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NAKAMUTA, Makoto
Department of Internal Medicine, Fukuoka City Hospital

OHASHI, Masao
Department of Internal Medicine, Fukuoka City Hospital

GOTO, Kiminobu
Department of Internal Medicine, Fukuoka City Hospital

TANABE, Yuichi
Department of Internal Medicine, Fukuoka City Hospital

他

https://doi.org/10.15017/7326000

出版情報：福岡醫學雜誌. 85 (6), pp.187-194, 1994-06-25. 福岡医学会
バージョン：
権利関係：

The Re-evaluation of Sex Steroids Metabolism in Patients with Non-Alcoholic Liver Cirrhosis

Makoto NAKAMUTA[1], Masao OHASHI*[1], Kiminobu GOTO[1]
Yuichi TANABE[1], Kaichiro HIROSHIGE[1] and Hajime NAWATA[2]

[1] *Department of Internal Medicine Fukuoka City Hospital, Fukuoka 812*
[2] *Third Department of Internal Medicine Faculty of Medicine Kyushu University 60, Fukuoka 812*

Abstract We examined the serum levels of testosterone (T), androstenedione (Δ_4-A), estrone (E1), estradiol (E2), and dehydroepiandrosterone sulfate (DHEA-S) in the non-alcoholic cirrhotic male patients when divided into compensated or decompensated state. Serum level of T was significantly elevated in compensated cirrhotic patients (9.63±1.00 ng/ml, mean±SE) compared to that in decompensated cirrhotic patients (5.63±0.69ng/ml, $p<0.01$) and in aged-matched normal controls (4.95±0.38 ng/ml, $p<0.01$). Serum levels of E1, E2 and Δ_4-A tended to be increased in decompensated cirrhotic patients, while there was not a significant difference statistically. Serum levels of DHEA-S were markedly reduced in both compensated and decompensated cirrhosis compared to those of normal controls. Serum concentration of cholinesterase, indicative one of the representative residual liver function, showed a good positive correlation to T ($r=0.53$, $p<0.01$), and a negative correlations to E1 ($r=-0.67$, $p<0.01$), E2 ($r=-0.77$, $p<0.01$), Δ_4-A ($r=-0.57$, $r=p<0.01$). Also, we examined the relationship of the serum levels to gynecomastia or esophageal varices. The cirrhotics with gynecomastia showed significantly higher serum levels of E1, E2, and Δ_4-A, and lower level of T than those without gynecomastia. And the cirrhotics with esohageal varices showed the greater level of T than those without esophageal varices.

Our study suggests that low serum testosterone level of men with nonalcoholic cirrhotic is not a common finding, especially in compensated state. Serum ratios of T/Δ_4-A and E2/T indicated high conversion from Δ_4-A to T and low conversion from T to E2 in compensated cirrhotic patients, thus contributing to the high level of serum testosterone in non-alcoholic cirrhotic men. However, the mechanism of hypertestosteronemia in these cirrhotics will be unknown.

Introduction

Advanced liver disease in men, especially liver cirrhosis, is frequently complicated by gynecomastia and loss of libido, which reflect the feminizing or demasculinizing characteristics of cirrhosis. Despite of the frequent existence of these physical signs, the precise pathophysiologic mechanisms responsible for their development are poorly understood.

Many investigators have observed the elevated levels of serum estrogens and reduced level of serum testosterone in advanced alcoholic liver disease[1)10)12)]. These changes may be explained by altered production rate and retarded metabolic clearance rate of sex steroids, while primary gonadal failure with long-term alcohol toxicity also appears to contribute to the hypotestosteronemia in alcoholic liver cirrhosis[3)8)13)]. Recent evaluation of the hypoth-

* To whom correspondence should be addressed: Department of Internal Medicine Fukuoka City Hospital 13-1 Yoshizuka-Honmachi, Hakata-ku, Fukuoka 812, Japan

alamo-pituitary-gonadal axis of adult hemophiliacs men with hepatitis virus induced advanced liver disease demonstrated that serum testosterone levels were not reduced when compared with those of age matched controls[14]. This evidence suggests that the etiology of the disease may be an important factor for influencing on the hypothalamo-pituitary-gonadal functions of individuals with liver disease, and that the ultimate clinical picture and complications, such as individual liver function per se, gynecomastia and, portosystemic shuting[6][15], may affect on the metabolism of sex steroids. Although considerable information is available for evaluating the levels of serum sex steroids in individuals with alcohol-induced liver cirrhosis, only a few data are reported concerning the levels of sex steroids in individuals with non-alcoholic liver cirrhosis[2][5][17].

