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THE SPECTRUM OF THYROID ABNORMALITIES IN LIVER DISEASE AND ITS CORRELATION WITH LIVER FUNCTION

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CERTIFICATE

This is to certify that the dissertation titled "A STUDY ON THE SPECTRUM OF THYROID ABNORMALITIES IN LIVER DISEASE AND ITS CORRELATION WITH LIVER FUNCTION" is the bonafide original work of Dr. ANWAR C VARGHESE in partial fulfillment of the regulation for M.D. Branch–I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in MARCH 2010. The Period of study was from January 2009 to August 2009.

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DECLARATION

I, **Dr ANWAR. C. VARGHESE,** solemnly declare that dissertation titled "**A STUDY ON THE SPECTRUM OF THYROID ABNORMALITIES IN LIVER DISEASE AND ITS CORRELATION WITH LIVER FUNCTION"** is a bonafide work done by me at Madras Medical College and Govt. General Hospital from August 2008 to October 2009 under the guidance and supervision of my unit chief **PROF.A RADHAKRISHNAN, MD**, Professor of medicine.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulations for the award of M.D. Degree (Branch – I) in General Medicine.

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CONTENTS

ABBREVIATIONS

ALD- ACUTE LIVER DISEASE

ALT- ALANINE AMINOTRANSFERASE

ANOVA- ANALYSIS OF VARIANCE

AST- ASPARTATE AMINOTRANSFERASE

CAH- CHRONIC ACTIVE HEPATITIS

CL- CIRRHOSIS LIVER

CLD- CHRONIC LIVER DISEASE

CPS- CHILD PUGH SCORE

D1- DEIODINASE 1

D2- DEIODINASE 2

D3- DEIODINASE 3

DCLD- DECOMPENSATED CHRONIC LIVER DISEASE

FT3- FREE TRIIODOTHYRONINE

FT4- FREE THYROXINE

INR- INERNATIONAL NORMALISED RATIO

MELD- MODEL FOR END-STAGE LIVER DISEASE

PBC- PRIMARY BILIARY CIRRHOSIS

PSC- PRIMARY SCLEROSING CHOLAMGITIS

RT3- REVERSE TRIIODOTHYROXINE

SGOT- SERUM GLUTAMIC-OXALOACETIC TRANSAMINASE

SGPT- SERUM GLUTAMIC-PYRUVIC TRANSAMINASE

TBG- THYROID BINDING GLOBULIN

TIPS – TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC

INTRODUCTION

"The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds." ***Keynes, John Maynard***

In most chronic illness, defects arise in thyroid hormone metabolism, resulting in the sick euthyroid syndrome. This is characterized by a normal total T4, normal/high free T4, low total T3, low free T3 and an elevated rT3. These changes reflect a reduction in D1 activity, an increase in D3 and changes in the plasma concentration of thyroid-binding proteins and free fatty acids (which displace thyroid hormones from binding proteins) There are also non-thyroidal influences on the hypothalamic-pituitary-thyroid axis, e.g. cortisol inhibiting TSH secretion[(1)]. It has been suggested that this syndrome may confer a survival advantage, which adapts an organism to chronic illness by reducing the basal metabolic rate within cells and thereby reducing caloric requirements.

In the different types of liver disease, similar processes 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 is also found. Many studies have been carried out in liver disease patients assessing their thyroid status; mostly in European countries and Japan. Most of these studies are limited by the number

of patients in which these studies have been conducted. This study tries to find out the relationship between thyroid function and liver disease in the context of a tertiary care hospital in India. This study focuses on patients with complications of liver disease who are sicker than the patients in other studies.

Aims and objectives

1. To determine the spectrum of thyroid abnormalities in both chronic and acute liver disease patients admitted in medical wards in Government General Hospital.

2. To compare the thyroid hormone levels in the liver diseases- both acute and chronic patients to that of healthy controls.

3. To assess the correlation between thyroid function and the level of liver dysfunction.

4. To assess the utility of thyroid function tests as a biomarker to differentiate acute from chronic liver disease.

Review of literature

Review of Literature

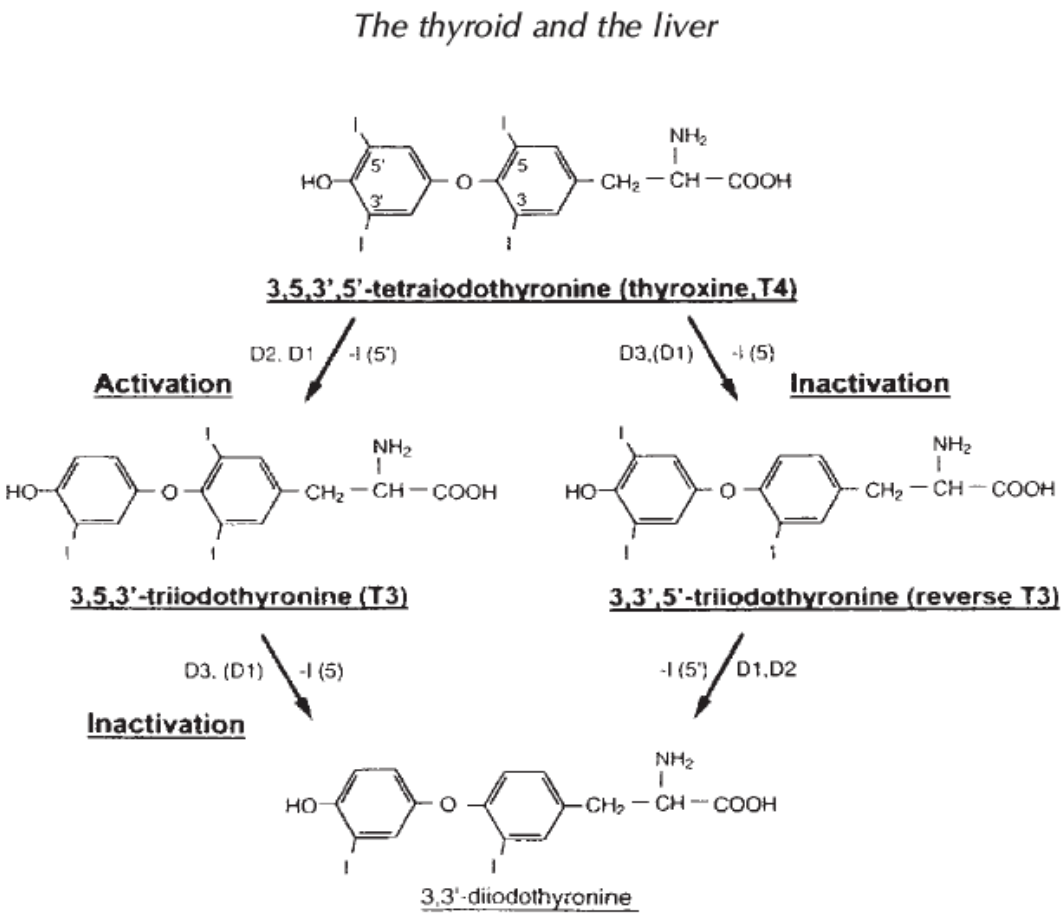
In normal subjects, the thyroid gland secretes 110 nmol of thyroxine and 10 nmol of triiodothyronine each day[2]. Tri-iodothyronine has a ten times greater affinity and ten times greater efficacy than thyroxine for the nuclear receptor, thus even though thyroxine is quantitatively secreted at much higher levels, it should be regarded as a pro-hormone that requires deiodination and conversion to T3 to become biologically active[3]. 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). They are responsible for the activation of T4 to T3, inactivation of T4 to rT3 and the conversion of rT3 and T3 to T2.

