogonadism, commonly associated with male patients having cirrhosis is mainly due to a decreased plasma concentration of testosterone, and to an increased plasma concentration of estrone and estradiol. Leydig cell function can be examined by the measurement of testosterone levels after the administration of hCG, which stimulates secretion of testosterone. Southren et al.³⁾ and Mowat et al.⁶⁾ examined Leydig cell function by hCG stimulation, and found a positive response in male cirrhosis patients, but Kley

et al.⁵⁾, Baker et al.⁹⁾ found a lowered response in male patients with cirrhosis compared with normal male subjects. The present study revealed a lower testosterone response to hCG in male patients with alcoholic liver disease as well as in those with liver cirrhosis, but not in patients with chronic hepatitis without alcohol abuse, indicating that basal plasma levels of testosterone in patients with chronic liver disease is mainly regulated by Leydig cell function.

The hormonal abnormalities associated with alcoholic liver disease have been studied in great detail. Alcohol consumption itself has been proven to lower the plasma testosterone level. Studies on healthy volunteers and patients with alcoholic liver disease showed that alcohol has both a central nervous effect and gonadal effect, and increases the metabolic clearance rate of testosterone^{1, 11, 12)}. The present study also supports a direct alcohol action on gonads in alco-

Fig. 2. Relationship of gonadal function to liver tests.

holic cirrhosis because gonadal function at least partly recovered by abstinence from alcohol. This result coincides with the finding that sexual function recovered in 25% of abstinent alcoholic male patients, who had no testicular atrophy¹⁶⁾. However, abstinence is known to improve the nutritional state and liver function, which has also a favorable effect on gonadal function, so that it is difficult to evaluate the exact mechanism of abstinence on gonadal function.

Few studies have been performed on gonadal function in non-alcoholic liver disease. Van Thiel et al.¹⁷⁾ reported that hemophiliacs associated with distinct chronic liver diseases without severe

hepatic dysfunction have almost normal gonadal function. In fact, the present study revealed that patients with chronic hepatitis without severe hepatic injury have normal plasma levels of testosterone and normal Leydig cell function. However, patients with non-alcoholic cirrhosis show a lowered level of testosterone and Leydig cell dysfunction, which are closely related to disturbances of hepatic function and/or of hepatic hemodynamics.

The exact mechanism responsible for Leydig cell dysfunction in male patients with severe liver disease, especially in non-alcoholic cirrhosis is not known at present. It is generally accepted that estrogen suppresses testosterone production in Leydig cells^{18,19)}. It has been reported that most cirrhosis patients have hyperestrogenism^{2,4,7)}, which is ascribed either to decreased estrogen removal or to an elevated production rate of estrogens²⁰⁾. For example, Gordon et al.⁸⁾ reported that plasma androstenedione level was elevated in male cirrhosis patients, where a large part of the plasma estrone and estradiol was derived from the increased conversion from adrenal and testicular androgens. Subsequently, Kley et al.²¹⁾ concluded that elevated plasma levels of estrogens in cirrhosis patients was predominantly from adrenal production. These studies indicate that hyperestrogenism in cirrhosis does not seem to be associated with alcohol abuse but with hormonal abnormalities related to hepatic dysfunction in cirrhosis *per se*.

It is assumed that hypogonadism in male patients causes a negative nitrogen balance and a lowered regenerative capacity of the liver. Therefore, the clinical application of testosterone and related compounds have been tried in cirrhosis patients. Our previous study revealed that anabolic steroid improved hepatic protein synthesis, especially albumin synthesis in male patients with non-alcoholic cirrhosis²²⁾. These observations support the usefulness of androgen therapy for cirrhosis patients. More recently Mendenhall et al.²³⁾ found that anabolic steroid had a beneficial effect on the long-term survival of patients with alcoholic hepatitis. Kley et al.¹⁰⁾ reported that after the administration of testosterone to cirrhosis patients, plasma levels of testosterone, andro-

stenedine, estrone and estrogen are increased, but the imbalance between heterosexual hormones is nearly normalized. However, because androgen and anabolic steroids have some untoward effects²⁴⁾, further clinical studies should be undertaken to evaluate androgen and anabolic steroid therapy for male cirrhosis patients in terms of preparations available for clinical use and their dosage.

