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A STUDY OF THYROID PROFILE IN PATIENTS WITH LIVER DISEASE.

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ABSTRACT

The thyroid hormones are the only iodine-containing compounds with established physiologic significance in vertebrates.Bioactivity of thyroid hormone is determined to the large extent by the hepatic monodeiodination of prohormone T_4 (Thyroxine). The best characterized activities of the liver with respect to thyroid hormone metabolism involve deiodinase reactions. Type I deiodinase is the major enzyme in the liver, and accounts for approximately 30-40% of extrathyroidal production of T_3 (tri-iodothyronine) it can carry out both 5'-and 5-deiodination of T_4 to T_3.Thyroxine and tri-iodothyronine are essential for normal organ growth, development and function. These hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function; the liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effects. Thyroid dysfunction may perturb liver function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs. In the present study of 140 subjects,70 subjects were patients with liver disease i.e 50 subjects were patients with alcoholic liver disease(ALD), 20 subjects were non alcoholic liver disease(NON-ALD) patients and 70 were healthy controls. This study was planned to evaluate the biochemical parameters like thyroid function tests and liver function tests on the above 140 subjects. This study demonstrated that the serum T_3 (Total T_3) and FT_3 (Free T_3) levels were decreased in patients with liver disease as compared to controls.

KEYWORDS: Liver disease, Total T_3, Free T_3, type 1 deiodinase.

INTRODUCTION

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] 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]

The primary function of the thyroid is production of the hormones T_3, T_4 and calcitonin. Up to 80% of the T_4 is converted to T_3 by organs such as the liver ,kidney and spleen. T_3 is several times more powerful than T_4, which is largely a prohormone, perhaps four [10] or even ten times more active.[11] In normal subjects, the thyroid gland secretes 110 nmol of thyroxine and 10 nmol of tri-iodothyronine each day.[12] triiodothyronine has a ten times greater affinity and ten times greater efficacy than thyroxine for the nuclear receptor, thus even though thyroxine is quantitatively secreted at much higher levels, it should be regarded as a pro-hormone that requires deiodination and conversion of T_3 to become biologically active.[13]

There are three groups of enzymes that regulate thyroid hormone metabolism, forming part of the iodothyronine seleno-deiodinase enzyme system (type 1=D1, type 2=D2 and type 3=D3). The type 1 deiodinase is mainly found in the liver and kidney,[14] and accounts for approximately 30–40% of extrathyroidal production of T3 (12 nmol). Bioactivity of thyroid hormone is determined to the large extent by the hepatic monodeiodination of prohormone T_4. The best characterized activities of the liver with respect to thyroid hormone metabolism involve deiodinase reactions. Within the liver, type I deiodinase activity may either result in formation of T_3, subsequent to the removal of an iodine from the outer phenolic ring by a selenium-dependent hepatic 5'-deiodinase enzyme, or it can remove iodine from the inner tyrosyl ring by 5-deiodinase resulting in formation of rT_3.[263]

Sulfation of phenolic hydroxyl group blocks the outer ring deiodination of T_4 to T_3, while it strongly stimulates the inner ring deiodination of both T_4 to rT_3 and T_3 to T_2. Since the net effect of activation of sulfation pathway appears to preferentially inhibit the formation of T_3 and increase the degradation, and since it can catalyze the degradation of T_4 to rT_3, it would seem capable of potentially exerting a profound effect on thyroid hormone metabolites.[15]

Liver is a major site of thyroid hormone peripheral metabolism and is involved in the conjugation, biliary excretion, oxidative deamination and the extrathyroidal deiodination of thyroxine (T_4) to triiodothyronine (T_3) and to reverse T_3.[16,17] In lost chronic illness, defects arise in thyroidal hormone metabolism, resulting in the sick euthyroid syndrome. This is characterized by a normal total T_4, normal/high freeT_4, low total T_3 low free $T_3$and an elevated rT_3.