The conversion of T4 to T3 in extra thyroidal tissue occurs through a rapidly equilibrating pool via the D1 enzyme system and a slowly equilibrating pool

Via the D2 system. The type 1 deiodinase is mainly found in the liver and kidney[4], and accounts for approximately 30–40% of extrathyroidal production of T3 (12 nmol). The type 2 deiodinase is found in the pituitary, the CNS, and skeletal muscle and contributes 60–70% of the extrathyroidal production of T3 (30 nmol)[5]. Although this enzyme system performs similar actions to the D1

group of enzymes, its kinetics, regulation and susceptibility to propylthiouracil[6] are different. Although both the D1 and D2 system can also inactivate T4 and T3, the major inactivator is the type 3 deiodinase system, which primarily exhibits inner-ring deiodination (unlike the other systems). It is found in the liver, skin and CNS, where it catalyses the conversion of T4 to rT3 and T3 to T2, both inactive metabolites; it also converts rT3 to rT2[7]. This enzyme system is also expressed in placenta, where it protects the foetus from maternal thyroid hormones[8].

Structures of principal iodothyronines and their interactions[1]



In addition to the central role in deiodination to activate and deactivate thyroid hormones, the liver performs specific functions relating to thyroid hormone transport and metabolism. The liver extracts 5–10% of plasma T4 during a single passage, as shown by studies using w131IxT4. This value is much higher than can be accounted for by the amount of free T4 delivered to the liver, indicating that a substantial amount of proteinbound T4 is available

for uptake[9]. An active stereospecific transport mechanism has been identified for transporting T4 and T3 across the hepatocytes membrane. The intracellular concentrations of the free hormone are higher than the plasma levels, and the process is energy-dependent[10].

The liver synthesizes a number of plasma proteins that bind the lipophilic thyroid hormones and thereby provide a large, rapidly exchangeable pool of circulating hormone. The thyroid hormones are 99% bound to thyroxine-binding globulin, thyroxine-binding prealbumin and albumin in plasma. The free hormone component within plasma is in equilibrium with the protein-bound hormone, and it is this free fraction which accounts for the hormone's biological activities. The plasma concentrations of free T4 and T3 are at a steady concentration, so that the tissues are exposed to the same concentrations of the free hormone. However, the free hormone concentrations in different tissues vary according to the transport and deiodinase activity within specific tissues. Thus tissue thyroid status depends not only on thyroxine secretion but also on normal thyroid hormone metabolism, delivery of T3 to nuclear receptors and on receptor distribution and function. Normal thyroid function, which is essential for normal growth, development and the regulation of energy metabolism within cells, is dependent on a normally functioning thyroid and liver axis.

Thyroid abnormalities in specific liver diseases Cirrhosis liver

The most consistent thyroid hormone profile in patients with cirrhosis are a low total and free T3[11] and an elevated rT3[12], similar changes to those in the sick euthyroid syndrome, probably reflecting a reduced deiodinase type 1 activity, resulting in reduced conversion of T4 to T3. This results in an increase in conversion of T4 to rT3 by the deiodanase type 3 system, and an increase in the rT3 to T3 ratio. The plasma T3:rT3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhotics[13]. Since T3 and rT3 bind to the same plasma proteins, the

T3/rT3 ratio provides a parameter of liver function that is largely independent of protein binding. Both the T3/rT3 ratio and free T3 levels in plasma thus

provide a correlate of liver function in cirrhosis, and are of prognostic value, albeit seldom used[14]. The low total and free T3 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. There are reports of improvement in liver function with the onset of hypothyroidism in patients with cirrhosis. Controlled induction of hypothyroidism might therefore be beneficial in cirrhotic patients[15], but further studies are required to test this hypothesis.

Acute hepatitis and acute liver failure

In acute hepatitis of mild or moderate severity, patients have elevated serum levels of total T4, due to increased thyroid-binding globulin[16], which is synthesized as an acute-phase reactant, but normal levels of free T4. In more severe cases with impending liver failure, the data is variable, and low total T4 levels may reflect reduced hepatocellular synthesis of thyroid-binding globulin. Serum T3 levels are extremely variable, but the free T3:T4 ratio correlates negatively with the severity of the liver disease and has prognostic value[16]. Again this probably reflects diminished type 1 deiodinase activity, resulting in a reduced conversion of T4 to T3; in general, however, these patients are clinically euthyroid. Some series have described patients with acute hepatic failure (especially viral hepatitis) as having goitres that resolved with improvement in liver function[17].

Specific forms of chronic liver disease

In patients with chronic hepatitis associated with primary biliary cirrhosis (PBC) or chronic autoimmune hepatitis, there is an increased prevalence of

autoimmune thyroid disease[18, 19]. Thus abnormalities may arise from thyroid gland dysfunction or as a consequence of the liver disease. Autoimmune hypothyroidism is a prominent feature in PBC, occurring in 10–25% of patients[20]. There is often an increase in total T4 in PBC, due to an increase in thyroid-binding globulin levels and this may mask hypothyroidism, emphasizing the need to perform a free T4 and TSH assay. Anti-thyroid microsomal antibodies are common in PBC (34%), as are antithyroglobulin antibodies (20%). Thyroid dysfunction may precede or follow the diagnosis of PBC. In autoimmune hepatitis, both Grave's disease (6%) and autoimmune hypothyroidism (12%) are relatively common[19]. Primary sclerosing cholangitis is associated with an increased incidence of Hashimoto's thyroiditis, Graves's disease and Riedel's thyroiditis[21].

In patients with chronic hepatitis who do not have co-existing autoimmune liver and thyroid disease, total T4, total T3, thyroxine-binding globulin levels are often increased, but TSH and free T4 levels are usually normal, and patients are clinically euthyroid[22].

Patients with decompensated liver disease complicated by hepatic encephalopathy subsequent to non-alcoholic cirrhosis were also found to have exceedingly low serum FT3 and T4 levels. Depressed serum FT3 and T4 levels, together with a prolonged prothrombin-time, appear to be characteristic of a

subgroup of decompensated non alcoholic cirrhotic patients prone to develop hepatic encephalopathy.

