

Assessment of thyroid and gonadal function in liver diseases

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ABSTRACT

Introduction: Liver is involved with the synthesis of carrier proteins and metabolism of various hormones and liver diseases may, therefore, be associated with various endocrine disturbances. This study was conducted to assess thyroid and gonadal function in subjects with acute hepatitis (AH), chronic liver disease (CLD), and those who had undergone liver transplantation (LT).

Materials and Methods: Patients with AH, CLD with Child-Pugh stage A (CLD-1) and Child-Pugh stage B or C (CLD-2), and LT seen at our tertiary level hospital were assessed clinically, biochemically, and for thyroid and gonadal functions besides 25 healthy controls.

Results: Thyroid dysfunction and hypogonadism were present in 14 (16%) and 24 (28%) patients with liver diseases respectively. Among thyroid dysfunction, the commonest was sick euthyroid syndrome six (7%), followed by subclinical hypothyroidism in three patients (3.5%), subclinical hyperthyroidism and thyrotoxicosis in two patients each (2.3%) and overt hypothyroidism in one patient. Among patients with LT and AH groups, the only abnormality was significantly lower total T3 compared with healthy controls. The CLD2 group had significantly lower levels of all thyroid hormones compared with controls and CLD1 group. Hypogonadism was commonest in patients with CLD-2 (14; 50%) followed by LT (3; 33%), CLD-1 (4; 20%), and AH (3; 14%). Hypogonadism was predicted by older age, lower levels of serum albumin, total cholesterol, and triglycerides and higher levels of plasma glucose, serum bilirubin, aspartate transaminases, and international normalized ratio. Gonadal functions showed recovery following LT. **Conclusions:** Thyroid dysfunction and hypogonadism form an important part of the spectrum of acute and CLD, and patients with LT. Deterioration of synthetic functions of liver disease predicts presence of hypogonadism.

Key words: Acute hepatitis, acute liver disease, chronic liver disease, gonadal function, hypogonadism, hypothyroidism, liver transplantation, thyroid function

INTRODUCTION

Liver is involved with the synthesis of carrier proteins and metabolism of various hormones. Thus, liver diseases have been shown to be associated with various endocrine disturbances.^[1,2] Liver diseases are common all over the world as well as in India; and the prevalence of liver diseases is likely to increase in future.^[3] Liver plays an important role in metabolism of thyroid and gonadal hormones like conjugation, excretion, peripheral deiodination, and

synthesis of thyroid-binding globulin (TBG) and sex hormone-binding globulin (SHBG).^[4-7] Hence, it is not surprising that thyroid and gonadal dysfunction have been reported in various spectra of liver diseases and associated with the severity of liver disease.^[8-10] These changes represent changes in biochemical abnormalities due to liver dysfunction and pathological changes associated with end organ damage. Acute liver failure is associated with increased circulating endotoxins and proinflammatory mediators, which is quite similar to clinical state of sepsis and results in dysfunction of endocrinal glands like sick euthyroid syndrome also termed nonthyroidal illness syndrome (NTIS) and hypogonadism.^[11] Also in stable cirrhosis, a state of hypothyroidism has been shown which correlates with slow progression of stage of cirrhosis.^[12,13] Finally, thyroid and gonadal functions improve after liver transplantation (LT).^[14,15] We conducted this study at a tertiary care centre to assess thyroid and gonadal function in subjects with acute hepatitis (AH), chronic liver disease (CLD), and post-LT.

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MATERIALS AND METHODS

This study was conducted as a cross-sectional study at the Army Hospital (Research and Referral), New Delhi from May 2010 to Dec 2011. Subjects with AH, CLD, and LT were recruited from outpatient department and inpatient ward/intensive care unit of gastroenterology department. AH was diagnosed on the basis of presence of acute onset of jaundice with raised transaminases ($\times 3$), no past history of liver disease, and absence of evidence of portal hypertension on ultrasonography of abdomen. CLD was diagnosed on the basis of evidence of liver disease of more than 6 months duration and/or evidence of portal hypertension on ultrasonography or upper gastrointestinal endoscopy. These subjects were classified as per Child-Pugh criteria – Child-Pugh stage A (CLD-1) and Child-Pugh stage B or C (CLD-2). Patients on steroids or those who had received thyroid hormone or testosterone or had alcoholic liver disease were excluded from this study. A total of 25 healthy controls were enrolled from outpatient department. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Institutional Human Ethics Committee at Army Hospital (Research and Referral). Written informed consent was obtained from all subjects/patients. All patients/controls were assessed clinically, biochemically, and for adrenal functions.

