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● *Original Contribution*

ALTERATIONS IN THYROID DOPPLER ARTERIAL RESISTANCE INDICES, VOLUME AND HORMONES IN CIRRHOSIS: RELATIONSHIPS WITH SPLANCHNIC HAEMODYNAMICS

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Abstract—The hypothesis of thyroid involvement in the haemodynamic alterations of cirrhosis was evaluated. We measured thyroid volume (thrV), free triiodiothyronine (FT_3), free thyroxin (FT_4), thyroid stimulating hormone (TSH), resistance index (thrRI) and pulsatility index (thrPI) in the inferior thyroid artery in 45 cirrhotic patients of different aetiologies and Child class, and in 13 healthy subjects. Portal vein velocity, flow, diameter and hepatic, splenic, and renal arterial resistance indices were also evaluated. ThrV was increased in Child-C patients ($p < 0.05$). FT_3 was decreased in cirrhotic patients ($p < 0.05$), TSH and FT_4 were not different. ThrPI and thrRI were increased in cirrhotic patients (thrPI: 1.01 ± 0.15 vs. 0.81 ± 0.11; thrRI: 0.62 ± 0.05 vs. 0.53 ± 0.04; $p < 0.01$) and were inversely correlated with FT_3 ($p < 0.05$), and directly correlated with hepatic, splenic and renal resistance indices ($p < 0.01$). In conclusion, thyroid is involved, primarily and secondarily, in the haemodynamic alterations of cirrhosis; a reduction in vasodilator FT_3 may play a role in the pathophysiology. (E-mail: david.sacerdoti@unipd.it)

Key Words: **Cirrhosis, Thyroid, Duplex sonography, Thyroid hormones, Splanchnic haemodynamics, Thyroid volume.**

INTRODUCTION

The liver plays a key role in thyroid hormone balance modifying the total circulating concentrations of thyroxin (T_4) and triidothyronine (T_3). It is the site of synthesis and degradation of carrier proteins (thyroxin-binding globulin, thyroxin-binding prealbumin, and albumin) and it is also a major site of peripheral conversion, degradation and excretion of thyroid hormones. In liver cirrhosis, abnormalities in thyroid hormone levels have been described. Circulating thyroid hormone levels may range from normal values (Majumdar et al. 1981) to the marked abnormalities seen in the "euthyroid sick syndrome" (Wartofsky and Burman 1982). Concerning the thyroid gland itself, variations in its volume have been described, but conflicting results can be found. In 1984, Hegedus (1984) described decreased thyroid volume in alcoholic cirrhosis, but Bianchi et al. (1991) found an increased volume, mainly in patients with post-necrotic cirrhosis.

Advanced liver cirrhosis is associated with a wide spectrum of circulatory changes. Portal hypertension is, indeed, associated with a hyperdynamic circulation with decreased arterial pressure, increased cardiac output and splanchnic arteriolar vasodilatation (Groszmann 1994). Blood flow in the intestines, stomach, spleen and pancreas is increased by approximately 50% (Vorobioff et al. 1984; Sabbà et al. 1991). On the other hand, renal blood flow is reduced and renal vascular resistance is increased in cirrhotic patients (Sacerdoti et al. 1993). Increased vascular resistance has been shown also in cerebral, muscle and cutaneous tissues (Guevara et al. 1998; Maroto et al. 1993). No data are available on thyroid circulation. Thyroid hormones also have effects on the vascular system: T_3 decreases systemic vascular resistance by dilating resistance arterioles of the peripheral circulation (Park et al. 1997; Ojamaa et al. 1996) through a direct effect on vascular smooth-muscle cells. Therefore, alterations in T_3 may participate in the haemodynamic alterations of cirrhosis. The

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Table 1. Clinical characteristics of studied subjects

	Healthy subjects (n = 13)	Cirrhotic patients (n = 45)
Age (ys)	51.3 ± 17.3	56.6 ± 11.5
Gender (M/F)	7/6	30/15
Body surface (m^2)	1.9 ± 0.1	1.8 ± 0.1
Heart rate (beats/min)	72 ± 9	70 ± 7
MAP (mmHg)	101 ± 12	94 ± 9*
Albumin (g/l)	38.3 ± 3.6	31.1 ± 6.3*
Prothrombin time (%)	91 ± 7.3	64.4 ± 18.6*
Creatinine (mmol/l)	83 ± 19	93 ± 10

*$p < 0.05$ in respect of healthy subjects

aim of this study was to evaluate alterations of thyroid volume, thyroid Doppler arterial vascular resistance and hormone levels in cirrhotic patients and their relationships with splanchnic haemodynamics.