Thyroid abnormalities associated with treatment of liver disease

Currently the treatment of viral hepatitis with alpha interferon has added another dimension to the abnormalities of thyroid function seen in chronic liver diseases. In different studies assessing patients treated with alpha interferon for hepatitis C, 2.5–10% developed thyroid dysfunction, with both thyrotoxicosis (due to acute thyroiditis) and hypothyroidism being observed. Although the reason is not altogether clear, the induction of an autoimmune reaction has been postulated, resulting in the development of anti-thyroid and antithyrotrophin receptor antibodies[23]. However, a distinct effect on intrathyroidal organification of iodine has also been suggested[24]. The risk factors for developing thyroid dysfunction with alpha interferon (which may persist after discontinuation of the drug) are female sex, underlying malignancy, high doses of long duration, combination immunotherapy (especially Il-2), and the presence of antithyroid peroxidase antibodies prior to commencing treatment[25,26,27]. It should be noted that interferon therapy causes weakness and muscle aching, and in this setting the myopathy of hypothyroidism may be missed. It is therefore recommended that thyroid function tests (including

thyroid antibodies) are performed prior to therapy, and subsequently monitored at 3–6 month intervals during interferon therapy[28].

Overall, the majority of patients with liver disease are clinically euthyroid, and this can be confirmed with a normal high sensitivity TSH test and a normal free T4. The latter test is routinely performed and obviates the need to take into account the variation in thyroid-binding globulin levels seen in patients with liver disease.

Hypothyroidism as a treatment option in liver disease

Hyperdynamic circulation observed in portal hypertension is characterized by pronounced vasodilatation, increased systemic and regional blood flows, and augmented cardiac index. Drugs used for the treatment of portal hypertension, such as β-adrenergic blocking agents, have also proved useful in controlling the cardiovascular manifestations of thyrotoxicosis. Moreover, propylthiouracil, a commonly used drug for the treatment of hyperthyroidism, has been used for the management of patients with alcoholic liver disease with favourable response. In a rat model of portal vein ligation, hypothyroidism caused amelioration of the hyperdynamic circulation followed by reduction of the portal pressure[29]. Therefore, alleviation of the

hypermetabolic state by thyroid hormone manipulation has been proposed as a treatment option for the hyperdynamic circulation observed in the portal hypertensive state

There is an interesting study demonstrating that hypothyroidism by chronic methimazole administration can alleviate the degree of liver injury and hepatic encephalopathy in bile-duct ligated cirrhotic rats[30]. However, the underlying mechanisms responsible for this phenomenon remain incompletely understood, but immunomodulation and minimization of oxidative liver injury are possible mechanisms. Further studies on the pathogenesis are needed to justify whether hypothyroidism can be used as a treatment option during conditions of liver injury and hepatic encephalopathy.

Liver abnormalities in thyroid disease

Hypothyroidism

Hypothyroidism may have features that mimic liver disease (pseudo-liver disease): examples include myalgias, fatigue and muscle cramps in the presence of an elevated aspartate aminotransferase from a myopathy[31], coma in myxoedema coma[32], and myxoedema ascites[33]. Myxoedema ascites, generally a high protein content ascites suggestive of an exudate, has been varyingly

interpreted as an intrinsic liver defect or a phenomenon mimicking liver disease. It had been proposed that the ascites was a consequence of chronic right-sided heart failure, resulting in central scarring of the liver[34]. The liver biopsy findings of central congestive fibrosis in a number of patients would support this. However, another study reported normal right heart pressures, and proposed that severe hypothyroidism caused enhanced permeability of vascular endothelium, resulting in ascites and serous effusions throughout the body. Following initiation of thyroid replacement therapy, myxoedema ascites resolves over a few months. There is also evidence that hypothyroidism may directly affect the liver structure or function. Hypothyroidism has been associated in a few case reports with cholestatic jaundice attributed to reduced bilirubin and bile excretion. In experimental hypothyroidism, the activity of bilirubin UDP-glucuronyltransferase is decreased, resulting in a reduction in bilirubin excretion[34]. The reduction in bile flow may be in part due to an increase in membrane cholesterol-phospholipid ratio and diminished membrane fluidity[34], which may affect a number of canalicular membrane transporters and enzymes, including the Naq, Kq-ATPase. The triad of reduced bilirubin excretion, hypercholesterolemia and hypotonia of the gall bladder seen in hypothyroidism increases the incidence of gallstones[35]. Recent studies have shown that the hepatic abnormalities associated with hypothyroidism can be reversible over a matter of weeks with thyroxine replacement, with no residual liver damage[36,37]. In rats, hypothyroidism may protect against acetaminophen

toxicity and diminish thioacetamide toxicity, but there is no evidence for this in man[38,39].

Hyperthyroidism

The clinical features of hyperthyroidism are diverse, involving nearly every system in the body. Liver injury caused by thyrotoxicosis is relatively common, and can be conveniently divided into hepatitic or cholestatic types.

An increase in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was reported in 27% and 37% of patients respectively[40], although the majority of these patients showed no other clinical or biochemical features of liver impairment. The mechanism of injury appears to be relative hypoxia in the perivenular regions, due to an increase in hepatic oxygen demand without an appropriate increase in hepatic blood flow. In mild cases, liver histology shows non specific changes, which on light microscopy consist of a mild lobular inflammatory infiltrate consisting of polymorphic neutrophils, eosinophils and lymphocytes, associated with nuclear changes and Kupffer cell hyperplasia. A small proportion of patients have a progressive liver injury, which histologically consists of centrizonal necrosis and perivenular fibrosis, affecting the areas in which hypoxia may be most prevalent. The

clinical presentation of this type of injury is usually that of a self-limiting hepatitis; however, there are a few case reports of thyrotoxic patients presenting with fulminant hepatic failure[41]. The precipitation of the clinical presentation is generally attributable to the onset of cardiac failure, often precipitated by arrhythmias[41].

Cholestatic injury

An elevated serum alkaline phosphatase is seen in 64% of patients with thyrotoxicosis[42]. However this is not necessarily liver-specific, as it can originate from bone and/or liver. It is therefore important to look at elevations in c-glutamyl transpeptidase (17%) and bilirubin (5%) as an indicator of cholestasis[42]. In patients with cholestatic injury, the histological features are similar to the nonspecific changes seen in hepatitic injury. However, in addition there appears to be centri-lobular intrahepatocytic cholestasis[43]. Jaundice is uncommon but when it occurs, complications of thyrotoxicosis (cardiac failure/sepsis) or intrinsic liver disease need to be excluded. It is difficult to establish which features seen in thyrotoxic liver injury are from tissue thyroid status alone, and which are in combination with complications such as cardiac failure, malnutrition and sepsis. It is probably impractical to try and separate the causes out, as awareness of the presentation, complications and treatment are of greater importance. A spectrum of pathological changes from focal necrosis

with fatty change to cirrhosis has been reported in untreated hyperthyroidism[43]. Modern therapies have made chronic liver disease a very rare complication of hyperthyroidism[44]. In the vast majority of cases, the hepatic abnormalities associated with hyperthyroidism are reversible, following the early recognition and treatment of the disorder[44].

