《原 著》

An Evaluation of Factors Which Affect Circulating Thyroid Hormone Levels in Liver Diseases

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Abstract Serum concentrations of thyroid hormones, thyroxine binding globulin (TBG) and TSH were measured in 12 patients with acute hepatitis, 18 with chronic active hepatitis (CAH), 23 with chronic persistent hepatitis (CPH), 28 with compensated liver cirrhosis, 14 with decompensated liver cirrhosis and 45 normal subjects. In CAH, serum concentrations of T_4, T_3 and reverse T_3 (rT_3) increased but values for T_3-uptake decreased and free T_4 and T_3 indices did not differ from controls. Similar results were observed in CPH and compensated cirrhosis. These changes in circulating thyroid hormones were mainly due to the increase in serum TBG concentration which correlated significantly with serum GOT activities. In decompensated cirrhosis, serum T_4 and T_3 levels as well as free T_4 and T_3 indices decreased with concomitantly increased rT_3 levels and hence, serum rT_3/rT_3 ratios showed a marked increase. However, serum TBG levels and values for T_3-uptake did not differ from controls, indicating that changes in serum thyroid hormones were mainly due to the impaired peripheral conversion of T_4. In compensated and decompensated cirrhosis altogether, serum TBG levels correlated positively with serum albumin levels and inversely with serum bilirubin levels and ICG retension rates, and rT_3/T_3 ratios correlated inversely with serum albumin levels and positively with ICG retension rates. In acute hepatitis, serum TBG, T_4 and rT_3 levels increased with normal T_3 levels and serunm rT_3/T_3 ratios increased. It is suggested that abnormalities in circulating thyroid hormones in liver diseases are due to either changes in serum TBG concentrations, or impaired peripheral metabolism of thyroid hormones or both.

I. Introduction

Various abnormalities in circulating thyroid hormones have been demonstrated in liver diseases, however, there is disagreement concerning the reasons for the abnormalities. In liver cirrhosis, serum thyroxine (T_4) levels have been reported to be decreased[1~5] or normal [6~8] and serum triiodothyronine (T_3) concentrations lower[1~3,7] or higher[6] than those in normal subjects. Free T_4 levels or free T_4 indices were increased[2,3,6~8] or normal[5] and free T_3 levels or free T_3 indices were increased[6], decreased,[1~3] or normal.[7] Thyroxine binding globulin (TBG) or throxine binding capacity (TBC) in serum has been demonstrated to be increased[6], normal[1,2], decreased[9] or quite variable.[8] Serum reverse T_3 (rT_3) concentrations were increased.[1,3,10] In acute hepatitis, serum T_4 levels[7,10] and TBC[11,12] were reported to be increased. In chronic active hepatitis, Schussler et al. reported that TBC in serum was high, and serum T_4 and T_3 levels were increased slightly leading to decreased free hormone concentrations, probably because of decreased thyroid function in autoimmune liver disease[13]. In contrast, Sheridan found variable values for serum T_4 and T_3 levels but values for free T_3 and T_3 indices were within

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the normal range in chronic active hepatitis[14].

In order to elucidate factors which account for the aforementioned discrepancies, we have measured simultaneously many indices of circulating thyroid hormones, e.g. serum concentrations of T_4, T_3, rT_3, TSH and TBG, values for T_3-uptake (T_3-U), free T_4 and T_3 indices and titers of antithyroid autoantibodies in well classified types of liver disease. In the present study, liver diseases were classified to acute hepatitis, chronic active hepatitis (CAH), chronic persistent hepatitis (CPH), compensated and decompensated liver cirrhosis, according to the histological findings, values for liver function tests and clinical examination.

II. Patients and Methods

Patients: Studies were performed in 12 patients with acute hepatitis (10 males, 2 females; age range 27–65 yr, mean 43 yr), 18 with chronic active hepatitis (16 males, 2 females; age range 25-77 yr, mean 43 yr), 23 males with chronic persistent hepatitis (age range 25–66 yr, mean 45 yr), 28 with compensated liver cirrhosis (25 males, 3 females; age range 28–71 yr, mean 48 yr), 14 with decompensated liver cirrhosis (9 males, 5 females; age range 42–63 yr, mean 53 yr), and in 45 normal male subjects (age range 22–66 yr, mean 41 yr). The diagnosis of chronic active hepatitis (CAH), chronic persistent hepatitis (CPH) and liver cirrhosis was established by liver biopsy and/or laparoscopy, and the diagnosis of acute hepatitis was made by clinical signs and symptoms and liver function tests. Patients with decompensated liver cirrhosis had ascites and/or hepatic encephalopathy. Results of liver function tests in the patients studied are shown in Table 1.

