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Thyroid function tests in chronic liver disease: evidence for multiple abnormalities despite clinical euthyroidism

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SUMMARY To further evaluate thyroid function in patients with liver disease, we have measured total and free T_3 and T_4, thyroxine binding globulin, basal and thyrotropin releasing hormone-stimulated thyrotropin and thyroglobulin antibodies in 33 patients with liver cirrhosis, in 22 with chronic hepatitis and in 30 healthy controls. All the patients but one were clinically euthyroid. T_3, FT_3, T_3/thyroxine binding globulin and T_4/thyroxine binding globulin ratios and thyrotropin after thyrotropin releasing hormone were significantly reduced, while FT_4, thyroxine binding globulin and thyrotropin were significantly increased in liver cirrhosis. In chronic hepatitis group, FT_3 and T_3/thyroxine binding globulin ratio were significantly lower and thyroxine binding globulin and FT_4 were higher than in healthy controls. The between patients comparison revealed a significantly lower T_3, FT_3, T_3/thyroxine binding globulin and T_4/thyroxine binding globulin ratios and Δ thyrotropin in cirrhotics. Thyroglobulin antibodies were present at high titre only in two patients one of whom having evidence of Hashimoto's thyroiditis with subclinical hypothyroidism. The correlation coefficient between T_4/thyroxine binding globulin ratio and FT_4 were lower in patients than in controls. Furthermore an abnormal thyrotropin response to thyrotropin releasing hormone was shown in 10 cirrhotics and in four patients with chronic hepatitis. Serum T_3 significantly correlated with serum bilirubin, albumin, and prothrombin time in both groups of patients. The present data confirm the existence of several abnormalities of thyroid function tests in patients with chronic liver disease, although showing that euthyroidism is almost always maintained, probably as a result of low-normal FT_3 and high-normal FT_4. Furthermore, T_3 serum levels appear to parallel the severity of liver dysfunction.

The liver plays an important role in thyroid hormone metabolism being involved in their conjugation, excretion, peripheral deiodination and in synthesis of thyroxine binding globulin. Although almost all patients with liver disease are clinically euthyroid, some abnormalities in circulating hormone concentrations have been shown in previous studies.[1–4] These data, however, are still controversial as the discrepant results reported may depend on the different analytical methods used as well as the different groups of patients investigated. In fact, total and free thyroxine (T_4 and FT_4) serum concentrations have been reported as normal, increased or decreased in various liver diseases;[3–7] abnormalities in thyroxine binding globulin serum concentration and a reduced thyroid hormone binding capacity, perhaps because of a hypothetical circulating inhibitor, have been also reported.[8] Moreover, total and free triiodothyronine (T_3 and FT_3) concentrations are often decreased, sometimes profoundly and their levels correlate well with the severity of liver dysfunction.[4–9] In order to further evaluate thyroid function in liver disease, we have measured T_3, T_4, FT_3, FT_4 serum levels, thyroxine binding globulin, thyrotropin both in basal conditions and after thyrotropin releasing hormone administration, and thyroglobulin antibodies in a large number of patients with chronic liver diseases.

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Methods

SUBJECTS

Fifty five patients, 44 men and 11 women, with chronic liver disease, aged 27–72 years, have been

studied. They were divided in two different groups: patients with advanced liver cirrhosis and patients with chronic hepatitis.

LIVER CIRRHOSIS

This group included 33 patients (29 men and four women) aged 45–72 years. All of these subjects were hospitalised because of signs and symptoms of decompensated liver cirrhosis. None of them had evidence of oesophago-gastric bleeding, acute hepatic encephalopathy, or renal failure. Owing to either clinical conditions or coagulation abnormalities, liver biopsy was not performed in any of our cirrhotics.

CHRONIC HEPATITIS

This group included 22 subjects (15 men and seven women) aged 27–56 years. The diagnosis of chronic hepatitis was made in all cases by needle biopsy according to the criteria of an international group.[10] None of these patients showed evidence of nodular evolution in their liver specimen, although it is possible that needle biopsies in these patients may underestimate the number that have progressed to cirrhosis.

The data on histological features and on aetiological factors of our patients are summarised in Table 1. Moreover, liver chemistry tests are reported in Table 2.