Biochemical parameters

Patient's fasting blood samples were collected and analyzed for hematological parameters (complete blood count with platelet counts), liver function tests [Serum bilirubin, aspartate transaminases (AST), alanine transaminases, serum protein, serum albumin, and international normalized ratio (INR)]; blood glucose, serum creatinine, serum lipid profile, and electrolytes (serum sodium and potassium).

Hormonal assessment

Patient's blood was collected in fasting state and serum was separated and stored at -80°C . Hormone levels were measured using commercial kit provided by Bhabha Atomic Research Centre, Mumbai; and Immunotech, Beckman Coulter Company, France. Primary and subclinical hypothyroidism were defined as low free thyroxin (FT4) (normal 0.8-2.1 ng/mL) with raised thyroid-stimulating hormone (TSH) (normal 0.5-6.5 $\mu\text{IU/mL}$) and normal FT4 with raised TSH, respectively. NTIS was defined by alteration in thyroid hormones with normal TSH levels. Gonadal failure was defined as primary when luteinizing hormone (LH), and follicular-stimulating hormone (FSH) were twice the upper limits of normal ($>30\text{ IU/L}$ and $>40\text{ IU/L}$, respectively)

or secondary when LH and FSH were low associated with low testosterone (Te) levels in males (Te $<3.0\text{ ng/mL}$) or amenorrhea in females.

Statistical analysis

Statistical analysis was carried out using SPSS version 20.0 (SPSS Inc. Chicago, USA). Data were presented as mean \pm standard deviation or number (%) unless specified. All parametric data were analyzed by independent student's t-test in categorical groups (two groups) and analysis of variance test ($>$ two groups). All nonparametric data were analyzed by Chi-square test. Pearson's correlation coefficient was calculated to assess the strength of relationship between thyroid and gonadal functions and other parameters. A $P < 0.05$ was considered statistically significant.

RESULTS

In this study, we studied 25 patients of AH; 20 patients of CLD with relatively preserved liver functions (CLD1) which included Child-Pugh stage A and 30 patients with more advanced CLD2 which included Child-Pugh stage B or C, and 10 patients who were post-LT. Most of the subjects with AH were acute viral hepatitis ($n = 18$); however, etiology could not be assessed in all cases. Four of these patients with AH had acute liver failure. Among 50 subjects with CLD, 29 were hepatitis B virus (HBV)-related cirrhosis, 8 were hepatitis C virus (HCV)-related cirrhosis, 3 had HBV and HCV coinfection, and 10 had cryptogenic cirrhosis with probable autoimmune etiology in six. The indications for LTs were HBV related cirrhosis in 5 patients, cryptogenic cirrhosis in 3 patients, and HCV-related cirrhosis in 2 patients. There were only 8 females (one postmenopausal) and rests were males. Basic parameters of all subjects is given in Table 1.

Thyroid dysfunction

Thyroid dysfunction was present in 16% (14/75) patients with liver diseases. Among thyroid dysfunction, the commonest was NTIS 8% (6/75), which was present in four patients of AH (all with acute hepatic failure) and two patients of CLD-2. Subclinical hypothyroidism and primary hypothyroidism were present in three patients and one patient in CLD group, respectively. Subclinical hyperthyroidism and thyrotoxicosis were observed in two patients each in CLD group. None of the patient with LT had thyroid dysfunction.

Thyroid function test were evaluated after excluding three patients with overt hypothyroidism and thyrotoxicosis. Among patients with LT and AH group, the only abnormality was significantly lower total T3 compared

with healthy controls. CLD-2 group had significantly lower levels of all thyroid hormones compared with controls and CLD-1 group. Serum TSH was not significantly different between any group [Table 2].