PATIENTS AND METHODS

Patients

A total of 45 patients with liver cirrhosis and 13 healthy subjects were studied (Table 1). The diagnosis of cirrhosis was based on liver histology or was clinical, on the evidence of portal hypertension (varices, ascites, encephalopathy). According to Child–Pugh classification (Pugh et al. 1973), 15 patients were class A, 15 patients were class B and 15 patients were class C. The aetiology of cirrhosis was posthepatitic in 28 patients (5 posthepatitis B, 22 posthepatitis C, 1 posthepatitis B+C), it was alcoholic in 11 patients, it was alcoholic + posthepatitic in 4 patients, and it was cryptogenic in 2 patients. At the time of the study, 35 patients had ascites and/or were taking diuretics because of previous ascites: 14 patients were taking antialdosteronic drugs, 21 patients were also taking furosemide. None of the patients was on interferon therapy. Patients with known thyroid disease, advanced renal disease, malignant neoplasm or advanced hepatic encephalopathy were excluded. None of the healthy subjects had a history of thyroid disease or abnormalities in thyroid hormone levels. All subjects included in this study lived in a noniodine-deficient area. The study was carried out in accordance with the 1975 Declaration of Helsinki and all subjects gave their informed consent to take part in the study.

Methods

All subjects were investigated after an 8-h fast. The thyroid volume was measured by sonography. The volume was calculated by the ellipsoid method (width × length × thickness × $\pi/6$) as described elsewhere (Bruneton et al. 1987; Fobbe et al. 1989). The sum of the two lobes volume was considered to be the total volume; the isthmus component was not taken into account (Bruneton et al. 1987). The Doppler study was performed with an ATL HDI 5000 (Seattle, WA) equipment with a 7.5-MHz linear probe. After a longitudinal scan of the thyroid lobe, the inferior thyroid artery was identified using colour Doppler; the sample volume of the Doppler system was placed where the artery lies longitudinally behind the posterior surface of thyroid lobe and the blood flow velocity waveform was analysed using an angle between 30° and 60°. In all subjects, the resistance indices were calculated according to the following formulas: *resistance index (RI) = (maximal systolic − end-diastolic velocity)/maximal velocity; pulsatility index (PI) = (maximal systolic − minimal velocity)/mean velocity*. Each result was the mean of three measurements. In cirrhotic patients, portal vein diameter, portal vein velocity and blood flow and hepatic, splenic and renal arterial RIs were also measured by echo Doppler. The portal vein was visualised longitudinally in B-mode and the sample volume was positioned inside it immediately after the cross-point between the hepatic artery and the portal trunk, at an angle of less than 60° between the vessel and the ultrasound (US) beam. The maximum portal blood flow velocity (PVV) and the portal diameter (PVD) were then measured during suspended respiration and averaged over a few s. The mean PVV was calculated according to Sabbà et al. (1995) as mean (time-averaged) maximum velocity (automatically calculated after the operator had manually traced the border of the Doppler waveform) multiplied by 0.57 and expressed as cm/s. Portal blood flow volume (PVF) was calculated as PVV multiplied by cross-sectional area, calculated from the PVD and, thus, assumed to be circular, and was expressed as ml/min.

Colour Doppler allowed the identification of the right and left branches of the hepatic artery. The sample volume of the Doppler system was placed inside these vessels, and the blood flow velocity waveform was recorded. Peak systolic, end diastolic and temporal mean flow velocity were then determined and, from them, the PI and RI were calculated (Sacerdoti et al. 1995).

To evaluate splenic Doppler indices, the transducer was positioned below the left costal margin and/or in the left costal spaces. Colour Doppler allowed the identification of the main branches of the splenic artery. The sample volume of the Doppler system was placed inside these vessels, near the hilum, and the blood flow velocity waveform was recorded. Peak systolic, end diastolic and time-average maximal velocity were then determined and, from them, PI and RI were calculated (Bolognesi et al. 2001). Doppler indices were measured using the for-

