

# SERUM THYROID HORMONE LEVELS IN LIVER CIRRHOSIS

Pages with reference to book, From 179 To 183

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## Abstract

Levels of thyroid hormones, serum thyroxine, triiodothyronine (T<sub>3</sub>), free thyroxine (FT<sub>4</sub>), free triiodothyronine (FT<sub>3</sub>) and thyrotropin (TSH) were measured in 55 patients with liver cirrhosis using radioimmunoassay techniques. Results were compared with 78 controls. The mean serum concentration of T<sub>3</sub>, FT<sub>3</sub> and FT<sub>4</sub> were significantly decreased in cirrhotics, while no significant change was noted in serum T<sub>4</sub> and TSH levels. T<sub>3</sub>/T<sub>4</sub> ratio was also lower than the normal. This indicates an impaired liver conversion of T<sub>4</sub> to T<sub>3</sub> in peripheral tissues. Serum T<sub>3</sub> and FT<sub>3</sub> showed an inverse correlation with serum bilirubin and a positive correlation with serum albumin. T<sub>3</sub>, FT<sub>3</sub> and T<sub>3</sub>/T<sub>4</sub> ratios were significantly low in patients who had ascites as compared to those who had no ascites. This study confirms the presence of abnormalities in serum thyroid hormone levels in cirrhosis of liver. Alteration in serum T<sub>3</sub> and FT<sub>3</sub> levels correlate well with the disease severity and may be useful in assessing the course and prognosis in cirrhotic patients (JPMA 39:179, 1989).

## INTRODUCTION

The liver plays an important role in thyroid hormone metabolism being involved in conjugation, excretion, peripheral deiodination and in synthesis of thyroxine binding globulin. It is now generally accepted that the serum concentrations of thyroid hormones will vary in patients with hepatic disorders, especially in patients with liver cirrhosis.<sup>1</sup> In some studies of liver cirrhosis where the peripheral conversion of thyroxine (T<sub>4</sub>) to triiodothyronine (T<sub>3</sub>) was examined, the liver was found to be one of the major sites of this peripheral conversion<sup>2,3</sup>. This study was undertaken to examine the changes of serum levels of thyroid hormones in patients with cirrhosis and to examine whether the abnormality in the metabolism of thyroid hormones in liver cirrhosis would parallel the degree of hepatic damage or not.

## MATERIAL AND METHODS

Fifty five clinically, biochemically and biopsy proven patients with cirrhosis were studied. Gastroscopy, ultrasonography and liver scan were also done in some patients. Standard laboratory tests included prothrombin time, total proteins, albumin, globulin, bilirubin, alkaline phosphatase, serum aspartate transaminase (AST) and serum alanine transaminase (ALT). In addition presence and absence of ascites was also recorded. Samples of blood were drawn in the morning, serum was separated and after biochemical analysis, stored at -20°C. Stored frozen serum samples were assayed for thyroxine (T<sub>4</sub>), triiodothyronine (T<sub>3</sub>), thyrotropin (TSH), free thyroxine (FT<sub>4</sub>) and free thyronine (FT<sub>3</sub>) by radioimmunoassay techniques using Amersham Amerlex RIA kits (supplied by Amersham International Ltd. U.K.). Each assay was performed on duplicate serum samples. A set of quality control sera (Amersham U.K.) was also analysed with each assay to check the accuracy and performance of the assay. The radioactivity was counted in Multi-detector computerised Gamma counter (model 1612-Nuclear Enterprises) using a 4 parameter non-linear curve fitting model. As a control group 78 controls

of the same age group were investigated for thyroid hormones and TSH.

## **STATISTICAL METHODS**

Results were analysed on a MITAC personal computer, comparison between patients and controls were made using the Student's "C" test. Correlation analyses between the different indices were done and P values were calculated using Fisher and Yates statistical table A "F" value of less than 0.05 was considered to be statistically significant. All results were expressed in SI Units i.e. nmol T3/L, nmol T4/L, pmol FT4/L, pmol FT3/L and TSH ml U/L.