Hepatic Dysfunction Associated With Treatment of Hyperthyroidism

Increased serum levels of aspartate aminotransferase and alanine aminotransferase occur in about 30% of patients treated with propylthiouracil[45]. The rise in AST appears to be dose-related, so that AST and ALT levels are highest during the first few weeks of treatment, falling rapidly with a dose reduction[46]. In the majority of patients, serum aminotransferases return to normal, with clinical improvement following withdrawal of treatment. Rarely, a persistent hepatitis occurs with clinical, biochemical (elevated bilirubin, AST and ALT) and histological features of hepatocellular necrosis[47]. This is an idiosyncratic reaction that can develop at any time, but usually occurs within the first 2 to 3 months of treatment in about 1% of patients, usually women aged -30 years. It is considered to be an allergic host response, which generally resolves over a protracted period of time[48]. A small proportion of patients develop fulminant hepatic failure, with the presence of severe acidosis or a combination of grade III/IV encephalopathy, renal failure and

coagulopathy. Abnormalities of liver function are much less common with carbimazole and methimazole. These agents induce cholestasis, as an idiosyncratic reaction to the drug[49]. An elevation of the bilirubin, alkaline phosphatase, and c-glutamyl transpeptidase levels are the predominant abnormalities. Such liver dysfunction usually presents within 2–3 weeks of initiation of treatment, and can persist for several months despite discontinuation of the offending drug[50]. The predominant feature on liver biopsy is intrahepatic cholestasis. Predicting the occurrence of hepatic injury in individual patients is difficult, and it is therefore recommended that liver function tests be performed in all patients within 3 months of commencing therapy.

Other thyroid and liver interactions

The liver is the major site for cholesterol and triglyceride metabolism, and the thyroid hormones play an integral part in hepatic lipid homeostasis. Thyroid hormones increase the expression of LDL receptors on the hepatocytes[51], and increase the activity of lipid-lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels[52]. Thyroid hormones also increase the expression of apolipoprotein A1, a major component of high-

density lipoprotein[53]. The above effects of the thyroid hormones could be beneficial in reducing the onset of atherosclerosis if they were elicited without the deleterious effects, particularly cardiac effects such as atrial arrhythmias[54,55]. A series of 3,5-diodo-3-aryl-substituted thyronines have been developed, which show a potent cholesterol-reducing effect in hypercholesterolaemic rats, without producing tachycardia. The tissue selectivity of these agents was attributed to selective uptake by the liver rather than TR subtype selectivity[56]. Subsequently, a series of novel thyronine type derivatives (dimethyl-isopropylbenzylphenoxy- acetic acid) (GC-1) have reduced serum cholesterol in rats, without tachycardia, by selective activation of the TRb isoform.

Diseases Affecting both Thyroid and Liver

Diseases causing diffuse infiltration like malignancies, amyloidosis and hemochromatosis can cause both thyroid and liver dysfunction. Of the infiltrating malignancies, non-Hodgkin's lymphoma is the commonest cause, and the presentation is usually dominated by goitre (with or without lymphadenopathy), jaundice and a paraneoplastic illness[57]. Occasionally, other forms of hepatic impairment (e.g. coagulopathy) and hypothyroidism can occur

as part of the presentation[58]. Secondary amyloidosis due to systemic inflammatory diseases (e.g. Crohn's, tuberculosis, familial Mediterranean fever) is the commonest cause of amyloid deposition into the liver and thyroid gland[59], characterized by the deposition of the serum amyloid A (AA) protein[60]. The synthetic function of each organ is usually well maintained, thus amyloid organ function is better followed by serial measurement of serum amyloid A protein and amyloid P scintigraphy[61]. Transfusion-related iron deposition (secondary hemochromatosis) can rarely cause multiple endocrine abnormalities (including hypothyroidism) and cirrhosis from iron deposition into the respective organ. The toxicity of the iron deposition into the thyroid (and thus degree of hypothyroidism) is potentiated by hypoxia and anemia, making these patients difficult to treat[62].

Drugs Affecting both Thyroid and Liver Diseases

Amiodarone is the most notable drug that effects both the liver (fibrosis) and the thyroid gland (hypo/ hyperthyroidism), and its effects may remain even following drug withdrawal[63]. The antimalarial drug mefloquine can cause a self-limiting hepatitis and thyrotoxicosis from acute thyroiditis, but the symptoms appear to resolve when the drug is withdrawn[64]. Another major drug class affecting both organs is the anti-epileptics, of which carbamazepine can cause hepatic impairment and subclinical hypothyroidism from abnormal thyroid hormone metabolism[65]. Finally, the treatment of malignant disease using radical radiotherapy regimes, including those containing 131I MIBG and modern chemotherapy schedules have been associated with a greater degree of toxicity affecting both organs[66]. Studies on the use of tri-iodothyronine as a hepatic growth factor has shown it to be a primary mitogen for the liver in animal models (i.e. it induces hepatocyte proliferation and increases liver mass when administered at high doses in the absence of hepatic injury)[67]. The ability to increase liver mass in the absence of liver damage, and to enhance proliferation during compensatory hyperplasia after liver damage, could be therapeutically valuable if applicable to man. More generally, the ability to manipulate liver cell proliferation in vivo may be helpful in designing cell transplantation and gene therapy approaches to liver diseases[68].

Prognostic markers in liver disease

Identifying patients with poor prognosis is important in planning treatment as well as in explaining the situation to the relatives of the patient. Prognostication of these patients is usually done by clinical examination and history. The introduction of liver cell transplantation as a very viable treatment modality has increased the importance of accurate prognostication in liver diseases. This has led to a search for newer biomarkers to better identify the prognosis. Various scoring systems like Child-Pugh, MELD and others have been devised to effectively identify patients with poor prognosis and those who will benefit from liver transplantation. The various prognostic indictors used in liver disease are briefly described below.

Child –Pugh score

Dr C.G. Child and Dr J.G. Turcotte of the University of Michigan first proposed the scoring system in 1964[69]. It was modified by Pugh in 1972. He replaced Child's criterion of nutritional status with the prothrombin time or INR, and thus eliminated the most subjective part of the score. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity

of liver transplantation. The score employs five clinical measures of liver disease[70]. Each measure is scored 1-3, with 3 indicating most severe derangement. In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/l (4 mg/dl) and the upper limit for 2 points is 170 µmol/l (10 mg/dl).