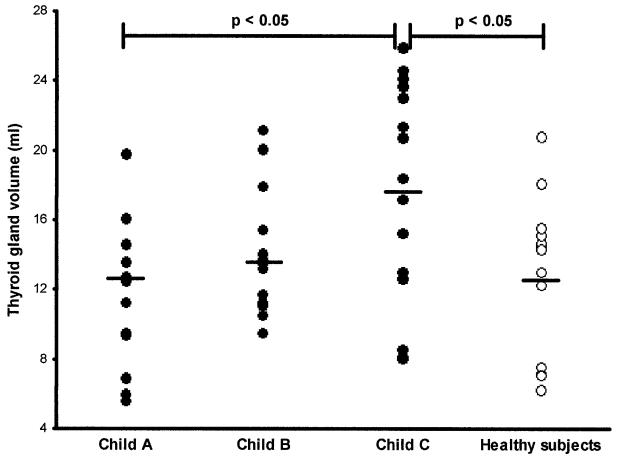

Fig. 1. Thyroid volume in healthy subjects and in cirrhotic patients.

mulas described above. To evaluate renal Doppler indices, colour Doppler allowed the identification of the interlobar arteries and, then, blood flow velocity waveform was recorded in these vessels. Peak systolic, end diastolic and temporal mean flow velocity were then determined, and from them PI and RI values were calculated according the formulas described above (Sacerdoti et al. 1993).

FT_3, FT_4 and TSH levels were measured using routine enzymatic immunoassay (EIA). Serum levels of albumin, total protein, prothrombin time and creatinine were measured by standard techniques.

Statistical analysis. Results were expressed as mean ± SD. Differences between groups were analysed by ANOVA and Student's *t*-test. Correlations were investigated by the least squares method. The results were considered to be statistically significant at $p < 0.05$.

RESULTS

Thyroid volume was significantly increased only in Child C patients (Fig. 1). In compensated cirrhosis, the volume was not different from that in healthy subjects (controls: 12.7 ± 4.5 mL, Child A: 12.7 ± 6.0 mL, Child B: 13.6 ± 3.5 mL, Child C: 17.6 ± 6.3 mL; ANOVA $p < 0.05$). Thyroid volume was not different in patients with posthepatitic and alcoholic cirrhosis (14.6 ± 6.2 ml vs. 15.5 ± 5.2 ml, p = NS). In both cirrhotic patients and healthy subjects, the right lobe was bigger than the left one (8.2 ± 3.5 ml vs. 6 ± 2.4 ml, $p < 0.05$), as previously reported (Rasmussen and Hjrth 1974). In Table 2, thyroid hormone levels are reported. FT_3 levels were significantly decreased in cirrhotic patients, without any correlation with the severity of the disease. FT_4 and TSH levels were not different in healthy and cirrhotic subjects. Only one cirrhotic patient showed a variant of euthyroid sick syndrome with increased FT_4 and normal TSH level (FT_4 = 30.7 pmol/l, TSH = 1.3 mU/l). No correlation was found between FT_3, FT_4, TSH and albumin and prothrombin times. Thyroid volume inversely correlated with TSH levels ($r = -0.34$, $p < 0.05$). The splanchnic haemodynamic parameters of cirrhotic patients are shown in Table 3. Figure 2 shows Doppler indices in the inferior thyroid artery (thrPI and thrRI) in healthy subjects and cirrhotic patients. The thrPI and thrRI were significantly increased in cirrhotic patients in respect of healthy subjects (thrPI = 1.01 ± 0.15 vs. 0.81 ± 0.11, $p < 0.01$), (thrRI = 0.62 ± 0.05 vs. 0.53 ± 0.04, $p < 0.01$). thrPI and thrRI were significantly increased in advanced cirrhosis (Child C patients: thrPI = 1.06 ± 0.14, thrRI = 0.64 ± 0.05) as compared with Child A patients (thrPI = 0.94 ± 0.14, thrRI = 0.59 ± 0.05, $p < 0.05$). The thrPI and thrRI were significantly increased in ascitic patients (thrPI = 1.05 ± 0.07; thrRI = 0.63 ± 0.04) as compared with patients without ascites (thrPI = 0.87 ± 0.16, $p < 0.05$; thrRI = 0.57 ± 0.07, $p < 0.05$).

Table 2. Thyroid function in healthy subjects (n = 13) and cirrhotic patients (n = 45)

	FT3 (pmol/l)	FT4 (pmol/l)	TSH (mU/l)
—Healthy subjects	5.13 ± 1.06	16.06 ± 3.0	1.54 ± 0.73
—Cirrhotic patients	4.26 ± 1.22*	15.07 ± 4.01	2.10 ± 1.33
Child A (n = 15)	4.30 ± 0.86	13.70 ± 3.66	1.71 ± 1.61
Child B (n = 15)	4.04 ± 1.16	13.89 ± 1.99	2.68 ± 1.26
Child C (n = 15)	4.38 ± 1.56	17.03 ± 4.75	2.03 ± 1.04

*$p < 0.05$ in respect of healthy subjects.