## **RESULTS**

Of 55 patients with cirrhosis 28 were males and 27 were females, the mean age was 41 (s.e.±2.8) years with a range of 5 to 80 years. In 78 controls, (54 males and 24 females) the mean age was 41 (s.e. ± 1.73) years and the range was 14 to 87 years. In most of the cases diagnosis of cirrhosis was made on liver biopsy. Other factors used in the diagnosis of cirrhosis included disturbed liver function tests, presence of portal hypertension, Ultrasonography and liver scintigraphy. Upper G.I. endoscopy showed oesophageal varices in 40 cases. Ultrasonography showed changes in the liver parenchyma consistent with cirrhosis in 28 cases while ascites was present in 41 cases. Liver scintigraphy showed reduced patchy uptake of the iso-tope by the liver, splenomegaly with increased uptake and marrow uptake in 10 cases.

**TABLE 1. Liver function tests in Patients with Cirrhosis of liver.**

	Mean $\pm$ S.E.	(Range)	Normal Range
Bilirubin (U Mols/L)	49.78 $\pm$ 13.7	6.3– 631.3	3.3–16.6
Total Protein (G/100ML)	6.53 $\pm$ 0.1	5 –7.9	6 –8
Albumin (G/100 ML)	3.18 $\pm$ 0.09	1.9–4.9	3.5–5.5
Globulin (G/100ML)	3.33 $\pm$ 0.12	1.6–5.6	Upto–2.5
SGOT (IU/L)	153.8 $\pm$ 33.79	28 –1319	10–35
SGPT (IU/L)	89.24 $\pm$ 10.69	19 –377	8 –35
Alk.Phospha- tase (IU/L)	56.2 $\pm$ 7.27	10 –272	9–35
Prothrombin Time (S)	15 $\pm$ 0.24	12 –22	13–15

Table 1 shows the biochemical findings in cirrhotics<sup>5</sup>. Bilirubin was normal ( $< 17.0$   $\mu$  mol/L) in 29 (53%) patients while 18 (33%) patients had values between 17 to 100  $\mu$  mol/L and 7(13%) had values greater than 100  $\mu$  mol/L. Serum albumin was low ( $< 3.5$  g/dl) in 30 (56%) and globulins were elevated ( $> 2.5$  g/dl) in 41 (76%) cases. Transferases were elevated in the majority of patients. A prolongation of prothrombin time ( $> 15$  minutes) was noted in 10 (18%) patients. As there was no significant difference in various hormone levels between the two sexes both in patients and controls, the data is reported in total subjects.

**TABLE II. Thyroid hormones and TSH Levels in Patients with cirrhosis and in Controls.**

	Patients (55)		Controls (78)	
T <sub>4</sub> (SIU)	95.83	± 4.91	106.40	± 2.12
T <sub>3</sub> (SIU)	*1.09	± 0.07	1.72	± 0.04
TSH(SIU)	2.16	± 0.22	1.71	± 0.08
FT <sub>4</sub> (SIU)	*12.50	± 0.44	17.03	± 0.48
FT <sub>3</sub> (SIU)	*2.71	± 0.24	6.17	± 0.17
T <sub>3</sub> /T <sub>4</sub> (SIU)	*0.012	± 0.001	0.0165	± 0.0004

All results are in mean ± SE

\*P < 0.001 compared with controls.

Table II shows the mean values for the indices of thyroid function in patients with cirrhosis and in controls. Cirrhotic patients showed significantly reduced mean serum levels of T<sub>3</sub>, FT<sub>3</sub> and FT<sub>4</sub>. Mean T<sub>3</sub>/T<sub>4</sub> ratio was also significantly low in patients with cirrhosis. Though the mean serum T<sub>4</sub> level in cirrhosis was low compared with controls but the difference was statistically insignificant. Four (10%) patients had raised T<sub>4</sub> levels (>136 nmol/L) and in 14 (33%) T<sub>4</sub> was low (<77nmol/L), while 24 (57%) patients had normal T<sub>4</sub> levels. Significant difference was found between patients and controls in mean FT<sub>4</sub> levels. In 14 (25%) patients the FT<sub>4</sub> levels were lower than those of controls. The mean levels of T<sub>3</sub> and FT<sub>3</sub> were significantly lower in cirrhotic patients. Low T<sub>3</sub> levels were found in 14 (25%) patients while FT<sub>3</sub> levels were low in 48 (87%) patients. Of the total 48 patients with low FT<sub>3</sub>, 35 (73%) had normal FT<sub>4</sub> and 13 (27%) had low FT<sub>4</sub> levels. The mean value of TSH in cirrhotics was above the mean in normal controls but without statistical significance. Serum TSH levels were normal in all patients except 4 cases (4.9, 63, 63 and 93mIU) with levels above the normal range. Simple correlation analysis showed that among the liver function tests, bilirubin, albumin and prothrombin time had significant correlation with thyroid hormones but alkaline phosphatase, transferases, total proteins and globulins had no correlation with any of the thyroid hormones. Serum T<sub>3</sub> and FT<sub>3</sub> both showed an inverse correlation with bilirubin but the relation was statistically significant only between FT<sub>3</sub> and bilirubin (Figure 1).