Measure	**1 point**	**2 points**	**3 points**	**units**
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	µmol/l (mg/dl)
Serum albumin	>35	28-35	<28	g/l
INR	<1.7	1.71-2.20	> 2.20	*no unit*
Ascites	None	Mild	Severe	*no unit*
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	*no unit*

Figure 1 child Pugh score

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

MELD SCORE

The **Model for End-Stage Liver Disease**, or **MELD**, is a scoring system for assessing the severity of chronic liver disease. It was initially developed to predict death within three months of surgery in patients that had undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure[71]. It uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. This score is also used by the United Network for Organ Sharing (UNOS) and Eurotransplant for prioritizing allocation of liver transplants. It is calculated according to the following formula[72]:

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

Caveats with the score include:

- The maximum score given for MELD is 40. All values higher than 40 are given a score of 40
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used).

In interpreting the MELD Score in hospitalized patients, the 3 month mortality is:

- 40 or more — 100% mortality
- 30–39 — 83% mortality
- 20–29 — 76% mortality
- 10–19 — 27% mortality
- <10 — 4% mortality

The equation seeks to calculate a patient's likelihood of dying within three months from their liver disease. This scoring system is preferred by many centers for selecting patients for liver transplantation.

Other models

Other models for assessing the prognosis in liver disease include the following.

The original PBC model[73]

In this model, survival probability of a patient with primary biliary cirrhosis without treatment is estimated based on the following variables. The variables employed are age, serum bilirubin, serum albumin, prothrombin time, presence of peripheral edema and usage of diuretics.

Updated PBC model for prediction of short-term survival[74]

In this model, short-term survival probability of a patient with primary biliary cirrhosis is estimated based on repeated observation. The same variables used in the original PBC model are used in this model also.

New PSC Model[75]

In this model, survival probability of a patient with primary sclerosing cholangitis is estimated based on the following variables. The variables are age, serum bilirubin, serum albumin and AST.

The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index (ANI)[76]

The ANI is a novel scoring system that is highly accurate in distinguishing alcoholic liver disease (ALD) from nonalcoholic fatty liver disease (NAFLD). The ANI may be a useful tool for the frequent clinical scenarios in which it is useful to ascertain an alcohol basis for steatohepatitic liver injury. Short short-term abstinence does not significantly affect the performance characteristics of the ANI therefore the ANI is unlikely to be useful in detecting surreptious alcohol consumption in patients with known ALD. Other liver diseases should first be excluded before utilizing the ANI. The ANI is most accurate when the MELD Score is below 20. The variables used are AST, ALT, MCV, weight, height and gender.

Prothrombin time

The prothrombin time is a measure of the extrinsic pathway of coagulation and quantifies the activity of coagulation factors VII, V, and X, along with their ability to produce fibrin from fibrinogen through the action of thrombin[77]. As some of the coagulation factors have short half lives-for example, factor VII has a half life of only two to five hours -the prothrombin time is a good marker of the synthetic capacity of the liver and hence reflects the severity of hepatic necrosis. It has been observed that the prothrombin time peaks on the third day after paracetamol overdose in those patients who are going to survive and on the fourth day or later in those who will not[78]. This presumably reflects either a greater degree of hepatic necrosis or a delay in hepatocyte regeneration in those patients who die. Prothrombin time is reproducible and nearly always available. Prothrombin time has emerged as a very discernible indicator of liver cell function especially acute liver cell function.

Other coagulation factors[77]

Factor VII concentration has been shown to provide a good indication of prognosis in acute liver diseases. The use of serial factor VII concentrations has

also been shown to improve the predictive power of this test. Bernuau et al in Paris, using multivariate analysis, found that a reduced factor V concentration was the most sensitive prognostic indicator in patients with fulminant hepatitis B infection. However Assay of individual clotting factors is not a routine investigation in most laboratories and this limits the usage of these indicators in routine clinical practice[78].

Aminotransferases

The serum aminotransferases (formerly called transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases, such as hepatitis[79]. The activities of alanine aminotransferase (ALT), formerly serum glutamic-pyruvic transaminase (SGPT), and aspartate aminotransferase (AST), formerly serum glutamic-oxaloacetic transaminase (SGOT), in serum are the most frequently measured indicators of liver disease. These enzymes catalyze the transfer of the α-amino groups of alanine and aspartic acid, respectively, to the α-keto group of ketoglutaric acid. This results in the formation of pyruvic acid and oxaloacetic acid.

There is a poor correlation between the extent of liver cell necrosis and elevation of serum aminotransferases levels. Similarly, absolute elevation of aminotransferase levels is of little value in predicting the outcome of acute hepatocellular disorders. Rapid decreases in serum aminotransferase levels usually are a sign of recovery from disease. This may be a poor prognostic sign in fulminant hepatitis, in which decreasing serum values may reflect the massive destruction and loss of viable hepatocytes. AST has been validated as an independent prognostic marker in drug induced liver disease[80]. Other enzymes like lactate dehydrogenase, glutamate dehydrogenase, isocitrate dehydrogenase and sorbitrate dehydrogenase has been used as indictors of liver cell damage but none of them has been validated as prognostic indicators.

Bilirubin

A recognition of the potentially grave significance of yellow discoloration (jaundice) long preceded any knowledge of bilirubin and is mentioned in clay tablets of Mesopotamia (3000 BC) and the writings of Hippocrates (460–377 BC). In the practice of medicine over the centuries, the skin discoloration often evoked fear and loathing[81]. The concentration of bilirubin in plasma varies directly with the generation of bilirubin and inversely with the hepatic clearance of bilirubin. Bilirubin is incorporated in most of the scoring systems assessing the prognosis in liver diseases. Bilirubin has

separately been validated as an independent prognostic marker in drug induced liver diseases[80].

Other prognostic markers in liver disease

Computerized tomagraphic liver volumetry has been validated as a prognostic indicator in acute liver disease[82]. The newer methods used in prognostication of liver diseases are ER6Q,Vimentin, actin alpha 1 skeletal muscle protein, hMFAP and tropomyosin[83]. Serum electrophoresis has been suggested as an indicator of prognosis in chronic liver disease.When an electrophoretic analysis of the serum proteins was included, marked decreases in the concentrations of albumin and the alpha-globulins alpha-1-antitrypsin and haptoglobin were observed in terminal liver cirrhosis, indicating impaired liver function[84]. In patients with alcoholic cirrhosis, plasma calprotectin has been suggested as a new prognostic marker of survival, which seems independent of the severity of liver disease[85]. Furthermore, high plasma calprotectin levels may characterize a group of patients with cirrhosis with recurring bacterial infections.

Hyaluronic acid is a strong predictor of liver-related events in HIV/viral hepatitis-co-infected patients. Patients developing liver-related events during follow-up had substantially larger increases in HA compared to patients without

such events. Plasma Hyaluronic acid may be useful to monitor progression of liver disease in this population[86].