Our patients did not show clinical symptoms or signs of thyroid dysfunction and did not receive medications that might have affected the radioimmunoassays performed in this study. As a control group 30 healthy subjects (23 men and seven women aged 25–73 years) were investigated.

Serum T_3,[11] T_4,[12] thyrotropin[13] and thyroxine binding globulin[14] were determinated by standard radioimmunoassay methods. T_4/thyroxine binding globulin and T_3/thyroxine binding globulin ratios were calculated to give a free T4 and a free T_3 index. Thyroglobulin antibodies were evaluated by a radioassay procedure.[15] Serum FT_3 and FT_4 were measured by direct radioimmunoassay with the method of Romelli *et al*[16] by using a Lepetit kit (Milano). The thyrotropin releasing hormone test (200 μg intravenously) was performed in the morning, samples for thyrotropin determination being collected at −15, 0, 20, 30 and 60 minutes.

Table 1 *Clinical diagnosis of our patients and aetiological factors*

	No. patients	*Alcoholic*	*Postviral*	*Others*
Chronic persistent hepatitis	2	0	2	0
Chronic active hepatitis	20	7	11	2*
Cirrhosis	33	19	9	5†

* Cryptogenic
† Two haemochromatosis and three cryptogenic

Table 2 *Biochemical indices of liver function in 22 patients with chronic hepatitis and in 35 cirrhotics*

	GOT	*Bilirubin*	*Albumin*	*Prothrombin time*
Chronic hepatitis	74·5±17·1	1·3±0·3	3·6±0·1	77·6±3·8
Cirrhosis	30·8±8·4	2·3±0·6	2·7±0·1	50·5±3·2

The normal ranges in our laboratory for the above determinations are as follows: T_3, 80–200 ng/dl; T_4, 4·5–12 μg/dl; thyroxine binding globulin, 18–32 ng/ml; T_3/thyroxine binding globulin index, 3·4–9; T_4/thyroxine binding globulin index (×10),1·8–4; FT_3, 2·7–6·6 pg/ml; FT_4, 6·3–16·4 pg/ml; basal thyrotropin, <2·5 μU/ml and maximum thyrotropin increase (Δ thyrotropin) after thyrotropin releasing hormone, 5–25 μU/ml for women and 3·5–15 μU/ml for men.

The statistical analysis was carried out using the Student's *t* test and linear correlation as appropriate. Data are expressed as mean±SE.

Results

The mean values for the different indices of thyroid function in the two groups of patients with liver disease and in normal controls are reported in Table 3. Cirrhotic patients showed significantly reduced serum levels of T_3, T_3/thyroxine binding globulin ratio, FT_3, T_4/thyroxine binding globulin ratio and Δ thyrotropin and significantly increased levels of thyroxine binding globulin, FT_4 and basal thyrotropin *versus* normals. Subjects with chronic hepatitis showed significantly lower T_3/thyroxine binding globulin ratio and FT_3 and higher thyroxine binding globulin and FT_4 levels than in controls.

The comparison between the first and the second group of patients revealed that cirrhotics have significantly lower T_3, T_3/thyroxine binding globulin ratio, FT_3, T_4/thyroxine binding globulin ratio and Δ thyrotropin. Antithyroglobulin antibodies were absent in all patients, but one with chronic alcoholic hepatitis and one with cirrhosis in whom high titres were present (1:10 000); one of them (chronic alcoholic hepatitis) also had high serum thyrotropin concentrations (14 μU/ml) with exaggerated response to thyrotropin releasing hormone, with normal total and free T_3 and T_4, suggesting the coexistence of Hashimoto's thyroiditis and preclinical hypothyroidism.

Table 3 *Indices of thyroid function in patients with chronic liver disease (22 with chronic hepatitis, 33 with cirrhosis) and sex and age-matched healthy controls (mean±SE).*

	T_3 ng/dl	T_4 μg/dl	TBG ng/ml	T_3/TBG ratio	T_4/TBG ratio (×10)	FT_3 pg/ml	FT_4 pg/ml	TSH μU/ml	ΔTSH μU/ml
Chronic hepatitis	130±8·2	7·5±0·5	28·6±1·7†	4·67±0·51*	2·84±0·16	3·6±0·2*	11·9±0·8*	2·7±0·2	9·3±1·1
Cirrhosis	78±5·4‡‖	6·7±0·4	26·5±1*	2·99±0·19†¶	2·54±0·10‡§	2·9±0·1‡¶	11·9±0·5†	3·1±0·2*	6·4±0·8†§
Controls	140±6·9	7·3±0·2	23·7±0·5	5·97±0·28	3·05±0·07	4·2±0·1	9·9±0·3	2·4±0·1	11·1±1

* $p<0·05$ *vs* controls; † $p<0·01$ *vs* controls; ‡ $p<0·001$ *vs* controls; § $p<0·05$ *vs* chronic hepatitis; ¶ $p<0·01$ *vs* chronic hepatitis; ‖ $p<0·001$ *vs* chronic hepatitis.