In the present study, we reevaluated the serum levels of sex steroids in male patients with non-alcoholic liver cirrhosis based on the severity of liver cirrhosis. Also, we examined the relationship of the serum levels to gynecomastia or esophageal varices.

Materials and Methods

Patients and normal controls: Twenty eight patients with non-alcoholic liver cirrhosis (posthepatitic B 3, posthepatitic C 25) aged 46 to 65 years and 8 strictly age matched normal males (54.9±1.1 yo) were participated in this study (Table 1). The diagnosis of liver cirrhosis was based on the clinical manifestations, liver function tests, and the histology of liver biopsy. Patients with marked obesity (>130% of the standard body weight), diabetes mellitus (HbA_1>9.0%), history of the steroid therapy, large hepatocellular carcinoma (more than 2 cm in diameter), and history of a surgical portocaval anastomosis were eliminated from this study. The patients were independently classified into two groups on the basis of the clinical and laboratory findings which included 1) compensated (Child-Pugh A) or decompensated state (B or C) 2) the existence of feminization sign such as a gynecomastia 3) the existence of esophageal varices observed by endoscopy.

Measurement of Sex Steroids: Blood was taken from an antecuvital vein of the subjects fasting in the morning. After blood sampling, the serum was immediately frozen and stored at −20°C until assay. Sensitive and specific

Table 1 Liver functions of the patients with non-alcoholic liver cirrhosis

	Compensated (n=11)	Decompensated (n=17)
Age (yo)	56.9±3.1	56.3±1.4
ALT (IU/L)	63.1±13.1	54.7±8.4
ALP (IU/L)	185.2±14.4	216.2±16.3
ChE (IU/L)	181.9±13.6	112.8±14.7
Albmin (g/dl)	3.86±0.07	3.09±0.11
PT (%)	81.8±4.4	59.9±2.5
Child-Pugh		
A	11	
B		14
C		3
mean score	5.9±0.1	8.6±0.4

(Mean±SE)

ALT=alanine aminotransferase; ALP=alkaline phosphatase; ChE=cholinesterase; PT=prothrombin time

radioimmunoassay were used to measure the serum concentrations of testosterone (Diagnostic Products Corporation, Los Angeles, CA, USA), Δ_4- androstenedione (Wein Laboratories, Suceasunna, NJ, USA), estrone (SRL, Tokyo, Japan), estradiol (Daiichi Radioisotope Laboratories, Tokyo, Japan), and dehydroepiandrosterone sulfate (Wein Laboratories, Suceasunna, NJ, USA).

Statistical Analysis: The serum concentrations of sex steroids from each group were expressed as mean ± SE. Multiple comparison to assess the significant differences among the two groups of cirrhotics and normal controls was performed by Kruskall-Wallis non-parametric one way analysis of variance (ANOVA) and Scheffé test. The significant difference among the groups was considered at $P<0.05$. Non-parametric Spearmann correlation conefficient was used to examine the relationship.

Results

Serum levels of sex steroids in patients with compensated or decompensated liver cirrhosis (LC) and healthy males are shown in Table 2. Serum level of testosterone (T) was significantly higher in the patients with compensated cirrhosis than that in patients with decompensated cirrhosis or that in age matched normal controls, although there was not a significant difference between decompensated cirrhotic patients and normal controls. Serum levels of estrone (E1), estradiol (E2) and androstenedione (Δ_4-A) tended to be increased in the patients with decompensated cirrhosis among three groups. Serum level of dehydroepiandrosterone sulfate (DHEA-S) was markedly decreased in both compensated cirrhosis (389.5±43.0 ng/ml) and decompensated cirrhosis (401.2±66.2 ng/ml) compared to that of normal control (1617.6±215.7 ng/ml, $p<0.01$). The serum cholinesterase concentrations in LC patients showed a good positive correlation to that of T ($r=0.53$, $p<0.01$), while negative correlations to E1 ($r=-0.67$, $p<0.01$), E2 ($r=-0.77$, $p<0.01$) and Δ_4-A ($r=-0.57$, $p<0.01$) except DHEA-S (Fig. 1).