Thyroid function tests as prognostic indicators in liver disease

The abnormalities of serum concentrations of thyroid hormones are commonly found in liver diseases. The degree of abnormalities may be noted according to the type of disease or its severity. The estimation of free thyroid hormones is important in liver diseases because changes of the binding protein in blood.

According to Takahashi et al in chronic liver diseases, serum FT3 is decreased according to the degree of liver dysfunction in conditions such as CPH, CAH and LC, and seemed to reflect the severity of the liver damage[87]. Serum FT3 may reflect directly the disturbance of the conversion from T4 to T3 in liver. It is also decreased in AH as in LC. Therefore serum FT3 may become an index of liver damage because serum FT3 showed favourable correlation with each of ICGR15,

PT and albumin which were considered to reflect the reserved hepatic capacity. As to the significance of free thyroid hormones as an index of the severity of liver damage, serum FT3 decreased according to the degree of liver dysfunction in both chronic liver diseases and AH. In consequences it is considered that serum FT3 may become a sensitive index of liver dysfunction; serum FT4 decreased in only LC[87]. It is considered that decrease of serum FT4 was noted

under the critical condition in liver diseases as in other diseases. Therefore serum FT4 is assumed to be a useful index for prognosis, and has a different significance

from serum FT3.

Yamanaka et al reported that T3/T4 value decreased only decompensated liver cirrhosis, but no significant changes were noted in other liver diseases[88]. Yamaba et al reported that T3/T4 value decreased most in acute hepatitis, and slightly decreased in chronic persistent hepatitis and chronic active hepatitis, while no significant difference was noted in liver cirrhosis compared with controls[89].

Ertugˇ rul Kayacetina, Gurcan Kısakolb, Ahmet Kayab found no significant difference in functional thyroid parameters between patients surviving and not surviving hepatic encephalopathy ($p < 0.375$)[90]. They concluded that patients with decompensated liver disease complicated by hepatic encephalopathy subsequent to non-alcoholic cirrhosis were found to have exceedingly low serum FT3 and T4 levels. Depressed serum FT3 and T4 levels, together with a prolonged prothrombin-time, therefore appear to be characteristic of a subgroup of decompensated cirrhotic patients prone to develop hepatic encephalopathy.

Hepner and Walfish reported a significant inverse correlation between

serum T3 concentrations and the severity of liver dysfunction[91,92]. A progressive decrease in T3 levels in chronic liver diseases was described as an indicator

of poor prognosis. Authors ascribed this finding to diminished conversion of T4 to T3 and impaired metabolism of thyroxine-binding proteins. Borzio et al. compared cirrhotics with normal subjects and chronic hepatitis patients. They suggested that T3 serum levels inversely paralleled severity of liver dysfunction. Thyroid function tests have also been performed in acute hepatitis. T4 has been found to be elevated in patients with acute viral hepatitis due to elevation of TBG

(Possibly secondary to release from injured hepatocytes).

In a large group of alcoholic patients Israel et al reported a significant inverse correlation between serum T3 concentrations and the severity of liver dysfunction as well as a progressive T3 increase in those subjects eventually displaying a favourable outcome, suggesting that T3 concentrations in patients with advanced liver disease may be considered as a helpful prognostic indicator[93]. Only little data have been previously reported on direct measurement of free thyroid hormones in liver patients. Green et al found normal FT3 and FIT4 in a small group of cirrhotic patients while low FT4 and normal FT3 concentrations were present in alcoholic fatty liver[94]. Many studies

performed with equilibrium dialysis, however, showed decreased FT3 and normal or frequently increased FT4 concentrations.

S. OZSOY et al found out that chronic alcohol consumption may cause long-term thyroid dysfunction[95]. This may be manifested as a subclinical hypothyroidism in clinical settings and may be related to the severity and duration of alcoholism, family history, and aggression tendency of the patient. Although decreased thyroid hormone levels seem to be a result of persistent effect of chronic alcohol use on thyroid gland, it cannot be disregarded that it may also be a trait marker of proneness to alcoholism.

Conclusion

The liver is closely involved in the metabolism and homeostasis of thyroid hormones. Liver synthesizes most of the thyroid binding proteins and is also involved in the peripheral conversion and inactivation of thyroid hormones. Clinically chronic liver disease may mimic hypothyroidism and thyroid dysfunction may exacerbate liver disease. Though most of the liver disease patients remain euthyroid, subtle abnormalities in thyroid function tests are common. The abnormalities found in a particular liver disease patient depend on the type and duration of illness. The thyroid abnormalities found in acute liver disease differs from that in chronic liver disease and reflects mostly the underlying inflammatory status. The thyroid abnormalities in chronic liver disease patients have been suggested to be an adaptive response to the disease state. It has also being suggested that induced hypothyroidism may be therapeutic in cirrhotic patients. Apart from this thyroid and liver dysfunction can coexist as part of consequences of drugs, radiation or other systemic disease process.

Accurate prediction of prognosis in liver disease is important in selecting the optimum treatment is especially important if liver transplantation is being planned. Several prognostic markers and scoring systems have been developed and validated in this regard. But the search for newer prognostic markers is still on. Several studies have suggested that thyroid function tests could powerful predictors of prognosis in liver disease. It has also being suggested that thyroid function tests can be used to differentiate between acute and chronic liver diseases.

Materials and Methods

Settings

Institute of internal medicine,

Madras Medical College and Government General Hospital

Chennai - 600 003.

Ethical approval

Obtained

Study duration

This study was conducted for a period of eighteen months from Jan 2008 to October 2009.

Study Design

A cross sectional study to determine the spectrum of thyroid abnormalities in acute and chronic liver disease patients getting admitted to general medical wards during the study period.

Inclusion criteria

1] Patients admitted in medical wards in Government General Hospital with diagnosis of acute or chronic liver disease from January 2008 to October 2009 were selected for the study. The first 50 patients admitted during the period with

diagnosis of chronic liver disease were studied under the chronic liver disease category. Similarly the first 10 patients with the diagnosis of acute liver disease were studied.

2] Age greater than 12 years.

Exclusion criteria

1) Age less than 12 years

2) Patients refusing to undergo the study

Methods

A detailed clinical history was elicited from patients selected for the study. A comprehensive physical examination was carried out on them, followed by a thorough review of their hospital records. Data was collected regarding the duration of symptoms, clinical features of liver disease and features of thyroid disease. Patients were divided into acute or chronic liver disease based on history, physical examination, and imaging. Any patient with duration of illness more than 2 months was considered to have chronic liver disease. On imaging coarse echoes and features suggestive of cirrhosis was taken as markers of chronic liver disease. Ascites was graded into three categories; 0- no ascites, 1- easily controlled ascites, 2- difficult to control

ascites. Hepatic encephalopathy was graded into 3 categories; 0-none, 1-minimal and 2-advanced.