The results obtained with total and free T_3 and T_4 concentrations in the individual patients are shown in Figs. 1–3. Low T_3 values were observed in 18 cirrhotics and in two patients with chronic hepatitis. T_4 was normal in all cases, except for five cirrhotics with low values and one subject for each group with slightly raised concentrations (Fig. 1). FT_3 was reduced in 18 cirrhotics and in four subjects with hepatitis (Fig. 2). FT_4 was normal in all instances except two cases with low, and four with raised concentrations (Fig. 3). Figure 4 shows that almost all patients with low FT_3 had normal or sometimes raised FT_4.

T_3/thyroxine binding globulin and T_4/thyroxine binding globulin ratios were significantly correlated with the actual FT_3 and FT_4 concentrations, respectively, both in subjects with cirrhosis and chronic hepatitis (Figs. 5, 6). While the correlation coefficient, however, between T_3/thyroxine binding globulin ratio and FT_3 was not different from that observed in normal controls ($r=0·65$, $p<0·001$), the coefficients between T_4/thyroxine binding globulin ratio and FT_4 were lower, particularly in cirrhotics, than that observed in normals ($r=0·82$, $p<0·001$). Basal serum thyrotropin concentrations above the normal range were found in two cirrhotic patients (6·5 and 7·8 μU/ml) and in the above mentioned subject with chronic hepatitis and Hashimoto's thyroiditis. The thyrotropin response to thyrotropin releasing hormone was normal in 23 and impaired in 10 patients with cirrhosis; among subjects with chronic hepatitis 18 had normal, two impaired and two exaggerated responses. The delayed pattern of thyrotropin response to thyrotropin releasing hormone – that is, 60 minute concentrations higher than 20 minute concentrations, was observed in eight cirrhotics.

Simple correlation analysis showed that serum T_3

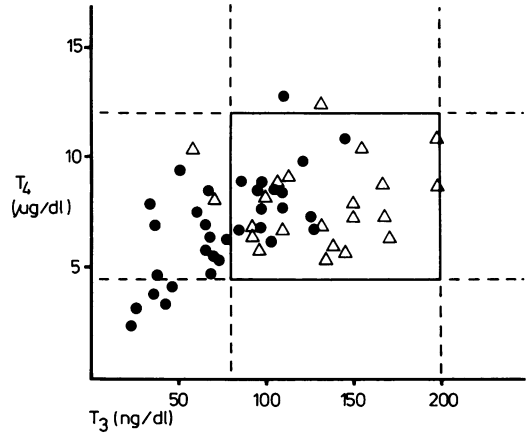

Fig. 1 *Serum T_4 vs T_3 concentrations in individual patients with liver cirrhosis (•) and chronic hepatitis (△). Solid lines outline normal range.*

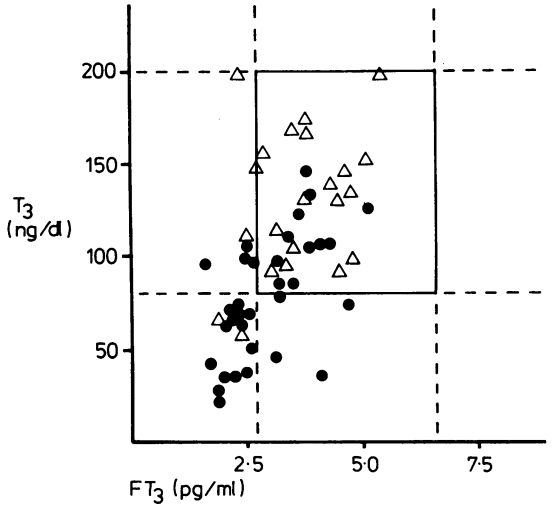

Fig. 2 *Serum T_3 vs FT_3 concentrations in patients with cirrhosis and chronic hepatitis. Symbols as in Fig. 1.*