Table 3 depicted the ratios of E2/T, E1/Δ_4-A, T/Δ_4-A, and E2/E1 among these groups. The patients with compensated LC showed much higher T/Δ_4-A ratio and lower E2/T ratio than the patients with decompensated or normal controls. The ratio of E2/E1 was decreased in both the patients with compensated and decompensated LC in compared to nor-

Table 2 Serum levels of sex steroids in liver cirrhosis and controls

	Compensated	Decompensated	Controls
E1 (ng/ml)	52.14±11.24	91.06±28.00	50.08±6.00
E2 (ng/ml)	57.80±24.94	142.92±55.70	64.43±9.55
T (ng/ml)	9.63±1.00	5.63±0.69	4.95±0.38
	★★		
	★★		
Δ_4-A (ng/ml)	0.98±0.17	1.13±0.12	0.78±0.06
DHEA-S (ng/ml)	389.5±43.0	401.2±66.2	1617±215.7
		★★	
	★★		

(Mean±SE)

E1=estrone; E2=estradiol; T=testosterone; Δ_4-A=androstenedione; DHEA-S=dehydroepiandrosterone sulfate.
★★=$P<0.01$

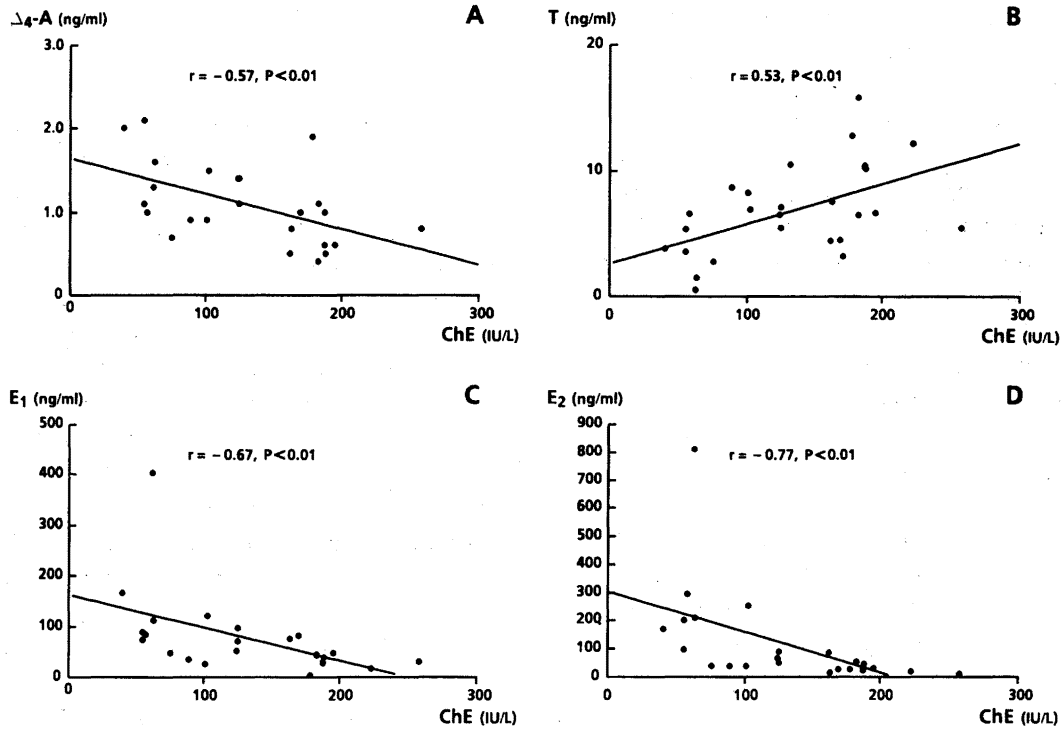

Fig. 1 Correlation between serum levels of cholinesterase (ChE) and that of sex steroids. A: androstenedions (Δ_4−A), B: testosterone (T), C: estrone (E1), D: estradiol (E2).