Gonadal dysfunction

Hypogonadism was present in 40% (30/74) patients with liver diseases excluding a postmenopausal woman. Hypogonadism was commonest in patients with CLD-2 (16/30; 53%), followed by LT (4/10; 40%), AH (6/25; 24%), and CLD-1 (4/20; 20%). All the patients had secondary hypogonadism. Among patients with AH, four patients with acute liver failure had low testosterone and low LH (<5 IU/L). Among gonadal hormones, the consistent abnormality detected was significantly lower testosterone levels in all groups with liver disease compared with controls. Serum estradiol levels were higher in all groups compared with controls, but were statistically significant only in AH and CLD1 group [Table 2]. Hypogonadism was predicted by older age, lower levels of serum albumin, total

cholesterol and triglycerides and higher levels of plasma glucose, serum bilirubin, AST and INR [Table 3].

DISCUSSION

Endocrine dysfunction are common with liver diseases,^[1] which is correlated with severity of liver dysfunction^[2] and improve after LT.^[15] In this study, we have assessed thyroid and gonadal functions in complete spectrum of severity of liver diseases and after LT.

In present study, thyroid dysfunction was present in 16% of patients with liver disease. NTIS was the commonest, was present in patients with acute liver failure and CLD. NTIS is characterized by a normal total T4, normal/high free T4, low total T3, low free T3, and an elevated rT3.^[16] Among patients with CLD, cases with primary hypothyroidism and thyrotoxicosis were observed. CLD due autoimmune etiology is known to have associated autoimmune thyroid disease. In autoimmune hepatitis, both Grave's disease (6%)

Table 1: Basic parameters of various groups

	AH	CLD1	CLD2	LT	P
Age (years)	35±12.7	40.5±10.6	44.0±9	44±10	0.016
Sex ratio (M/F)	19/5	20/0	28/2	9/1	
Serum protein (g/dL)	6.9±0.5	6.8±0.24	5.9±0.7	6.2±0.45	<0.0001
Serum albumin (g/dL)	3.92±0.4	3.6±0.3	2.95±0.3	3.84±0.3	<0.0001
Plasma glucose F (mg/dL)	95±28	91.5±16.3	108.7±22.09	98.6±16.7	0.048
Plasma glucose PP (mg/dL)	132.3±35.3	130.3±29.2	158.3±37.3	143.40±30.5	0.014
Serum bilirubin (mg/dL)	12.37±5.3	1.5±0.3	3.1±1.4	1.1±0.3	<0.0001
AST (U/L)	736.3±285	37±9	51±26	28±11	<0.0001
ALT (U/L)	939±310	40±18	64±29	31±8	<0.0001
Total cholesterol (mg/dL)	184±28	198±32	176±30	189±41	0.128
LDL (mg/dL)	105.5±29.3	117.8±26.1	106±26.8	115±33.5	0.386
HDL (mg/dL)	41.57±12.5	44.95±8.19	35.7±6.8	41.2±2.29	0.005
Serum triglycerides (mg/dL)	186±71	176±60	172±49	161±44	0.674
VLDL (mg/dL)	37±14	35±12	34±10	32±9	0.701

AH: Acute hepatitis, CLD-1: Chronic liver disease (Child-Pugh stage A), CLD-2: Chronic liver disease (Child-Pugh stage B or C), LT: Liver transplantation, AST: Aspartate transaminases, ALT: Alanine transaminases, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

Table 2: Thyroid and gonadal hormones in subjects with liver diseases compared with controls