These changes reflect a reduction in D1 activity, an increase in D3 activity.[18] Specific lifestyle factors can have significant impact of peripheral metabolism of thyroid hormones. In addition to these factors, a number of physiological and pathological events perturb the deiodination pathway, leading to a decrease in T_3peripheral genesis and reciprocal changes in the circulating levels of T_3 (which decreases) and rT_3 (which increases). The biological effects resulting from these changes are not currently completely understood but are potentially important in the body`s adjustments to stressful or catabolic states.[19]

MATERIALS AND METHODS

The present study consists of 140 subjects, 50 subjects were patients with alcoholic liver disease(ALD), 20 subjects were non alcoholic liver disease(NON-ALD) patients and 70 were healthy controls.The study was conducted at Goa Medical College and Hospital , Bambolim-Goa during the period of 2012-2013.Ethical clearance was obtained from the institution's ethical committee.

Collection Of Blood Samples

7-8ml of fasting samples were collected in plain bulbs by venepuncture, under aseptic conditions of the above mentioned subjects. Serum was seperated by centrifuging blood samples at 3000 rpm in clinical centrifuge for 10 minutes. Serum was used to perform thyroid function tests and liver function tests on the above mentioned 140 subjects.

Table 1: Distribution Of Subjects

Groups	Number of cases
Alcoholic liver disease	50
NonAlcoholic liver disease	20
Controls	70
Total No. of subjects	140

A) THYROID FUNCTION TESTS.

Total T_3

Principle

ARCHITECT Total T_3 assay is a two step immunoassay to determine the presence of Total T_3 in human serum and plasma using CMIA (Chemiluminescent Microparticle ImmunoAssay) technology with flexible assay protocols , referred to as chemiflex.

In the first step, sample and anti T_3 coated paramagnetic microparticles are combined. T_3 present in the sample binds to the anti-T_3 coated microparticles. After washing, T_3 acridinium-labeled conjugate is added in the second step.

Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as relative light units (RLUs). An inverse relationship exists between the amount of Total T_3 in the sample and RULs detected by the ARCHITECT i optical system.

Reagents

ARCHITECT Total T_3 reagent kit

Microparticles: 1 or 4 bottles (6.6ml/27.0ml) anti-T_3 coated particles in MES buffer with sheep IgG Stabilizers.

Preservative: antimicrobial agent.

Conjugate: 1 or 4 bottles (5.9ml/26.3ml)T_3 acridinium-labeled conjugate in citrate buffer with NaCl and triton X-100 stabilizers.

Preservative: antimicrobial agent.

Calibration

To perform an ARCHITECT Total T_3 calibration, test calibrators 1and 2 in duplicate.

Calibrators should be priority loaded. Calibrator Range:0.0-8.0ng/mg.

RESULTS

The ARCHITECT Total T_3 utilizes a 4 parameter logistic curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve. The default result unit for the ARCHITECT Total T_3 assay is ng/mL.

Expected Values

A normal range of 0.58 ng/mL to 1.59 ng/mL.[20]

Total T_4

Principle

ARCHITECT Total T_4 assay is a two step immunoassay to determine the presence of The Total T_4 in human serum and plasma using CMIA technology with flexible assay protocols , referred to as chemiflex.

In the first step, sample and anti T_4 coated paramagnetic microparticles are combined. T_3 present in the sample binds to the anti-T_4 coated microparticles. After washing, T_4 acridinium-labeled conjugate is added in the second step.

Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as RLUs. An inverse relationship exists between the amount of Total T_4 in the sample and RULs detected by the ARCHITECT i optical system.

Reagents

ARCHITECT Total T_4 REAGENT KIT.

Microparticles: 1 or 4 bottles (6.6ml/27.0ml) anti-T_4 coated particles in TRIS buffer with sheep IgG Stabilizers.

Preservative: Sodium Azide.