None of the patients had clinical evidence of thyroidal disorders or other endocrine diseases, or signs of cardiac, renal or febrile illness. They were well fed for at least a week before collecting blood samples, except some patients with acute hepatitis and decompensated liver cirrhosis. Eight patients with CAH were taking maintenance doses (10–15 mg) of prednisolone and 5 patients with compensated cirrhosis and all the patients with decompensated cirrhosis were being given diuretics. Since most of the patients with hepatitis studied in the present study were male, controls were chosen only from male subjects.

Measurement of Serum Concentrations of Thyroid Hormones, TBG and TSH: Serum T_4 and T_3 concentrations were measured with T_4-RIA^R and T_3-RIA kit^R, and T_3-U with Triosorb M kit^R of Dainabot Radioisotope Laboratory. Serum rT_3 concentrations were determined by RIA according to a method described previously[15]. Serum TBG concetrations were determined by a specific RIA using RIA-gnost TBG kit^R obtained from Hoechst, Japan, Ltd. Serum TSH concentrations were measured by HTSH kit^R of Daiichi Radioisotope Laboratory. Free T_4 Index (FT_4I) and free T_3 index (FT_3I) were calculated from the following equations[16]: FT_4I=serum T_4 levels$\times T_3$-U as a ratio to normal, FT_3I=serum T_3 levels$\times T_3$-U as a ratio to normal.

Determination of Thyroid Antibodies: Antibodies to thyroglobulin and thyroidal microsomes were measured by the tanned red cell hemagglutination technique, using commercially available kits (thyroid test and microsome test, respectively from Fujizoki Pharmaceutical Co., Ltd. Tokyo).[17),18] Antibody titers of less than 200 were judged as being negative for both thyroglobulin and microsome tests.

Liver Function Tests: Serum albumin and

Table 1 Liver Function Tests in Patients with Liver Diseases.

Diagonosis	No. of case	Albumin (g/dl)	Bilirubin (mg/dl)	GOT (K.U.)	ICG(15′) (%)
Acute hepatitis	12	3.75±0.09	3.88±0.98	349±95	——
Chronic active hepatitis	18	4.11±0.07	0.71±0.07	165±15	15.1±3.0
Chronic persistent hepatitis	23	4.26±0.07	0.67±0.03	57± 8	12.0±1.1
Compensated liver cirrhosis	28	3.73±0.08	1.15±0.10	78± 8	27.5±1.7
Decompensated liver cirrhosis	14	2.71±0.11	4.33±1.16	88±13	45.2±2.9
Normal range		4.0—5.0	0.3—1.2	8—28	<10

bilirubin levels were determined with a Technicon SMA 12/60 autoanalyzer. Serum GOT activity was expressed as Karmen Units using an LKB 8600 reaction rate analyzer. ICG retension rate was the percent retension of indocyanine green at 15 min after a single intravenous injection.

Results were expressed as means±SEM and the significance of the difference of the means was assessed by Student's test. Correlation coefficients were caluclated by means of standard linear regression analysis.

III. Results

Serum Concentrations of Thyroid Hormones, TBG and TSH

Chronic Hepatitis: Serum T_4 and T_3 concentrations were significantly higher in patients with chronic active hepatitis (CAH) and chronic persistent hepatitis (CPH) than in controls, as shown in Table 2. Serum rT_3 concentrations were also significantly higher in patients with CAH than in controls. However, the ratio of rT_3/T_3 in serum were not significantly different among CAH, CPH and controls (Fig. 1). Serum concentrations of TBG were significantly greater and values for T_3-U were significantly lower in both patients with CAH and CPH than in controls, respectively. On the other hand, values for FT_4I and FT_3I in patients with CAH and CPH did not differ significantly from those in controls, and serum TSH concentrations in these patients were within the normal range.

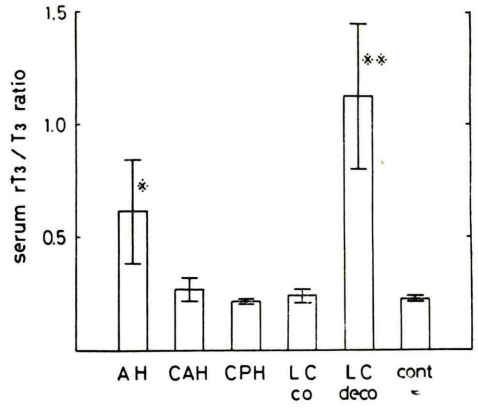

Fig. 1 Serum rT_3/T_3 ratios in patients with liver diseases. AH; acute hepatitis, CAH; chronic active hepatitis, CPH; chronic persistent hepatitis, LC co; compensated liver cirrhosis, LC deco; decompensated liver cirrhosis, cont: controls. Vertical bars give SEM. ※<0.01, ※※<0.001 as compared with controls.