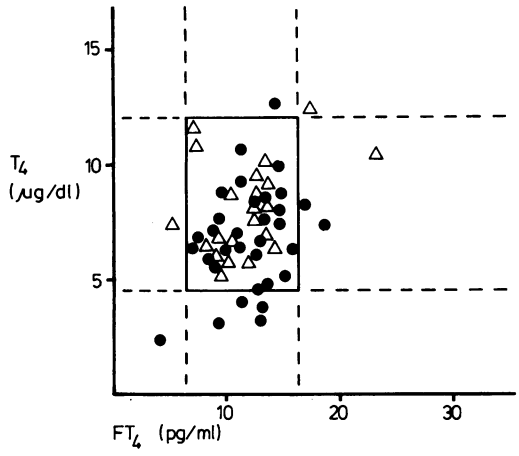

Fig. 3 *Serum T_4 vs FT_4 concentrations in patients with cirrhosis and chronic hepatitis. Symbols as in Fig. 1.*

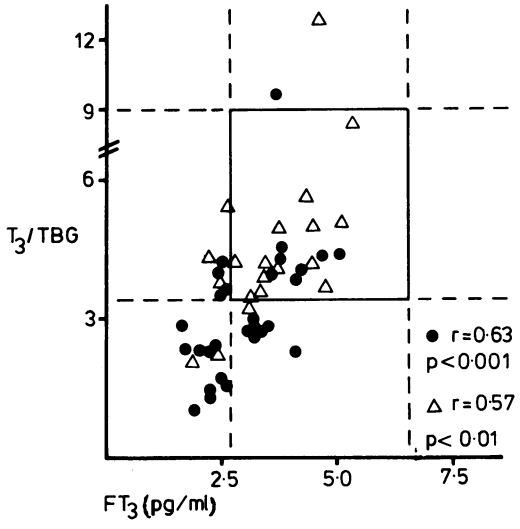

Fig. 5 *T_3/TBG ratios vs FT_3 values in patients with cirrhosis and chronic hepatitis. Symbols as in Fig. 1.*

concentration was significantly correlated in both patient groups with serum bilirubin albumin, and prothrombin time, but not with transaminases.

Discussion

The existence of the so called low T_3 syndrome – that is, low total T_3 with normal total T_4 and thyrotropin 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,[1-3 6 17] and it has been shown to depend on impaired liver conversion of T_4 to T_3.[2]

Our data also confirm a highly significant reduction of T_3 serum concentration in liver disease, the

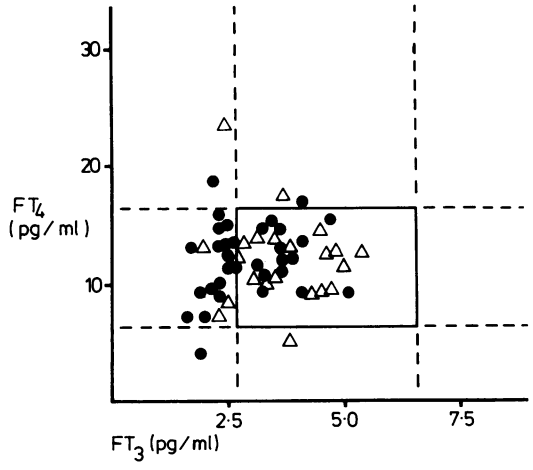

Fig. 4 *Serum FT_4 vs FT_3 concentrations in patients with cirrhosis and chronic hepatitis. Symbols as in Fig. 1.*

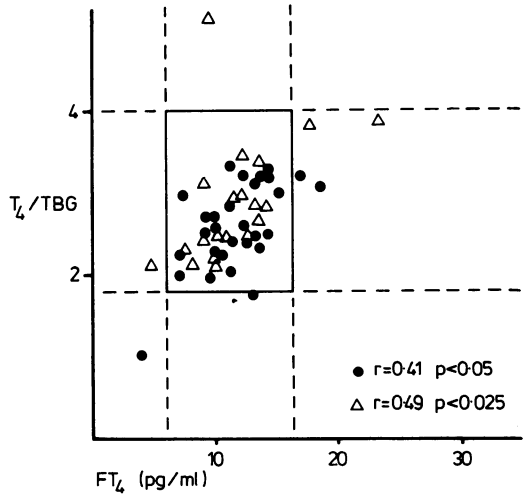

Fig. 6 *T_4/TBG ratios vs FT_4 values in patients with cirrhosis and chronic hepatitis. Symbols as in Fig. 1.*

lowest values being found in cirrhotics, with generally normal total T_4 and thyrotropin concentrations.