	Control (N=25)	AH (N=25)	CLD-1 (N=20)	CLD-2 (N=27)	LT (N=10)
Thyroid functions (excluding primary hypothyroidism and primary thyrotoxicosis)					
T3	1.5±0.3	1.0±0.3*1	1.3±0.3**1	1.0±0.3*1;***1	1.2±0.7*2
T4	8.7±1.4	8.3±2.9	9.2±2.6	7.9±1.6*3;***2	8.6±4.3
FT3	3.1±0.5	3.0±0.84	3.1±0.4	2.8±0.4*3;***1;***2	2.9±0.4
FT4	1.2±0.2	1.1±0.4	1.3±0.2*3	1.1±0.3***3	1.2±0.3
TSH	3.1±1.6	2.4±1.8	3.1±2.7	2.4±1.6	2.9±1.6
	N=22	N=21	N=20	N=28	N=9
Gonadal hormones (males only)					
LH	6.9±1.9 (6.7)*	6.7±6.7 (5.5)	5.3±2.1 (4.9)*4	5.5±3.9 (4.8)	5.9±2.6 (5.6)
FSH	7.2±2.6 (6.8)	7.3±9.8 (5.6)	6.1±2.6 (6.2)	7.2±5.5 (6.3)	6.9±3.2 (6.3)
Testosterone	7.3±1.9 (7.7)	5.3±2.2 (5.4)*5	3.2±2.3 (4.5)*1	3.2±2.3 (3.0)*1;***2	4.1±1.9 (3.4)*1
Estradiol	15.0.6±6.1 (15.0)	34.6±30.4 (24.7)*6	27.9±23.6 (22.1)*7	20.6±16.8 (15)	24.1±13.1 (17.8)

P values (analysis of variance) among four groups were significant only for total T4 (0.019) and testosterone (0.013). *P value (<0.00001; ⁰0.0002; ³0.03; ⁴0.01; ⁵0.001; ⁶0.007; ⁷0.02) between respective Group and controls. **P value (†0.01; †0.002) between respective group and acute hepatitis. ***P value (†0.007; †0.02; †0.003) between respective group and chronic liver disease (Child-Pugh stage A). *Value in parenthesis indicates median value. AH: Acute hepatitis, CLD-1: Chronic liver disease (Child-Pugh stage A), CLD-2: Chronic liver disease (Child-Pugh stage B or C), FSH: Follicular-stimulating hormone, LH: Luteinizing hormone, LT: Liver transplantation, TSH: Thyroid-stimulating hormone

Table 3: Clinical and biochemical predictors of hypogonadism in patients with chronic liver disease

Parameter	Hypogonadism-present (n=20)	Hypogonadism-absent (n=30)	P value
Age (years)	46±11	40±8	0.05
Serum protein (g/dL)	6.1±0.6	6.4±0.8	0.18
Serum albumin (g/dL)	3.0±0.5	3.4±0.4	0.007
FPG (mg/dL)	112±24	95±70	0.007
PPBG (mg/dL)	160±39	138±33	0.04
Serum bilirubin (mg/dL)	3.2±1.8	2±0.7	0.007
AST (U/L)	53±30	40±11	0.04
ALT (U/L)	62±36	49±20	0.12
INR	1.6±0.4	1.3±0.3	0.01
Total cholesterol (mg/dL)	169±27	196±32	0.002
TG (mg/dL)	159±53	189±48	0.009
LDL (mg/dL)	93±23	112±31	0.11
HDL (mg/dL)	39.2±10.9	39.6±7	0.85

ALT: Alanine transaminases, AST: Aspartate transaminases, FPG: Fasting plasma glucose, HDL: High-density lipoprotein, INR: International normalized ratio, LDL: Low-density lipoprotein, PPBG: Post-75 g glucose plasma glucose, TG: Triglycerides

and autoimmune hypothyroidism (12%) are common.^[17] Subclinical hypothyroidism has been reported in patients with hepatitis-C related CLD, which has been attributed to direct cytopathic effect of hepatitis-C virus on thyroid cells,^[18] underlying latent autoimmune disease,^[19] and treatment related.^[20]

Serum total T3 was lower in all forms of liver disease when compared with controls. However, FT3 was significantly lower in patients with CLD-2. This was due to decreased hepatic uptake and type-1 deiodinase activity (D1), which converts T4 to T3.^[5] Liver disease is also associated with increase in inflammatory cytokines that negatively affect hypothalamo-thyroid axis,^[11,21] which may explain lower TSH levels (statistically not significant) observed in patients with liver disease as compared to controls in this study. Other studies have reported higher levels of TSH in CLDs,^[8,22] but these studies have not excluded patients with overt thyroid dysfunction, which we have excluded in this study before analysis. One study reported normal TSH response to TSH releasing hormone.^[2] Serum total T3 was lower in AH and CLD-2 compared with CLD-1 in this study, reflecting associated severity of liver disease.^[8-10] Most consistent abnormality of thyroid functions reported is lower total and free FT3 and increase in rT3 in patients with cirrhosis of liver.^[2,4,5] The plasma T3:rT3 ratio has a negative correlation with the severity of cirrhosis.^[23] In present study, we could not measure rT3. Thyroid hormone is associated with basal metabolic rate, and low total and free T3 levels may reflect adaptive hypothyroid state. This will reduce the basal metabolic rate and may help to preserve hepatocytes and liver function. Occurrence of hypothyroidism in cirrhotic patients has been shown to be associated with a biochemical