Conjugate: 1 or 4 bottles (5.9ml/26.3ml)T_3 acridinium-labeled conjugate in MES buffer with NaCl and triton X-100 stabilizers. Minimum concentration: 0.2 ng/mL. Preservative: ProClin.

Calibration

To perform an ARCHITECT Total T_4 calibration, test calibrators 1and 2 in duplicate.

Calibrators should be priority loaded. Calibrator Range:0.0-24.0 µg/dL.

RESULTS

The ARCHITECT Total T_4 utilizes a 4 parameter logistic curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve. The default result unit for the ARCHITECT Total T_4 assay is µg/dL.

Expected Values

A normal range of 4.87 µg/dL to 11.72 µg/dL.

TSH

Principle

The ARCHITECT TSH assay is a two step immunoassay to determine the presence of thyroid stimulating hormone (TSH) in human serum and plasma using CMIA technology with flexible assay protocols, referred to as chemiflex.

In the first step, sample and anti-β TSH antibody coated paramagnetic microparticles and TSH Assay Diluent are combined .TSH present in the sample binds to the anti-TSH coated microparticles. After washing, anti-α TSH acridinium labeled conjugate is added in the second step.

Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemilumiescent reaction is measured as RLUs. A direct relationship exists between the amount of TSH in the sample and RULs detected by the ARCHITECT i optical system.

Reagents

ARCHITECT TSH REAGENT KIT

Microparticles: 1 or 4 bottles (6.6ml/27.0ml) anti- β TSH coated particles in TRIS buffer with protein (bovine) Stabilizers. Minimum concentration: 60 ng/mL. Preservative: antimicrobial agent.

Calibration

To perform an ARCHITECT TSH calibration, test calibrators 1and 2 in duplicate. Calibrators should be priority loaded.

Calibrator Range: 0.0000-100.0000 µlU/mL.

Results

The ARCHITECT TSH assay utilizes a 4 parameter logistic curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve. The default result unit for the ARCHITECT TSH assay is µlU/mL.[21]

Expected Values

A normal range of 0.35 µlU/mL to 4.94 µlU/mL.

Free T_3

Principle

The ARCHITECT Free T_3 assay is a two step immunoassay to determine the presence of free (unbound) T_3 in human serum and plasma using CMIA (Chemiluminescent Microparticle ImmunoAssay) technology with flexible assay protocols, referred to as chemiflex.

In the first step, sample and anti T_3 coated paramagnetic microparticles are combined. Free T_3 (unbound) present in the sample binds to the anti-T_3 coated microparticles. After washing, T_3 acridinium-labeled conjugate is added in the second step.

Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as RLUs. An inverse relationship exists between the amount of Free T_3 in the sample and RULs detected by the ARCHITECT i optical system.

Reagents

ARCHITECT Free T_3 REAGENT KIT:

Microparticles: 1 or 4 bottles (6.6ml/27.0ml) anti-T_3coated particles in MES buffer with sheep IgG Stabilizers.

Preservative: antimicrobial agent.

Conjugate: 1 or 4 bottles (5.9ml/26.3ml)T_3 acridinium-labeled conjugate in citrate buffer with NaCl and triton X-100 stabilizers.

Preservative: antimicrobial agent.

Calibration

To perform an ARCHITECT Free T_3 calibration, test calibrators 1and 2 in duplicate.

Calibrators should be priority loaded. Calibrator Range:0.0-30.0pg/ml.

Results

The ARCHITECT Free T_3 utilizes a 4 parameter logistic curve fit data reduction method (4PLC,Y-weighted) to generate a calibration curve. The default result unit for the ARCHITECT Total T_3 assay is pg/mL.