Liver Cirrhosis: In patients with compensated liver cirrhosis, serum concentrations of T_4 were significantly higher than in controls. Serum T_3 and rT_3 concentrations as well as serum rT_3/T_3 ratios in compensated cirrhotics did not differ significantly from those in controls. Serum concentrations of TBG were significantly greater and

Table 2 Serum Concentrations of Thyroid Hormones, Thyroxine Binding Globulin (TBG) and TSH in Patients with Liver Diseases.

Diagnosis	T_4 (μg/dl)	T_3 (ng/dl)	rT_3 (ng/dl)	T_3-U (%)	Free hormone index[a] FT_4I	FT_3I	TBG (mg/l)	TSH (μU/ml)
Acute hepatitis (12)[b]	12.2±1.2[d]	129±19	56.5±16.5[d]	23.8±1.1[d]	9.5±0.8	97±13[c]	42.6±4.4[c]	3.1±0.4
Chronic hepatitis								
Active (18)	13.0±0.4[e]	184±11[d]	45.0±3.8[e]	21.8±0.5[e]	9.6±0.5	132± 9	36.9±3.3[e]	3.2±0.5
Persistent (23)	10.5±0.5[d]	151± 7[d]	30.9±2.5	26.4±0.8[d]	9.3±0.4	131± 7	26.1±1.8[c]	3.6±0.7
Liver cirrhosis								
Compensated (28)	9.4±0.3[c]	138± 6	31.7±3.1	26.0±0.7[c]	8.6±0.3	124± 6	28.8±2.7[d]	3.7±0.4
Decompensated (14)	7.0±0.4[d]	70± 6[e]	63.0±9.5[e]	31.6±1.3	7.3±0.4[d]	73± 6[e]	18.2±1.4	3.4±0.5
Controls (45)	8.5±0.2	124± 3	27.9±1.1	29.9±0.8	8.8±0.3	124± 5	19.2±1.1	3.6±0.4

Data are presented as means±SEM. [a] FT_4I=serum $T_4\times T_3$-U as a ratio to controls, FT_3I=serum $T_3\times T_3$-U as a ratio to controls. [b] Numbers in parenthesis represent numbers of subjects. However, serum TBG levels were measured in following numbers of subjects; 7 of acute hepatitis, 9 of chronic active hepatitis, 9 of chronic persistent hepatitis, 12 of compensated cirrhosis, 8 of decompensated cirrhosis, and 16 of controls. [c] $p<0.05$, [d] $p<0.01$, [e] $p<0.001$ as compared with controls.

values for T_3-U were significantly lower in compensated cirrhotics than in controls. In these patients, however, values for FT_4I and FT_3I did not differ significantly from those in controls, and serum TSH levels were within the normal range. These results were essentially the same as those in chronic hepatitis.

In patients with decompensated liver cirrhosis, serum concentrations of T_4 and T_3 were significantly lower and those of rT_3 were significantly higher than controls, respectively. As shown in Fig. 1, the increase in the ratio of rT_3/T_3 in serum was significant in patients with decompensated cirrhosis. Significant difference in serum TBG levels and values for T_3-U was not observed between decompensated cirrhotics and controls. Values for FT_4I and FT_3I were significantly lower than controls. Serum TSH concentrations, however, were within the normal range. Abnormal serum thyroid hormone levels can be explained only by the impaired peripheral conversion of T_4.

Acute Hepatitis: In patients with acute hepatitis, serum T_4 and rT_3 levels were significantly greater than controls, but serum T_3 levels did not differ from controls. Serum rT_3/T_3 ratios in patients with acute hepatitis were significantly higher than controls, as shown in Figure 1. Serum TBG concentrations were significantly higher and values for T_3-U were significantly lower than those in controls. Values for FT_4I were not significantly different from controls, but values for FT_3I showed a significant decrease. Serum TSH levels were within the normal range.