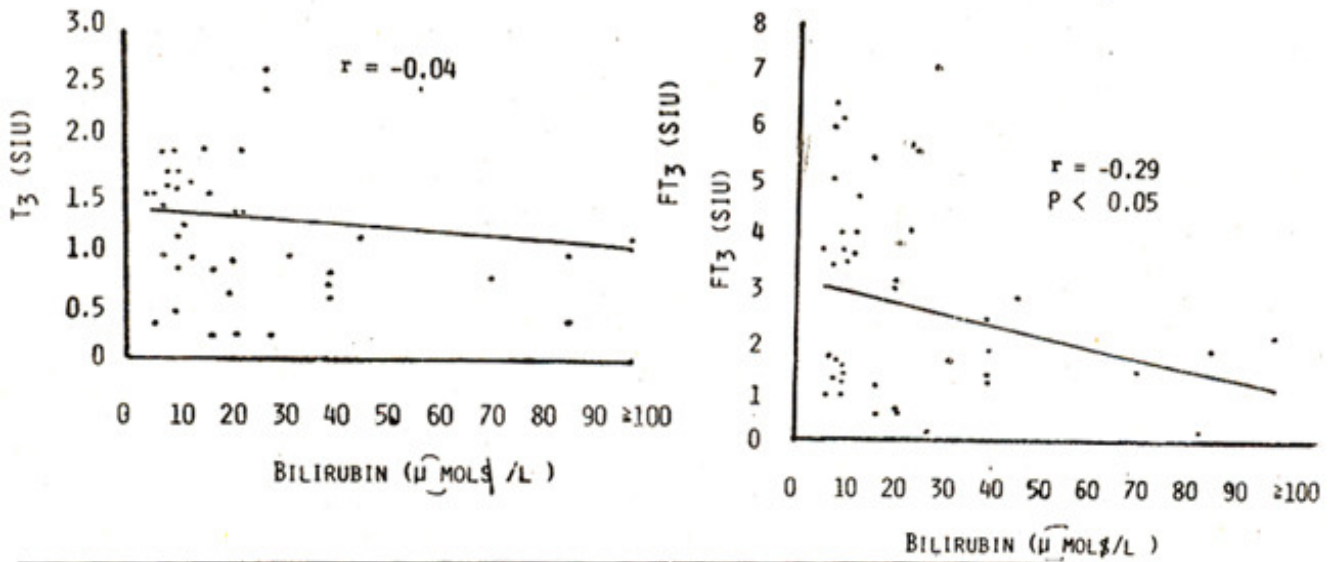


Figure 1. Relationship of T<sub>3</sub> (SIU) and FT<sub>3</sub>(SIU) to Bilirubin (μ Mol/L).

A significant positive correlation was also seen between T<sub>3</sub> and FF<sub>3</sub> v/s albumin (Figure 2);