improvement in liver function,^[12] and decreased rate of decompensation in cirrhosis.^[13] Total and free T4 was increased in CLD-1 but decreased significantly in patients with CLD-2. Increase in total T4 has been observed in patients with acute and CLD due to increase in TBG levels, which is synthesized as acute phase reactant.^[8] Serum total T3 increased significantly post-LT in present study.

Patients with liver diseases have increased low-density lipoprotein (LDL) and lower high-density lipoproteins HDL, which improves after LT. This can also be explained by alteration in thyroid functions. Thyroid hormones increase the expression of LDL receptors on the hepatocytes and increase the activity of lipid-lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels.^[24] Thyroid hormones also increase the expression of apolipoprotein A1, a major component of high-density lipoprotein.^[24] Hence, decrease in thyroid hormones associated with liver disease will adversely affect LDL disposal and decrease HDL synthesis.

In this study, 40% of patients with liver disease had secondary hypogonadism. It was commonest with CLD with Child Pugh stage B and C, and after LT. Hypogonadism can be predicted by older age and deteriorating liver functions. Hypogonadism has been reported in 50%-75% of patients with cirrhosis.^[25] In our study, serum total testosterone decreased progressively from acute liver disease to CLD and correlated with the increasing severity of liver disease. Serum LH levels were significantly lower in patients with CLD-1 but were comparable in other groups as was the FSH. A similar observation has been made by an Indian study.^[4] Another study reported higher level of LH in patients with cirrhosis of liver but lower LH response to gonadotropin-releasing hormone indicating involvement of hypothalamo-pituitary-gonadal axis at all levels. There was no difference in FSH level among patients and controls.^[2] A study assessed pulsatile pattern of LH in patients with CLD and found attenuated pattern of LH secretion, indicating hypothalamic dysfunction.^[26] On the contrary, few studies have suggested primary gonadal failure with compensatory in LH in patients with CLD.^[2,27] Alcohol is known to affect gonadal functions, which were not included in this study. A study similar to ours, also noticed reduced levels of total and free testosterone and increased levels of SHBG compared with controls with normal liver function in men with chronic nonalcoholic liver disease, which was related with severity of liver disease.^[6] In the present study, serum testosterone levels were higher in patients after LT, but remained lower than controls. Handelsman *et al.*,^[6] also reported gradual improvement in serum testosterone levels over 12 months post-LT, but levels remained subnormal. There was no change in LH and FSH after transplantation

in this study. However, one study reported increase in gonadotropins and testosterone, and decrease in estradiol levels after transplantation. This was probably due to more severe gonadal dysfunction in their study, as 90% of patients had hypogonadism.^[14] In the present study, serum estradiol levels were higher in all patients with liver disease compared with controls, which was similar to observed by others.^[2,4,27] Mao *et al.*,^[28] observed that serum estradiol levels were correlated with severity of liver disease and deteriorating liver functions in males with HBV-related liver disease.

The strengths of this study are the assessment of thyroid and gonadal functions at various stages of liver disease and exclusion of patients with alcoholic liver disease because alcohol is known to affect hypothalamo-gonadal axis. In the present study, most of the patients were stable and not critically ill except four patients with hepatic failure, leading to lesser confounding factors in thyroid and gonadal dysfunction. Our study had some limitations. First, we have not measured free testosterone, TBG, and SHBG due to financial constraints. Second, pituitary response to TRH and GnRH was not assessed, which could have highlighted underlying mechanism. Third, as this was a cross-sectional study, we could not assess factors which could have predicted mortality or morbidity.

In conclusion, hypogonadism and NTIS are common in the spectrum of acute and CLD. Deterioration of synthetic functions of liver disease predicts presence of hypogonadism.

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