Table 3. Splanchnic haemodynamic parameters of cirrhotic patients

	Mean ± SD
Portal vein diameter (mm)	13.5 ± 1.9
Portal mean velocity (cm/s)	12.9 ± 2.8
Portal blood flow (ml/min)	908 ± 172
Hepatic pulsatility index (PI)	1.37 ± 0.31
Hepatic resistance index (RI)	0.70 ± 0.07
Splenic pulsatility index (PI)	1.14 ± 0.24
Splenic resistance index (RI)	0.66 ± 0.07
Renal pulsatility index (PI)	1.27 ± 0.25
Renal resistance index (RI)	0.68 ± 0.07

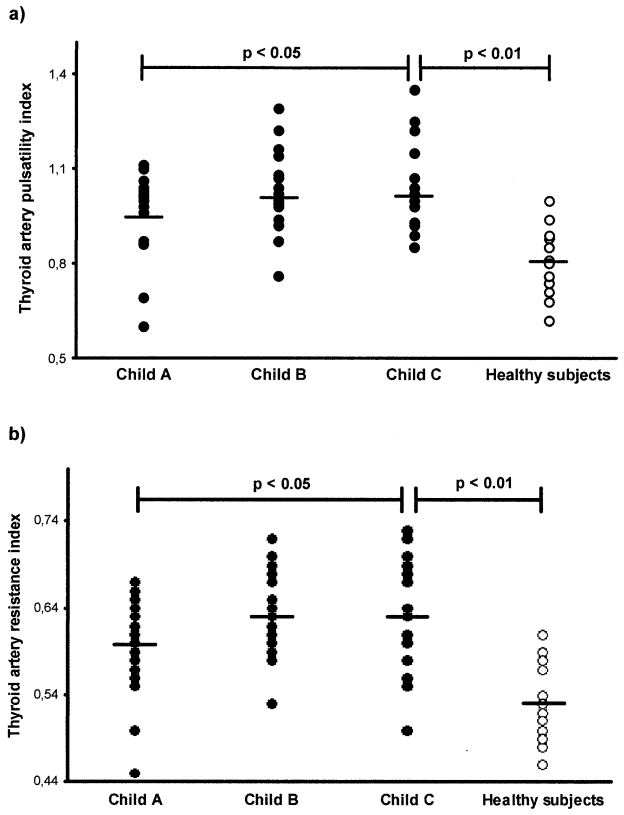

Fig. 2. Doppler arterial resistance indices in the inferior thyroid artery; (a) pulsatility index; (b) resistance index.

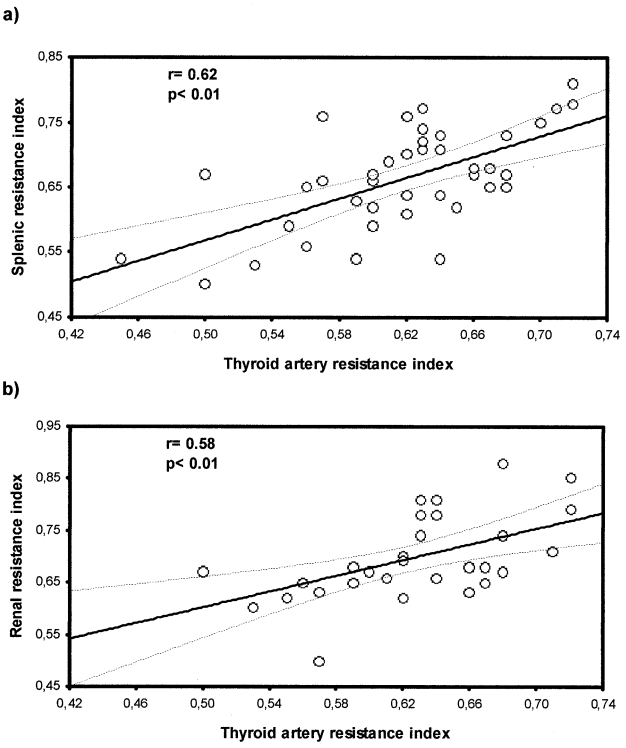

Fig. 3. Correlations between Doppler arterial resistance indices of the inferior thyroid artery and of (a) the spleen and (b) the kidney in cirrhosis.