Table 3 The serum ratios of E2/T, E1/Δ_4-A, T/Δ_4-A, and E2/E1 in liver cirrhosis

	Compensated	Decompensated	Controls
E2/T	7.1±3.7	140.7±123.5	13.1±1.6
		★	
		★	
E1/Δ_4-A	67.1±10.4	74.5±20.5	67.1±8.3
T/Δ_4-A	11.7±1.9	5.7±0.9	6.6±0.6
		★	
E2/E1	11.7±1.9	6.6±1.2	0.9±0.2
			★★
			★★

(Mean±SE)

E1=estrone; E2=estradiol; T=testosterone; Δ_4-A=androstenedione; DHEA-S=dehydroepiandrosterone sulfate.
★★=P<0.01, ★=P<0.05.

mal controls. There was not a significant difference in the ratio of E1/Δ_4-A among these groups.

The cirrhotic patients with gynecomastia showed significantly higher serum levels of E1, E2, and Δ_4-A, and lower level of T than those without gynecomastia, while there were no difference on the hepatic dysfunction severity

Table 4 Gynecomastia and serum levels of sex steroids in liver cirrhosis

Gynecomastia	− (n=20)	+ (n=8)	
E1 (ng/ml)	54.3±9.3	127.8±47.1	★
E2 (ng/ml)	62.2±17.4	238.8±100.3	★★
T (ng/ml)	7.83±0.79	4.45±0.99	★
Δ_4-A (ng/ml)	0.97±0.11	1.37±0.17	★
DHEA-S (ng/ml)	435.2±63.7	464.7±141.5	NS
Child-Pugh	7.1±0.3	8.8±1.0	NS
Age (yo)	56.8±1.9	53.4±2.6	NS

(Mean±SE)

E1=estrone; E2=estradiol; T=testosterone; Δ_4-A=androstenedione; DHEA-S=dehydroepiandrosterone sulfate.
★★=P<0.01, ★=P<0.05, NS=not significant

Table 5 Esophageal varices and serum levels of sex steroids in liver cirrhosis

Esophageal varices	− (n=13)	+ (n=15)	
E1 (ng/ml)	68.3±16.7	62.9±8.9	NS
E2 (ng/ml)	80.0±22.7	93.1±28.8	NS
T (ng/ml)	5.23±0.85	7.60±0.66	★
Δ_4-A (ng/ml)	0.98±0.17	1.10±0.13	NS
DHEA-S (ng/ml)	594.6±125.6	330.4±35.7	NS
Child-Pugh	7.5±0.48	7.4±0.4	NS
Age (yo)	53.1±2.9	57.2±1.8	NS

(Mean±SE)

E1=estrone; E2=estradiol; T=testosterone; Δ_4-A=androstenedione; DHEA-S=dehydroepiandrosterone sulfate.
★★=P<0.01, ★=P<0.05, NS=not significant

based on Child-Pugh scores and ages (Table 4). The presence of palmar erythema in LC patients was not related to the levels of those sex steroids (data not shown). The cirrhotics with esophageal varices showed the greater levels of T than those without esophageal varices, while the serum levels of other steroids had no relation to the presence of esophageal varices (Table 5).

Discussion

Although many investigators have observed the reduced level of serum T in advanced alcoholic liver disease[1)10)12)], recent studies in postnecrotic men showed that serum T levels were not reduced when compared with those of age matched controls[14)17)]. In this study, we noticed the significant elevation of serum T level in the patients with compensated LC compared to those in the patients with decompensated LC and age matched controls. The increased conversion from Δ_4-A to T and decreased conversion from T to E2 may be responsible for the elevated serum levels of T in compensated LC patients, while the cause of these metabolic changes of sex steroids remains to be unknown. The serum concentration of cholinesterase as an index of limited reserve of liver function in LC patients had a good positive correlation to the serum T level in all cirrhotics, reflective to that serum T levels were paralleled to the severity of cirrhosis. It was reported that the

sex hormone binding globulin (SHBG), preferentially bound to T, was markedly increased in LC especially in compensated LC in spite of reduced free T level[9]. Although we could not measure the serum levels of SHBG in these subjects, high concentrations of SHBG might contribute to the high levels of serum T in these compensated LC patients. The serum T level of the patients with decompensated LC made no difference to that of normal controls. This data may have a sampling problem because of the use of limited number of Child C patients (n=3) compared to Child B (n=10). In fact, serum T level of these 3 Child C patients was apparently low (mean=2.8ng/ml).