In a large group of alcoholic patients Israel *et al*[9] reported a significant inverse correlation between serum T_3 concentrations and the severity of liver dysfunction as well as a progressive T_3 increase in those subjects eventually displaying a favourable outcome, suggesting that T_3 concentrations in patients with advanced liver disease may be considered as a helpful prognostic indicator. Moreover, we have found a good correlation between T_3 concentrations and serum albumin, bilirubin, and prothrombin-time, while no correlation has been found with the hepatic inflammatory indices like the transaminases and γ globulins. These results suggest that T_3 concentrations should be considered a sensitive index of hepatic function in liver disease.

Only little data have been previously reported on direct measurement of free thyroid hormones in liver patients. Green *et al*[3] found normal FT_3 and FT_4 in a small group of cirrhotic patients while low FT_4 and normal FT_3 concentrations were present in alcoholic fatty liver. Many studies performed with equilibrium dialysis, however, showed decreased FT_3 and normal or frequently increased FT_4 concentrations.[2 18] These findings are confirmed by the present study with direct radioimmunoassay of FT_3 and FT_4, both in cirrhotics and in chronic hepatitis patients, although showing more severe abnormalities, especially lower FT_3 concentrations in the former group. These data suggest that in chronic liver disease euthyroidism is maintained by a subtle equilibrium between low FT_3 and raised FT_4 concentrations. The reason for the discrepancy between normal total T_4 and increased FT_4 concentrations in liver disease is unclear. The finding of increased, rather than decreased, thyroxine binding globulin serum concentration in our patients, in agreement with other reports,[19 20] as well as the finding of a reduced T_4/thyroxine binding globulin ratio with an increased FT_4 concentration is in agreement with previous suggestions for the presence of a circulating inhibitor (perhaps a IgM molecule) of T_4 binding to thyroxine binding globulin in non-thyroidal illnesses including liver cirrhosis.[7 8] Although we have found a significant correlation between T_4/thyroxine binding globulin ratio and FT_4 in our patients, the correlation coefficient was significantly lower than in normal controls, a finding compatible with the above hypothesis. Slightly increased serum thyrotropin concentration in liver cirrhosis has been previously reported,[2 3] but the possibility that this finding indicates the existence of hypothyroidism is unlikely in view of the normal or even reduced thyrotropin response to thyrotropin releasing hormone,[3] a finding confirmed in the present investigation. More likely, the abnormalities in thyrotropin secretion reflect the existence of hypothalamic-pituitary dysfunction in advanced liver disease. In particular, several lines of evidence suggest a reduced dopaminergic tone as a consequence of the accumulation of false neurotransmitters,[21 22] which might be responsible for raised basal thyrotropin concentrations, as dopamine has been shown to exert an inhibitory effect in the regulation of thyrotropin secretion.[23] True evidence for hypothyroidism, albeit at a preclinical stage, as suggested by clearly raised thyrotropin concentrations and increased thyrotropin releasing hormone response, has been only found in one patient of the present series, who was affected with Hashimoto's thyroiditis and severe alcoholic hepatitis. Only one of the other 54 patients with either liver cirrhosis or chronic hepatitis had high titres of thyroglobulin antibodies suggesting Hashimoto's thyroiditis, while this disease is relatively frequent in primary biliary cirrhosis and in autoimmune hepatitis.[24] In this connection it is to be pointed out that none of these two patients had positive tests for antinuclear, antismooth muscle and antimithocondrial antibodies.

In conclusion, the present investigation, in which thyroid function has been evaluated with all the clinically available indices, confirms the existence of several abnormalities in thyroid function tests in chronic liver disease, although showing that euthyroidism is maintained virtually in all patients, probably as a result of low-normal FT_3 and high-normal FT_4. Furthermore, T_3 serum concentrations appear to parallel the severity of liver dysfunction.

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