In cirrhotic patients, thrPI and thrRI showed a direct correlation with hepatic, splenic and renal arterial RIs ($p < 0.01$) (Fig. 3). The thrPI and thrRI (Fig. 4) were inversely correlated with FT_3 levels ($p < 0.05$). Finally, renal and splenic arterial RIs showed an inverse correlation with FT_3 levels ($p < 0.01$). No correlation was found between PVV and PVF, and thrPI, thrRI and thyroid hormones.

DISCUSSION AND SUMMARY

The results of this study show that, in cirrhosis, 1. thyroid volume is increased only in the advanced stage, without any correlation with aetiology; 2. thyroid arterial resistance indices increase progressively with the severity of cirrhosis, similarly to resistance indices in the kidney, spleen and liver; 3. the increased arterial resistance in the thyroid, spleen, and kidney is inversely correlated with FT_3; 4. FT_3 levels are decreased without any correlation with severity and aetiology.

Thyroid abnormalities have been reported in acute and chronic liver disease. In acute viral hepatitis, a marked increase in thyroid volume with normalisation after recovery has been shown (Hegedus 1986). An increase in thyroid volume has also been described in postnecrotic cirrhosis (Bianchi et al. 1991), whereas a decreased volume has been shown in alcoholic cirrhosis (Hegedus 1984). The mechanisms underlying thyroid modification during liver disease are unclear. The possibility of a direct viral involvement of the gland and a direct toxic effect of alcohol has been proposed (Hegedus 1984; Bianchi et al. 1991), but there is no

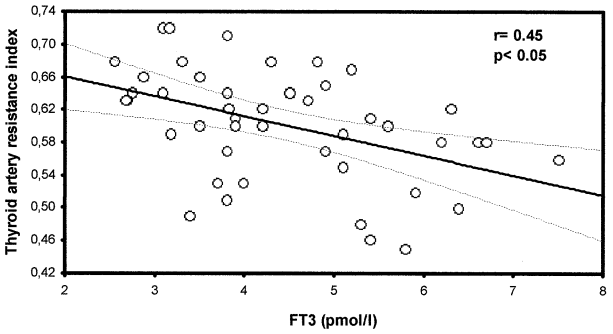

Fig. 4. Correlation between Doppler arterial resistance indices of the inferior thyroid artery and FT_3 levels in cirrhosis.

histologic study clarifying this issue. In this study, we found increased thyroid volume only in advanced liver cirrhosis, without any correlation with aetiology. In 47% of our patients, the anteroposterior diameter was $>$ 20 mm, a value considered normal by Bruneton et al. (1987). Thyroid volume was inversely correlated with TSH. To date, only two studies investigated thyroid volume in cirrhotic patients. Our results differ from those of Hegedus (1984), who described decreased thyroid volume in alcoholic cirrhosis, but they partially agree with those of Bianchi et al. (1991), who reported an increase in thyroid volume in patients with cirrhosis independently from the aetiology, even though the largest volumes were present in patients with postnecrotic cirrhosis. In our study, thyroid volume was not related to the degree of liver impairment. Factors responsible for increased thyroid volume in nonthyroidal diseases are not completely known. Thyroid volume increases with age and body weight, and some investigators recently demonstrated that lean body mass is a major determinant of thyroid size (Wesche et al. 1998). Our patients were matched with healthy subjects for age and body surface. Previous studies suggested a pathogenetic role of the hepatitis virus and alcohol to explain the abnormalities in gland volume in cirrhotic patients. In our group of patients with increased gland volume, the aetiology was: posthepatitic in 5 patients, alcoholic in 6 patients, mixed (posthepatitic + alcoholic) in 3 patients, cryptogenic in 1 patient. Because no difference has been shown between alcoholic and viral cirrhosis, the increased volume appears to be related only to the severity of hepatic disease. Finally, modification in circulating thyroid hormone levels could be responsible for volume abnormalities in cirrhotic patients. Both T_4 and thyroid volume were higher in Child C patients than in Child A-B, but, in agreement with Hegedus (1984), our data seem to exclude this hypothesis because we were not able to find any correlation between thyroid function and gland volume. In conclusion, this study suggests that the increase in thyroid volume in cirrhosis is not related to the aetiology or the hormonal status, but only to the severity of cirrhosis.