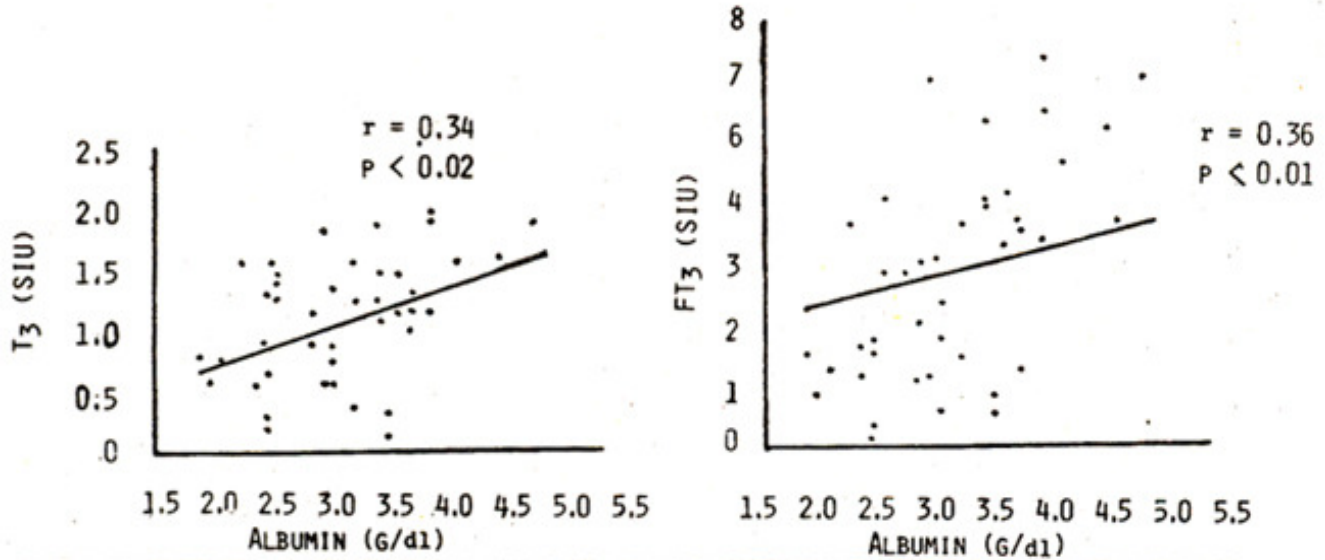


Figure 2. Relationship of T<sub>3</sub> (SIU) and FT<sub>3</sub>(SIU) to Albumin.

FF<sub>3</sub> showed greater significant correlation ( $P < 0.01$ ) with albumin than T<sub>3</sub> ( $P < 0.02$ ). Only FF<sub>4</sub> showed a positive significant correlation ( $r = 0.29$  and  $P < 0.05$ ) with prothrombin time. The mean thyroid hormone levels in cirrhotic patients with albumin levels of less than 3.5 g/dl were compared with those who had normal levels (Table III).

TABLE III. Thyroid Hormone Levels in Patients with Normal and Low albumin Levels & in Patients with and without ascites.

	Albumin		Ascites	
	<3.5g/dl (30)	>3.5g/dl (18)	Positive (41)	Negative (10)
T <sub>4</sub> (SIU)	92.83 ± 6.96	105.27 ± 8.4	96.34 ± 5.94	94.51 ± 5.32
T <sub>3</sub> (SIU)	*0.98 ± 0.08	1.36 ± 0.11	*0.98 ± 0.08	1.39 ± 0.1
FT <sub>4</sub> (SIU)	12.03 ± 0.63	13.53 ± 0.66	12.27 ± 0.5	13.92 ± 0.68
FT <sub>3</sub> (SIU)	**2.09 ± 0.24	3.93 ± 1.59	**2.29 ± 0.25	3.95 ± 0.37
T <sub>3</sub> /T <sub>4</sub>	0.011 ± 0.0007	0.0132 ± 0.0015	**0.010 ± 0.0007	0.016 ± 0.001

All results are in mean ± S.E.

\*P < 0.01

\*\*P < 0.001

A significant reduction in the mean T3 ( $P < 0.01$ ) and FT3 levels ( $P < 0.001$ ) was seen in patients with low albumin levels. Patients with ascites were found to have significantly lower levels of T3 and FT3. T3/T4 ratio was also significantly lower in these patients (Table III).