Complete thyroid profile (thyroid stimulating hormone [TSH], free thyroxine [FT4], total thyroxine [TT4], free triiodothyronine [FT3] and total triiodothyronine [T T3]) of patients selected for the study was carried out using chemilumiscent immunological method. Patients underwent complete liver function tests. This included total and direct bilirubin, enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [AP]), serum total protein and albumin and prothrombin time. Prothrombin time was estimated using method. All patients underwent an abdominal ultrasonogram to confirm the diagnosis and to look for ascites splenomegaly and features of portal hypertension.

Child-Pugh score was calculated for patients with chronic liver disease as a measure of the severity of liver disease.

Thirty age and sex matched healthy controls were selected from among the attendees of the patients. They were given a complete physical examination liver function test evaluation to exclude liver disease. A complete thyroid profile (TSH, FT4, TT4, FT3, and TT3) was carried out on them.

Statistical analysis

Data analysis was done with use of SPSS, version 10. Descriptive statistics were used to calculate the frequency, mean, median, and standard deviation. For all normally distributed variables, Student's *t* test and ANOVA test were used to determine the significant mean difference in various groups. The correlation between the various thyroid function variables and liver function variables was assessed by Pierson's method. The significance of the difference between the various coefficients of correlations was evaluated using z transformation test.

Observations and Results

Observations and Results

The analysis of the data from 50 patients with chronic liver disease, 10 patients with acute liver disease and 30 controls is given below.

Baseline characteristics

The baseline characteristics of each group of patients and controls are given below. The chronic liver disease group was composed 41 males and 9 females. The average age was 49 years. The mean duration of symptoms was 16.44 months. Twenty five patients had evidence of upper gastrointestinal bleed. Thirteen patients had evidence of hepatic encephalopathy with 4 of them having severe encephalopathy. Twenty nine patients had clinical evidence of ascites of which 6 were classified as difficult to control. Thirty four of these patients had serologic evidence of ascites. Of these patients 42 were clinically icteric while 30 had evidence of edema.

Of the chronic liver disease patients only one patient had clinical evidence of hypothyroidism and her thyroid profile showed gross hypothyroidism with TSH being 28.4. Two other patients had TSH between 5.5 and 10 with no clinical evidence of hypothyroidism. No patient was found to

have either laboratory or clinical evidence of hyperthyroidism. Other baseline characteristics are given in the chart below.

Characteristic	**Value**	**Standard deviation**
Total patients enrolled	50	
Male	41 (82%)	
Female	9 (18%)	
Mean age	49 yrs	12.8 years
Mean Duration of symptoms	16.44 months	19.8 months
Number with UG bleed	25 (50%)	
Number with encephalopathy	13 (26%)	
Number with severe encephalopathy	4 (8%)	
Number with ascites	29 (58%)	
Number with difficult to control ascites	6(12%)	
Number with jaundice	42 (84%)	
Number with edema	30 (60%)	
Patients with goiter	1 (2%)	
Patients with gall stones	3(6%)	
Patients with clinical hypothyroidism	1 (2%)	
TSH	2.3788 mIU/L	4.01
TT4	6.5778 micro g/dL	1.77
FT4	1.1632 ng/dL	0.362
TT3	102.64 ng/dL	38.0
FT3	1.8728 pg/mL	0.650
Total bilirubin	7.7390 mg/dl	5.69
Direct bilirubin	4.3340 mg/dl	3.44
AST	125.24 U/L	89.4
ALT	128.94 U/L	117
Alkaline phosphatase	198.26 U/L	59.8
Albumin	3.2980 gm/dl	0.446
Prothrombin time	24.086 seconds	6.34
Child-Pugh score	10.120	2.19
Liver size	11.170 cm	1.86
Spleen size	10.900 cm	2.68 cm

Baseline characteristics in acute liver disease patients

The acute liver disease group consisted of 7 males and 3 females. The mean age of the group was 33.3 years. The mean duration of symptoms was 0.360 months. All ten patients were jaundiced; none of the patients had upper gastrointestinal bleed, goiter or gall stones. One patient each had hepatic encephalopathy and ascites.

None of the patients had clinical or laboratory evidence of hypothyroidism or hyperthyroidism. The mean TSH was 1.7330 with a standard deviation of 1.04. The mean free T3 was 2.3090 with a standard deviation of 0.644. The other baseline characteristics of the group are given below.

Characteristic	Value	Standard deviation
Total patients enrolled	10	
Male	7 (70%)	
Female	3 (30%)	
Mean age	33.300 years	11.2 years
Mean Duration of symptoms	0.36600 months	0.119 months
Number with UG bleed	0	
Number with encephalopathy	1 (10%)	
Number with severe encephalopathy	0	
Number with ascites	1 (10%)	
Number with difficult to control ascites	1 (10%)	
Number with jaundice	10(100%)	
Number with edema	0	
Patients with goiter	0	
Patients with gall stones	0	
Patients with clinical hypothyroidism	0	
TSH	1.7330 mIU/L	1.04
TT4	9.9930 micro g/dL	2.52
FT4	1.2720 ng/dL	0.279
TT3	108.70 ng/dL	35.8
FT3	2.3090 pg/mL	0.644
Total bilrubin	7.7500 mg/dl	4.46
Direct bilrubin	4.3400 mg/dl	3.33
AST	317.30 U/L	219.
ALT	325.60 U/L	230
Alkaline phosphatase	208.00 U/L	38.1
Albumin	3.6900 gm/dl	0.224
Prothrombin time	16.260 seconds	2.12
Liver size	12.180 cm	1.38
Spleen size	7.6000 cm	0.745

Baseline characteristics of control group

The control group consisted of 30 patients of which 20 were males. The mean age of the patients was 43.200 years. None of the patients had clinical or laboratory evidence of thyroid dysfunction. The liver function was normal both clinically and by laboratory evidence.

Characteristic	**Value**	**Standard deviation**
Total patients enrolled	30	
Male	20 (66.67%)	
Female	10 (33.33%)	
Mean age	43.200 years	13.8 years
Patients with clinical hypothyroidism	0	
TSH	2.7440 mIU/L	1.56
TT4	7.4693 micro g/dL	1.46
FT4	1.2630 ng/dL	0.292
TT3	124.17 ng/dL	29.0
FT3	2.8850 pg/mL	0.582