Colour Doppler of the thyroid artery is useful for diagnosis and follow-up in diffuse thyreopathy. An increase of the resistance indices in the thyroid artery and a decrease after thyreostatic therapy has been documented in Grave's disease. (Sponza et al. 1997). Our results showed an increase in resistance indices in the thyroid artery of cirrhotic patients, particularly in those with advanced disease, and the increment was inversely correlated with liver function tests. Thyroid resistance indices were directly correlated with resistance indices in the liver, the spleen and the kidney. FT_3 serum levels were inversely correlated with resistance indices in the kidney, spleen and thyroid. Two mechanisms probably participate in thyroid arterial vasoconstriction, with thyroid playing a primary and/or a secondary role. 1. Portal hypertension is characterised by a spectrum of circulatory changes. According to the peripheral arterial vasodilatation theory (Schrier et al. 1988), systemic vasodilatation leads to activation of compensatory vasoconstricting mechanisms; in particular, the sympathetic nervous system, the renin-angiotensin-aldosterone and endothelin-1 (Henriksen et al. 1998; Moller and Henricksen 1996; Ring-Larsen et al.1982). Previous studies demonstrated increased arterial resistance indices in renal (Sacerdoti et al. 1993) and cerebral districts (Guevara et al. 1998), correlating with overactivity of vasoconstrictor systems. In our patients, Doppler indices in thyroid artery were directly correlated with resistance indices in the kidney. Thus, vasoconstriction in thyroid circulation could be part of the same haemodynamic picture of cirrhotic portal hypertension, secondary to increased vasoconstricting hormones. In addition, the correlation with hepatic and splenic resistance indices, although not with portal vein velocity, also suggests a role of portal hypertension in these alterations. 2. The inverse correlation between FT_3 levels and Doppler indices suggests that thyroid hormone could be directly involved in haemodynamic alterations. Thyroid hormones, particularly T_3, possess a direct vasodilating effect. Indeed, in experimental studies, T_3-mediated vasodilatation was attenuated, but not abolished, by endothelial denudation, cyclooxygenase inhibition and nitric oxide synthase inhibition (Park et al. 1997), suggesting a direct effect on smooth muscle cells. In normal and portal hypertensive rats, the hypothyroidism induced by methimazole causes a reduction in heart rate and cardiac index in both normal and portal hypertensive rats, and a reduction in renal blood flow only in portal hypertensive rats (Oren et al. 1995). In our patients, a correlation was also found between low FT_3 levels and increase in thyroid and kidney resistance indices. Therefore, an involvement of FT_3 reduction in renal and thyroidal vasoconstriction may be hypothesised.

The liver has a primary influence on circulating levels of thyroid hormones. Most of the metabolically active thyroid hormone, T_3, is generated in the liver from T_4 through a selenium-dependent 5[prime]-deiodinase. Another selenium-independent deiodinase acts on the phenolic ring of T_4 to produce the hormonally inactive rT_3 (Kelly 2000). The liver is also the site of synthesis and degradation of carrier proteins thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA)

and albumin. In cirrhosis, the most frequent abnormalities described involving thyroid function is the "low FT_3 syndrome" with increased reverse T_3 and decreased T_3:T_4 ratios (Rink et al. 1991; Kabadi et al. 1983; Gallo et al. 1990). Several mechanisms may be responsible for these abnormalities. In animal models, ethanol intake is associated with impaired hepatic 5[prime]-deiodination (Langer et al. 1988), suggesting that impaired hepatic deiodinase activity with decreased conversion of T_4 to T_3 could take part in the modifications in circulating hormone levels described in alcoholic cirrhosis. Moreover, it is well-established that a defective hepatocellular uptake and an inefficient production of TBG are present in cirrhosis. Thyroid hormone concentration is also affected by glucagon levels and, in liver cirrhosis, plasma glucagon concentration is frequently elevated (Smith-Laing et al. 1980; Marco et al. 1973). Kabadi et al. (1991) found a significant negative correlation between plasma glucagon and serum T_3, whereas a significant positive correlation was observed between plasma glucagon levels and serum reverse T_3, suggesting a role of hyperglucagonemia in the pathogenesis of low T_3 values in these patients.

In summary, thyroid volume is increased in patients with liver cirrhosis, independently from thyroidal hormonal status. In cirrhosis, thyroidal haemodynamics are characterised by an increase in Doppler arterial resistance indices. Low FT_3 values of cirrhotic patients may participate in the arterial vasoconstriction present in thyroid and in other organs such as the kidney. Measurements of thyroid volume, and RIs and thyroid hormones have, at the moment, no clinical utility. Future studies should examine the potential clinical usefulness of correcting low T_3 levels, which might improve renal and thyroidal haemodynamics.

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