Serum levels of E1, E2 and Δ_4-A tended to be increased in the patients with decompensated cirrhosis. These increases of sex steroids in the alcoholic patients were already reported by several investigators[1)10)12)]. Furthermore, we found that the serum levels of each sex steroid had a negative correlation to the serum concentration of cholinesterase. These data suggested that the decreased hepatic extracion of these sex steroids caused the high serum levels of these sex steroids. However, our preliminary data suggest that the increased formation of estrogens from androgens occurs in the advanved LC patients (unpublished observation). Serum levels of DHEA-S were significantly reduced in both compensated and decompensated cirrhosis compared to thoses of normal controls. As dehydroepiandrosterone is sulfated by dehydroepiandrosterone sulfotransferase (DHEA-ST) in the liver and adrenal gland[4], the low levels of DHEA-S in cirrhotics might be result from the reduction of hepatic DHEA-ST activity.

Interestingly, the LC patients with gynecomastia showed markedly higher levels of E1, E2 and Δ_4-A than those without gynecomastia, however, the presence of gynecomastia seemed to be not related to the severity of LC based on Child-Pugh scores. The long duration of LC may account for the presence of this complication because there was a wide variety of the periods to become LC in the patients with post-necrotic hepatitis. At present, we could say the high levels of serum E1 and E2 may affect on the development of gynecomastia not only in alcoholic LC but in post-necrotic LC.

Serum level of T was increased and E1, E2, and Δ_4-A levels were not changed in the LC patients with esophageal varices which was represented one of the portosystemic shunting. It has been reported that the experimental large portosystemic shunting in male rats caused the increasing the plasma level of E2 and decreasing that of T[6)7)11)16)17)]. This evidence is distinctively contrast to the high concentration of serum T level in LC patients with esophageal varices. We could not answer this discrepancy, but the difference of shunting volume between postnecrotic patients and experimental models may cause this discrepancy. In postnecrotic patiens, much smaller portsystemic shunting than experimental models may have little effects on the metabolism of sex steroids. Also, we could speculate the present of esophageal varices may induce the SHBG production in postnecrotic LC by some unknown mechanisms.

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(Received for publication April 27, 1994)

(和文抄録)

非アルコール性肝硬変症における性ステロイドホルモン代謝の再評価

福岡市民病院内科
中牟田 誠・大橋昌夫・後藤公宣
田辺雄一・廣重嘉一郎
九州大学医学部内科学教室第三講座
名和田 新

非アルコール性男子肝硬変症患者を代償性 (Child-Pugh 分類 A 群), 非代償性 (Child-Pugh 分類 B および C 群) に分類し血中各種性ステロイドホルモン (testosterone (T), androstenedione (Δ_4-A), estrone (E1), estradiol (E2)および dehydroepiandrosterone sulfate (DHEA-S)) 値を比較検討した. T は代償性肝硬変症患者群 (9.63±1.00 ng/ml, mean±SE) において非代償性肝硬変症患者群 (5.63±0.69 ng/ml, $p<0.01$) および健常者群 (4.95±0.38 ng/ml, $p<0.01$) より有意に高値だった. E1, E2, Δ_4-A は有意差と認めなかったが非代償性肝硬変症患者群に高値である傾向を認めた. DHEA-S は代償性, 非代償性肝硬変症患者両群ともに健常者群に比して著名に低下していた. 残存肝予備能のひとつの指標であるコリンエステラーゼ値は T ($r=0.53$, $p<0.01$) と正の相関, E1 ($r=-0.67$, $p<0.01$), E2 ($r=-0.77$, $p<0.01$), Δ_4-A ($r=-0.57$, $p<0.01$) と負の相関を示した. 肝硬変症患者全体においては, 女性化乳房を有する群は有しない群に比して有意な E1, E2, Δ_4-A の上昇と T の低下を認めた. また, 食道静脈瘤合併例群は非合併例群に比して T の上昇を認めた. 代償性肝硬変症患者群における T/Δ_4-A 比の有意な上昇は Δ_4-A より T への転換の増加を, また E2/T 比の低下は T より E2 への転換の低下を示した. この性ステロイド代謝異常が代償性肝硬変症患者群における高テストステロン血症の一因と考えられた.