## DISCUSSION

Significant alterations in serum thyroid hormone concentrations have been frequently reported in patients with chronic liver disease,<sup>1,2,4,7</sup> and in cirrhosis it depends up on the impaired liver conversion of T4 to T3.<sup>2,3,5</sup> The formation of T3 from T4 is catalyzed by iodothyronine-5-deiodinase. This enzyme is located predominantly in the microsomes and plasma membranes of the liver and kidney.<sup>5,8</sup> Decrease in serum T3 may therefore be contributable to a postulated deficiency of hepatic iodothyronine 5-deiodinase activity.<sup>5</sup> The decrease in serum T3 found in cirrhotic patients in the present study is in agreement with other reports<sup>1,5,6,9</sup>. The serum levels of T3 in liver cirrhosis vary from 33 ng/100ml to 90.8ng/100ml<sup>2,3,5,6</sup>. In present study on mean serum T3 level was 68.9 ng/100ml fairly close to the results of Hepner et al.<sup>5</sup> The low total T3 with generally normal total T4 and TSH concentrations in the absence of clinical hypothyroidism has been frequently reported in patients with chronic liver disease as well as in many other non-thyroidal illnesses<sup>1,2,4</sup> and it has conversion of T4 to T3. Our data also confirm a highly significant reduction of T3 in liver cirrhosis with generally normal total T4 and TSH concentration. The slight normal total T4 and TSH concentration. The slight decrease in serum total T4 in some patients seen in this study is also reported by other workers<sup>5,9-11</sup>. This appeared to be due to a reduction in plasma thyroid hormone protein binding capacity with increasing liver dysfunction<sup>9</sup> as the serum from patients with alcoholic liver cirrhosis bind thyroid hormones less strongly than normal and have normal or low T4 concentration.<sup>10,12</sup> As the peripheral conversion of T4 to T3 occurs mainly in the liver, the T3/T4 ratios in liver diseases were reported lower than normal.<sup>16</sup> A similar decrease in T3/T4 ratio is noted in the present study, which confirms that patients with cirrhosis have a reduced peripheral conversion of T4 to T3. There are only few reports on direct measurement of free thyroid hormones in liver patients.<sup>1</sup> Many studies performed with equilibrium dialysis, however, showed decreased FT3 and normal or frequently increased FT4 concentrations<sup>1,3,5</sup>. Green et al.<sup>4</sup> found normal FT3 and FT4 in a small group of cirrhotic patients. However, some studies have reported low FT4 levels in cirrhotic patients.<sup>10,11</sup> The finding of decreased FT3 in our patients may have been due in part to decreased deiodination of T4 to T3, as reported in other studies<sup>1,2,8-10,14</sup> but a significant decrease in mean FT4 found in this study is in contrast to increased or normal FT4 concentrations observed in alcoholic cirrhosis.<sup>1,9,12</sup> The reason for this discrepancy is unclear. This may reflect the heterogeneity of the patient population studied (in terms of type and severity of the disease). The different methods employed for estimation of FT4 levels may also account for the variation in results.<sup>13</sup> Though we did not measure thyroid antibodies for the presence of autoimmune thyroiditis<sup>10</sup> however, the presence of hypothyroidism in our cirrhotics is unlikely because serum TSH was within the normal range in most of the patients indicating euthyroid function. Elevation of baseline serum TSH has been reported in some patients with cirrhosis but TSH responses to thyroid releasing hormone (TRH) failed to indicate hypothyroidism<sup>3,4,8</sup>. In cirrhosis, a variable correlation has been reported between abnormalities in liver and thyroid function tests.<sup>4-6,9,14</sup> Several reports, however, documented a significant correlation between the clinical severity and prognosis of the disease and serum thyroid hormone levels<sup>5,9,14</sup>. Green et al.<sup>4</sup> found that serum T3 levels in cirrhotic patients correlated with serum albumin values and Israel et al.<sup>4</sup> reported that T3 levels correlated with the prothrombin time. Orzio et al.<sup>1</sup> found a good correlation

between T3 and serum albumin, bilirubin and prothrombin time while there was no correlation with transaminases and globulins in cirrhotics. The excellent correlation in our Study between serum T3 and FF3 and the severity of liver dysfunction as well as a progressive increase in T3 and FF3 in these patients eventually displaying a favourable outcome, suggests that T3 and FF3 concentrations in patients with advanced liver cirrhosis may be considered as a helpful prognostic indicator. This study confirms the existence of abnormalities in thyroid function tests in liver cirrhosis. It also appears that the degree of depression of serum T3 and FF3 correlate well with the severity of liver disease, and may be helpful in assessing the course and diagnosis of liver cirrhosis.

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