REFERENCES

- 1) Kent JR, Scaramuzzi RJ, Lauwers W, et al: Plasma testosterone, estradiol, and gonadotrophins in hepatic insufficiency. *Gastroenterology* 64: 111, 1973.
- 2) Galvao-Teles A, Anderson DC, Burke CW, et al: Biologically active androgens and oestradiol in men with chronic liver disease. *Lancet* I: 173, 1973.
- 3) Southren AL, Gordon GG, Olivo J, et al: Androgen metabolism 22: 695, 1973.
- 4) Chopra IJ, Tulchinsky D, Greenway FL: Estrogen-androgen imbalance in hepatic cirrhosis. *Ann Int Med* 79: 198, 1973.
- 5) Kley HK, Nieschlag E, Krüskemper HL: Estrone, estradiol and testosterone in patients with cirrhosis of the liver: Effect of HCG. *Horm Metab Res* 7: 99, 1975.
- 6) Mowat NAG, Edwards CRW, Fisher R, et al: Hypothalamic-pituitary-gonadal function in men with cirrhosis of the liver. *Gut* 17: 345, 1976.
- 7) Nagasue N, Ogawa Y, Yukaya H, et al: Serum levels of estrogens and testosterone in cirrhotic men with and without hepatocellular carcinoma. *Gastroenterology* 88: 768, 1985.
- 8) Gordon GG, Olivo J, Rafii F, et al: Conversion of androgens to estrogens in cirrhosis of the liver. *J Clin Endocrinol Metab* 40: 1018, 1975.
- 9) Baker HWG, Burger HG, De Kretser DM, et al: A study of the endocrine manifestations of hepatic cirrhosis. *Quart J Med* 65: 145, 1976.
- 10) Kley HK, Strohmeyer G, Krüskemper HL: Effect of testosterone application on hormone concentrations of androgens and estrogens in male patients with cirrhosis of the liver. *Gastroenterology* 76: 235, 1979.
- 11) Rubin E, Lieber CS, Altman K, et al: Prolonged ethanol consumption increases testosterone metabolism in the liver. *Science* 191: 563, 1976.
- 12) Gordon GG, Altman K, Southren AL, et al: Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. *N Engl J Med* 295: 793, 1976.
- 13) Van Thiel DH: Ethanol: its adverse effects upon the hypothalamic-pituitary-gonadal axis. *J Lab Clin Med* 101: 21, 1983.
- 14) Longcope C: The effect of human chorionic gonadotropin on plasma steroid levels in young and old men. *Steroids* 21: 583, 1973.
- 15) Weinstein RL, Kelch RP, Jenner MR, et al: Secretion of unconjugated androgens and estrogens by the normal and abnormal human testis before and after human chorionic gonadotropin. *J Clin Invest* 53: 1, 1974.
- 16) Van Thiel DH, Gavalier JS, Sanghvi A: Recovery of sexual function in abstinent alcoholic men. *Gastroenterology* 84: 677, 1982.
- 17) Van Thiel DH, Gavalier JS, Spero JA, et al: Patterns of hypothalamic-pituitary-gonadal dysfunction in men with liver disease due to differing etiologies. *Hepatology* 1: 39, 1981.
- 18) Yanaihara T, Toen P: Studies of the human testis. III. Effect of estrogen on testosterone formation in human testis in vitro. *J Clin Endocrinol Metab* 34: 968, 1972.
- 19) Kalla NR, Nisula BC, Menard R, et al: The effect of estradiol on testicular testosterone biosynthesis. *Endocrinology* 106: 35, 1980.
- 20) Adlercreutz H: Hepatic metabolism of estrogens in health and disease. *N Engl J Med* 290: 1081, 1974.
- 21) Kley HK, Keck E, Krüskemper HL: Estrone and estradiol in patients with cirrhosis of the liver: Effect of ACTH and dexamethasone. *Clin Endocrinol Metab* 43: 557, 1976.
- 22) Hirayama C, Kimura N, Masuya T: Anabolic steroid effect on hepatic protein synthesis in patients with liver cirrhosis. *Digestion* 3: 41, 1970.
- 23) Mendenhall CL, Anderson S, Garcia-Pont P, et al: Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 311: 1464, 1984.
- 24) Snyder PJ: Clinical use of androgens. *Ann Rev Med* 35: 207, 1984.