Expected Values

A normal range of 1.71-3.71pg/mL. [22]

Free T_4

Principle

The ARCHITECT Free T_4 assay is a two step immunoassay to determine the presence of free thyroxine (Free T_4) in human serum and plasma using CMIA technology with flexible assay protocols, referred to as chemiflex. In the first step, sample and anti T_4 coated paramagnetic microparticles are combined. Free T_4 (unbound) present in the sample binds to the anti-T_4 coated microparticles. After washing, T_3 acridinium-labeled conjugate is added in the second step.

Pre-trigger and trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as RLUs. An inverse relationship exists between the amount of Free T_4 in the sample and RULs detected by the ARCHITECT i optical system.

Reagents

ARCHITECT Free T_4 REAGENT KIT

Microparticles: 1 or 4 bottles (6.6ml/27.0ml) anti-T_4coated particles in TRIS buffer with sheep IgG Stabilizers.

Preservative: antimicrobial agent.

Conjugate:1 or 4 bottles (5.9ml/26.3ml)T_3 acridinium-labeled conjugate in MES buffer with NaCl and triton X-100 stabilizers.

Calibration

To perform an ARCHITECT Free T_4 calibration, test calibrators 1and 2 in duplicate.

Calibrators should be priority loaded. Calibrator Range:0.0-6.0pg/mg.[23]

Expected Values

A normal range of 0.70-1.48ng/dL.

Quality Control Procedures For TT_3, TT_4, TSH, FT_3, FT_4.

The recommended control requires a single sample of all control levels tested once every 24 hours each day of use.

Results

The ARCHITECT TT_3,TT_4,TSH,FT_3,FT_4,utilizes a 4 parameter logistic curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.[23]

LIVER FUNCTION TESTS

Total Bilirubin

Principle

Total (conjugated and unconjugated) Bilirubin couples with diazoreagent in the presence of surfactant to form azobilirubin.

The diazoreaction is accelerated by addition of surfactant as a solubilizing agent. The increase is absorbance at 548nm due to azobilirubin is directly proportional to the total Bilirubin concentration.

reagents: Surfactant,HCI;2, 4-dichloroaniline,Sodium Nitrite.

expected values

	Range (mg/dL)	Range (µmol/L)
Adult (serum and plasma) [15]	0.2 to 1.2	3.4 to 20.5

Direct Bilirubin

Principle

Direct (conjugated fractions) bilirubin couples with a diazonium salt in the presence of sulfamic acid to form the coloured compound azobilirubin. The increase in absorbance at 548 nm due to azobilirubin is propotional to the direct bilirubin concentration.

Reagents: Sulfamic Acid, 2,4-dichloroaniline**,** Sodium Nitrite**,** HCI.

Calibration: Total And Direct Bilirubin

Calibration is stable for approximately 14 days (336 hours) and is required with each change in reagent lot number.

Quality Control: Total And Direct Bilirubin

Two levels of controls (normal and abnormal) are to be run every 24 hours.

Expected Values:

	Range (mg/dL)	Range (µmol/L)
Adult	0.0 to 0.5	0.0 to 8.6

Aspartate Aminotransferase

AST present in the sample catalyzes the transfer of the amino group from *L*-aspartate to α-ketoglutarate, forming oxaloacetate and *L*-glutamate. Oxaloacetate in the presence of NADH

and malate dehydrogenase (MDH) is reduced to *L*-malate. In this reaction, NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.

Reagents: β-NADH**,** MDH**,** Lactate Dehydrogenase**,**
L-Aspartate, α- Ketoglutarate.

Calibration

Calibration is stable for approximately 30 days (720 hours) and is required with each change in reagent lot number.

Expected Values

Serum/Plasma	Range (U/L)
Adult	5 to 34

Alanine Aminotransfererase

Principle

ALT present in the sample catalyzes the transfer of the amino group from *L*-alanine to α-ketoglutarate, forming pyruvate and *L*-glutamate. Pyruvate in the presence of NADH and lactate dehydrogenase (LD) is reduced to *L*-lactate. In this reaction, NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340 nm due to the oxidation of NADH to NAD.