Relation to Liver Function Tests

As shown in Fig. 2, there was a significant and positive correlation between serum TBG levels and serum GOT activities in patients with CAH and CPH. Since serum GOT activities change rapidly in acute hepatitis, values in acute hepatitis were omitted in this figure.

In Table 3 is shown the correlation of serum TBG concentrations and serum rT_3/T_3 ratios with values for liver function tests in patients with liver cirrhosis. In this table, values in both compensated and decompensated cirrhosis are included. Serum TBG concentrations correlated significantly and positively with serum albumin levels and inversely with serum bilirubin levels and ICG retension rates but did not correlate with serum GOT activities. Serum rT_3/T_3 ratios in cirrhotics correlated inversely with serum albumin levels and positively with ICG retension rates but did not correlate with serum GOT activities and serum bilirubin levels.

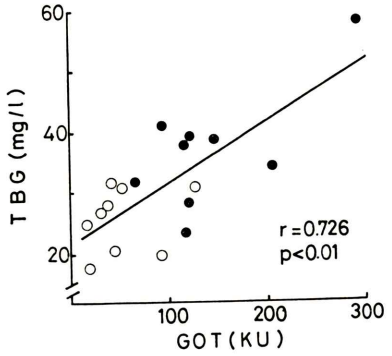

Fig. 2 Correlation between serum TBG levels and serum GOT activities in patients with chronic hepatitis. ● chronic active hepatitis, ○ chronic persistent hepatitis.

Table 3 Correlation of Serum Thyroxine Binding Globulin (TBG) Levels and Serum rT_3/T_3 Ratios with Values for Liver Function Tests in Patients with Liver Cirrhosis.[a]

	GOT (K.U)	Albumin (g/dl)	Bilirubin (mg/dl)	ICG (15′) (%)
TBG (mg/l)	0.137	0.728	−0.540	−0.693
	NS[b]	$p<0.001$	$p<0.05$	$p<0.01$
rT_3/T_3 ratio	0.164	−0.667	0.352	0.670
	NS	$p<0.001$	NS	$p<0.01$

[a] Patients with both compensated and decompensated cirrhosis altogether.
[b] Correlation is not significant.

Thyroglobulin and Thyroidal Microsomal Antibodies

Thyroglobulin and thyroidal microsomal antibodies in serum were determined in 11 patients with CAH, 9 with CPH, 6 with compensated and 3 with decompensated liver cirrhosis. One patient with CPH and one with compensated cirrhosis had both antibodies, and one with decompensated cirrhosis had thyroidal microsomal antibodies.

IV. Discussion

Since TBG is synthesized in and secreted by

liver parenchymal cells,[19~21] serum TBG concentrations may be affected by liver diseases, and may have an influence on serum concentrations of thyroid hormones. The other factor which may affect serum thyroid hormone levels in liver diseases is the abnormalities in peripheral metabolism of thyroid hormones.[22,23] Decreased T_3 and increased rT_3 levels in serum have been found in patients with liver cirrhosis and have been thought to be the result of decreased peripheral conversion of T_4 to T_3.[1,3,7]

In patients with CAH and CPH in the present study, serum TBG concentrations were significantly higher than those in controls and correlated significantly with serum GOT activities.

The abnormalities in circulating thyroid hormones in these patients were the increased concentrations of serum T_4, T_3 and rT_3, and the decreased values for T_3-U. Values for FT_4I and FT_3I as well as serum TSH levels did not differ from those in controls. Although serum rT_3 levels increased, serum rT_3/T_3 ratios were not different from controls. These results indicate that a major factor affecting serum levels of thyroid hormones in patients with CAH and CPH is the increase in serum TBG concentrations.

Schussler et al., however, reported a decrease in serum free thyroid hormone concentrations with an increase in total T_4 and T_3 levels in patients with CAH and suggested that the decrease in serum free hormone levels were probably due to autoimmune thyroiditis.[13] They found thyroid autoantibodies in 13 of 18 patients. Recently, Crowe et al. reported that a survey of throid function in 95 patients with primary biliary cirrhosis revealed the presence of throid autoantibodies in 24 females and one male.[24] Nine of this thyroid autoantibody positive group had some biochemical evidence of hypothyroidism. In our present study, however, thyroid autoantibodies were present in only one of 20 patients with chronic hepatitis. In Japan, autoimmune chronic active hepatitis (lupoid hepatitis) is relatively rare.[25]

Patients with liver cirrhosis in the present study were divided into two groups according to the presence of ascites and/or hepatic encephalopathy. Serum TBG concentrations were significantly higher in compensated cirrhotics than in controls, but were not different from controls in decompensated cirrhotics. In patients with compensated and decompensated cirrhosis altogether, serum TBG levels did not correlated with serum GOT activities but correlated positively with serum albumin levels and inversely with serum bilirubin levels and ICG retension rates.