Reagents: β-NADH,Lactate Dehydrogenase**,** *L*-Alanine, α-Ketoglutaric Acid, *L*-Alanine.

Calibration

Calibration is stable for approximately 27 days (648 hours) and is required with each change in reagent lot number.[24]

Expected Values

Serum /Plasma	Range (U/L)
Adult	0 to 55

Alkaline Phosphatase

Principle

Alkaline phosphatase in the sample catalyzes the hydrolysis of colorless *p*-nitrophenyl phosphate (*p*-NPP) to give *p*-nitrophenyl and inorganic phosphate. At the pH of the assay

(alkaline), the *p*-nitrophenol is in the yellow phenoxide form. The rate of absorbance increase at 404 nm is directly proportional to the alkaline phosphatase activity in the sample. Optimized concentrations of zinc and magnesium ions are present to activate the alkaline phosphatase in the sample.

Reagents

Alkaline Phosphatase is supplied as a liquid, ready-to-use, two-reagent kit which contains,2-Amino-2-methylpropanol, Magnesium, Zinc Sulfate, HEDTA.

Calibration

Calibration is stable for approximately 8 days (192 hours) and is required with each change in reagent lot number.

Expected Values

Serum/Plasma[12]	**Range (U/L)**
Male	
1 to 12 years	< 500
12 to 15 years	< 750
> 20 years	40 to 150
Female	
1 to 12 years	< 500
>15 years	40 to 150

Total Protein

Principle

Polypeptides containing at least two peptide bonds react with biuret reagent. In alkaline solution, cupric ion forms a coordination complex with protein nitrogen with very little difference between albumin and globulin on a protein-nitrogen basis.

Reagents

Sodium Potassium Tartate, Sodium Hydroxide, Potassium Iodide, Copper Sulfate.

Calibration

Calibration is stable for approximately 23 days (552 hours) and is required with each change in reagent lot number.

Expected Values

Serum	Range (g/dL)	Range (g/L)
Adult, Ambulatory	6.4 to 8.3	64 to 83
Adult, Recumbent	6.0 to 7.8	60 to 78
> 60 years	lower by ~ 0.2	lower by ~ 2

Albumin BCG

Principle

The Albumin BCG procedure is based on the binding of bromcresol green specifically with albumin to produce a coloured complex. The absorbance of the complex at 628 nm is directly propotional to the albumin concentration in the sample.

Reagents

Albumin BCG is supplied as a liquid, ready-to-use, single reagent kit which contains.

Bromcresol Green, TRIS, Succinic Acid.

Calibration

Calibration is stable for approximately 41 days (hours) and is required with each change in reagent lot number.

Expected Values

Serum/Plasma	Range (g/dL)
20 to 60 years	3.5 to 5.2
60 to 90 years	3.2 to 4.6
> 90 years	2.9 to 4.5

Quality Control

Two levels of controls (normal and abnormal) are to be run every 24 hours.

RESULTS

The ARCHITECT *c* System uses photometric technology to measure analyte concentrations in samples.[25]

Photometric data reduction methods include

- Absorbance method (photometric – *c* System)

  Factor method (photometric – *c* System)
- Linear.
- Logit-4.

- Spline.
- Factor and blank.

RESULTS AND DISCUSSION

The results of present study were analysed using windows SPSS 14.

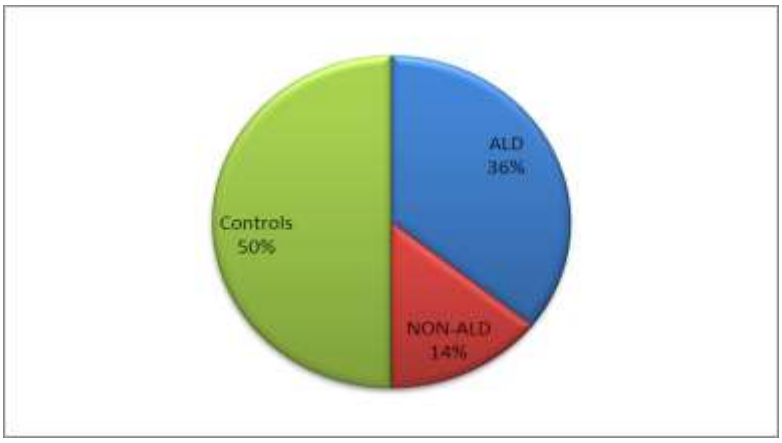

Figure 1: Distribution of subjects

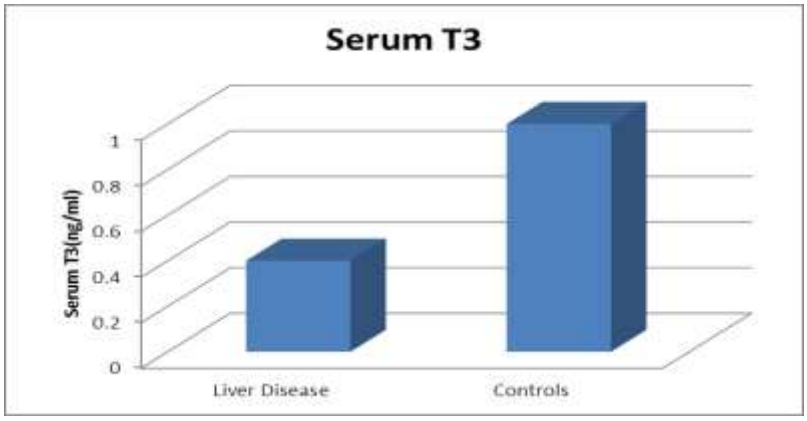

Figure 2: Diagramatic representation of mean serum T_3 levels in patients with liver disease and controls.

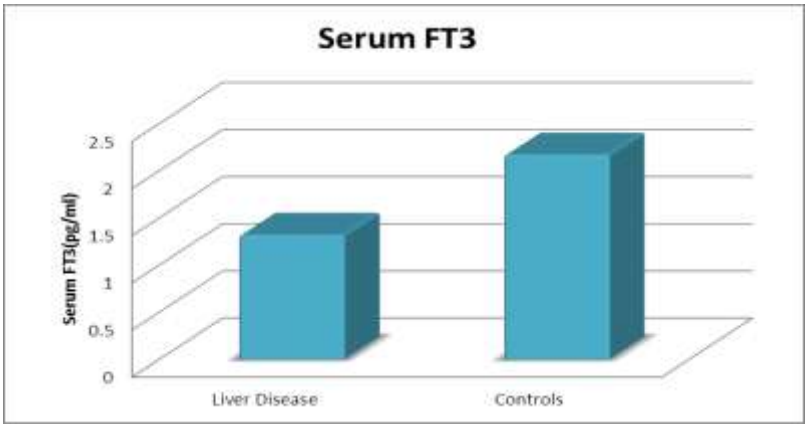

Figure 3: Diagramatic representation of mean serum FT_3 levels in patients with liver disease and controls.

In this study, patients with liver disease i.e patients with increased level of total bilirubin, direct bilirubin, SGOT, SGPT and decreased levels of total protein, albumin: globulin were selected and were evaluated for thyroid function tests i.e T_3,T_4, TSH, FT_3 and FT_4; and it was found that the serum T_3 and FT_3 levels were decreased in both alcoholic and non-alcoholic liver disease patients as compared to controls. The mean serum T_3 level in patients with liver disease was 0.40±0.096 and in control group was 1±0.267.This difference was statistically significant (p value <0.001).The mean serum FT_3 level in patients with liver disease was 1.32±0.341 and in control group was 2.17±0.62.This difference was statistically significant(p value<0.001).When the serum T_3 and FT_3 levels of both the study groups(ALD and NON-ALD) were compared, a significant difference was observed. This difference was statistically significant by ANNOVA.