In patients with compensated cirrhosis, serum T_4 concentrations increased and values for T_3-U decreased. These abnormalities could also be explained only by the increase in serum TBG concentrations. In patients with decompensated cirrhosis, serum TBG concentrations were not different from controls, but serum T_4 and T_3 levels decreased and rT_3 levels increased. Since values for T_3-U did not differ from controls, values for FT_4I and FT_3I were significantly decreased. However, serum TSH concentrations were within the normal range. Serum rT_3/T_3 ratios in these patients were significantly higher than those in controls. The increased serum rT_3/T_3 ratios in decompensated cirrhotics and normal ratios in compensated patients were also reported by Yamanaka et al.[26] In the present experiment, serum rT_3/T_3 ratios correlated inversely with serum albumin levels and positively with ICG retension rates when correlation coefficients were calculated from values in patients with compensated and decompensated cirrhosis altogether. On the other hand, the increase in serum rT_3/T_3 ratios has also been reported in patients with starvation,[3,27] febrile states,[3,28] postsurgical states[29] and myocardial infarction.[30] Therefore, it is not clear whether the changes in peripheral metabolism of T_4 in patients with decompensated cirrhosis are due to liver damage per se, or the results of the complications such as ascites or anorexia.

It has been reported recently that in very severely ill patients, serum total T_4 concentrations as well as FT_4I values were lower than the normal range. This "low T_4 sick state" was more seriously ill than in the low T_3 sick state and the mortality rate in patients with low FT_4I has been reported to be greater than 60%. In patients with decompensated cirrhosis in the present study, the decrease in FT_4I values could be considered to reflect the low T_4 sick state, since serum TSH levels were not increased. These results in patients with decompensated cirrhosis could be considered to be due to the impaired peripheral metabolism

of thyroid hormones.

In patients with acute hepatitis, serum TBG concentrations increased and values for T_3-U decreased. Serum T_4 concentrations increased and values for FT_4I were not different from controls. In spite of the increase in serum T_4 levels, serum T_3 levels were not different from controls and values for FT_3I were lower than those in controls. Serum rT_3 levels and serum rT_3/T_3 ratios in these patients were significantly higher than those in control subjects. These changes in serum thyroid hormones in patients with acute hepatitis could be explained by both the increase in serum TBG levels and the impaired peripheral conversion of T_4 to T_3.

From the results obtained in the present study, it is suggested that the abnormalities in circulating thyroid hormones in patients with liver diseases are due to either the changes in serum TBG concentrations, impaired peripheral metabolism of thyroid hormones, the presence of autoimmune thyroiditis or combination of these. The increased serum TBG concentration is the major factor in CAH, CPH and compensated liver cirrhosis and the impaired peripheral conversion of T_4 plays a major role in decompensated cirrhosis. The combination of two factors is often observed in patients with acute hepatitis.

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要　旨

肝疾患における血中甲状腺ホルモン濃度の変動について

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各種肝疾患患者の血中甲状腺ホルモン，TBG および TSH 濃度を RIA 法にて測定した．慢性活動性肝炎 (18 例) では T_4，T_3，rT_3 濃度とともに TBG 濃度が有意に上昇，T_3 摂取率は減少しており FT_4I，FT_3I は健常者と差がなかった．慢性非活動性肝炎 (23 例) と代償性肝硬変 (28 例) でも同様の変化を認めた．これらの変化は主に TBG の上昇によると考えられた．非代償性肝硬変 (14 例) では T_4，T_3 および FT_4I，FT_3I が有意に低下，rT_3，rT_3/T_3 比が有意に増加していた．しかし TBG，T_3 摂取率は健常者と差がなく，これらの変化は主に T_4 の末梢での代謝異常によるものと考えられた．なお TBG 濃度は慢性肝炎では SGOT と正の相関を，肝硬変ではアルブミンと正の相関を，ICG およびビリルビンと負の相関を認めた．急性肝炎 (12例) では TBG，T_4，rT_3 および rT_3/T_3 比が有意に増加していた．肝疾患の甲状腺ホルモン値異常には TBG 濃度と T_4 の末梢での代謝の変化を考慮すべきである．

Key Words: Thyroid hormone, Thyroxine binding globulin, Acute hepatitis, Chronic hepatitis, Liver cirrhosis