In the different types of liver disease, similar process may occur to those seen in the sick euthyroid syndrome, but in addition a number of changes specific to the type or stage of liver disease are also found. Ethanol intake was associated with impaired hepatic 5'-deiodination. Among patients with alcohol-induced liver cirrhosis, low T_3 and T_4, elevated rT_3, and normal TSH values have been observed.[26]

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 increases in those subjects eventually displaying a favourable outcome, suggesting that T_3 concentrations in patients with advance liver disease may be considered as helpful prognostic indicator. Moreover, they have found a good correlation between T_3 concentrations and serum albumin, bilirubin, and prothrombin-time. These results suggests that T_3 concentrations should be considered a sensitive index of hepatic function in liver disease.

A prospective study in 118 patients with cirrhosis demonstrated a 17% increase in thyroid glandular volume, assessed by ultrasonography, as compared to controls.[27] the most consistent thyroid hormone profile in patients with cirrhosis are a low total and free T_3 and an elevated rT_3, similar changes to those in the sick euthyroid syndrome, probably reflecting a reduced deiodinase type 1 activity, resulting in reduced conversion of T_4 to T_3.[28] This results in an increase in conversion of T_4 to rT_3 by the deiodinase type 3 system, and an increase in the rT_3 to T_3 ratio. The plasma T_3/rT_3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhotics.[29-32] Since T_3 and rT_3 bind to the same

plasma proteins, the T_3/rT_3 ratio provides a parameter of liver function that is largely dependent of protein binding. Both the T_3/rT_3 ratio and free T_3 levels in plasma thus provide a correlate of liver function in cirrhosis, and are of prognostic value, albeit seldom used.[33-35] The low total and free T_3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores. Indeed, a recent study in cirrhotic patients showed that the onset of hypothyroidism from intrinsic thyroid disease of various aetiologies during cirrhosis resulted in a biochemical improvement in liver function (e.g. coagulation profile) as compared to cirrhotic controls.[36] In acute hepatitis of mild or moderate severity, patients have elevated serum levels of total T_4, due to increased thyroid-binding globulin, which is synthesized as an acute-phase reactant, but normal levels of free T_4. In more severe cases with impending liver failure, the data is variable, and low total T_4 levels may reflect reduced hepatocellaular synthesis of thyroid-binding globulin.[31] Serum T_3 levels are extremely variable, but the free T_3:T_4 ratio correlates negatively with the severity of the liver disease and has prognostic value.[36]

In patients with chronic hepatitis associated with primary biliary cirrhosis (PBC) or chronic autoimmune hepatitis, there is an increased prevalence of autoimmune thyroid disease.[37] Thus abnormalities may arise from thyroid gland dysfunction or as a consequence of liver disease. Autoimmune hypothyroidism is a prominent feature in PBC, occurring in 10-25% of patients.[38]

A study by Romelli et al proves the existence of the so called low T_3 syndrome-that is, low that T_3 with normal total T_4 and thyrotropin concentrations in the absence of clinical hypothyroidism.[1,2]

A study by Wojciechowska-Durczynska and colleagues followed thyroid function prospectively in 51 patients with liver or pancreatic cancers who underwent abdominal surgeries. As expected, among these sick patients who experienced surgical stress, mean serum free T_3 decreased significantly over the 3 to 5 days following both minor and major surgeries. This proves that liver plays a major role in thyroid hormone synthesis.[39]

CONCLUSION

The mean T_3 and FT_3 levels were decreased in patients with alcoholic and non-alcoholic liver disease as compared to controls probably because type I deiodinase which is the major

enzyme in liver carries out 5' deiodination of T_4 to form T_3. This probably reflects diminished type 1 deiodinase activity, resulting in a reduced conversion of T_4 to T_3; in general, however,.these patients are clinically euthyroid.

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