Distribution of patients in various groups

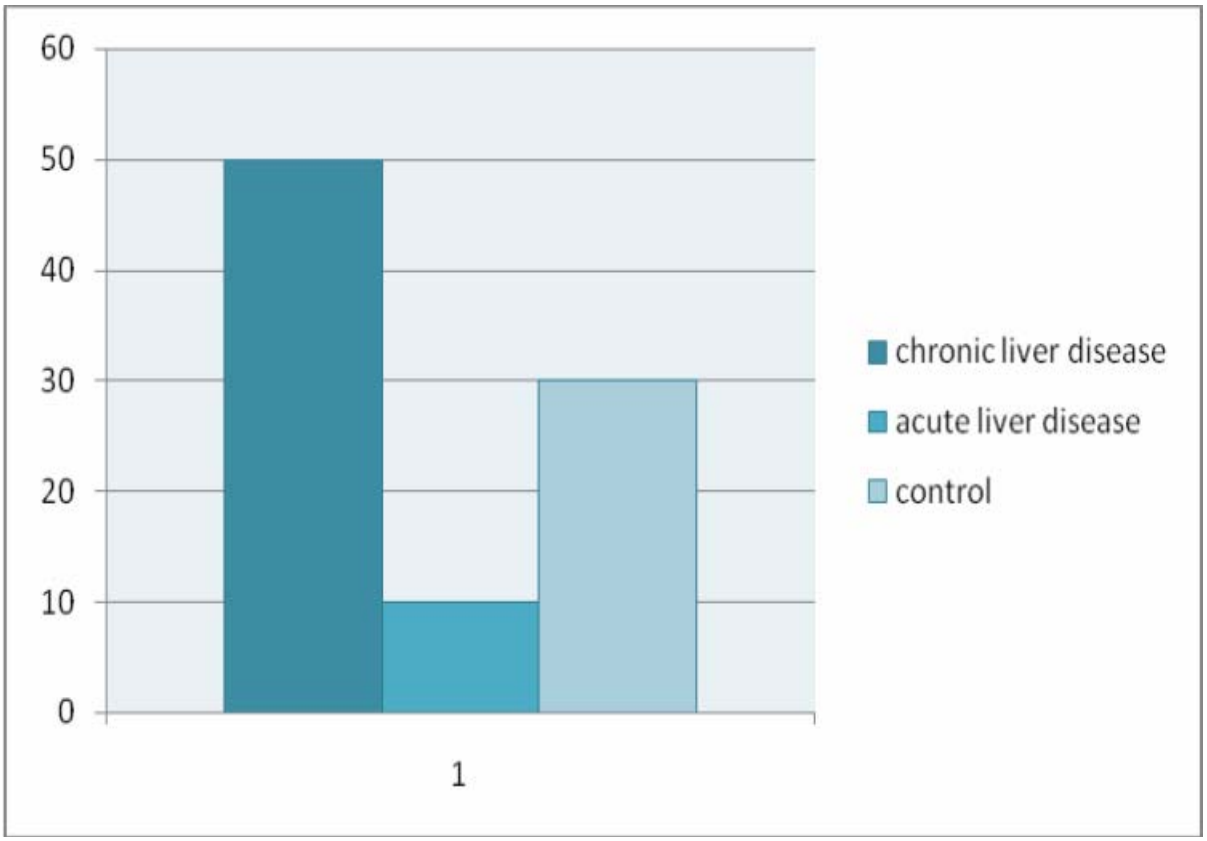


Figure 2 distribution of patients

Sex distribution in various groups

Chronic liver disease**.** Total number 50. Male-41, female-9.

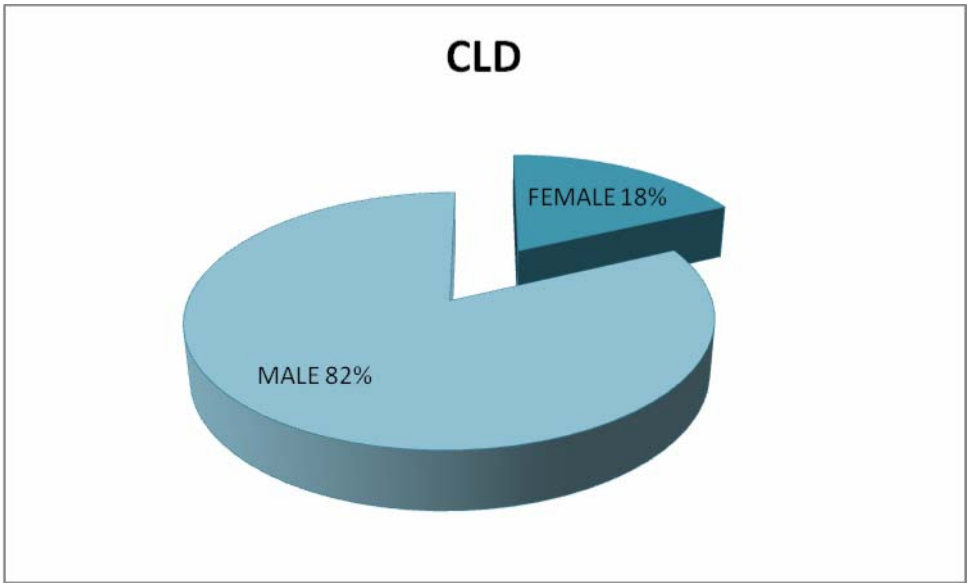


Figure 3 sex distribution CLD

Acute liver disease
Total number 10, female-3. Male-7

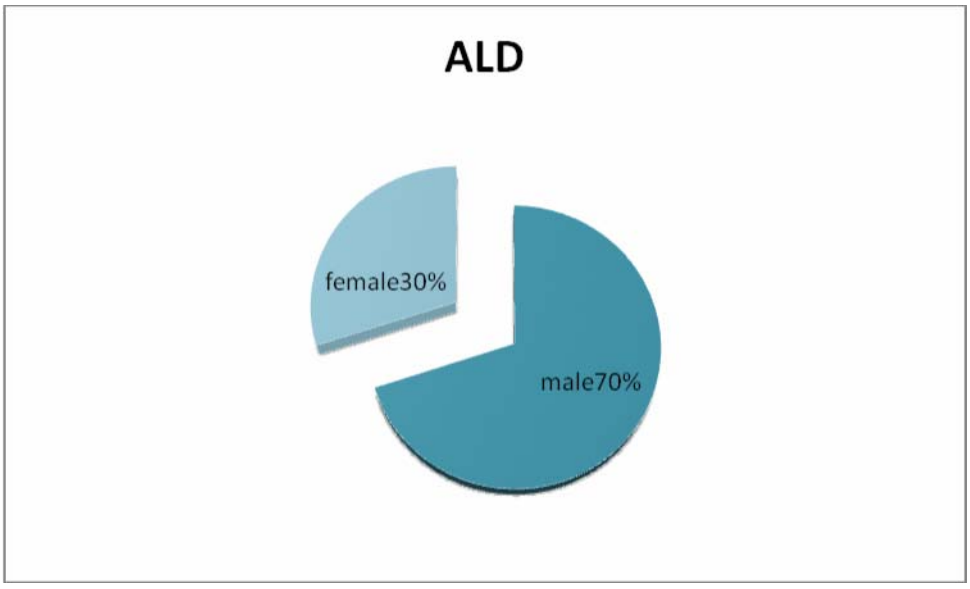


Figure 4 ALD sex distribution

Sex distribution in controls

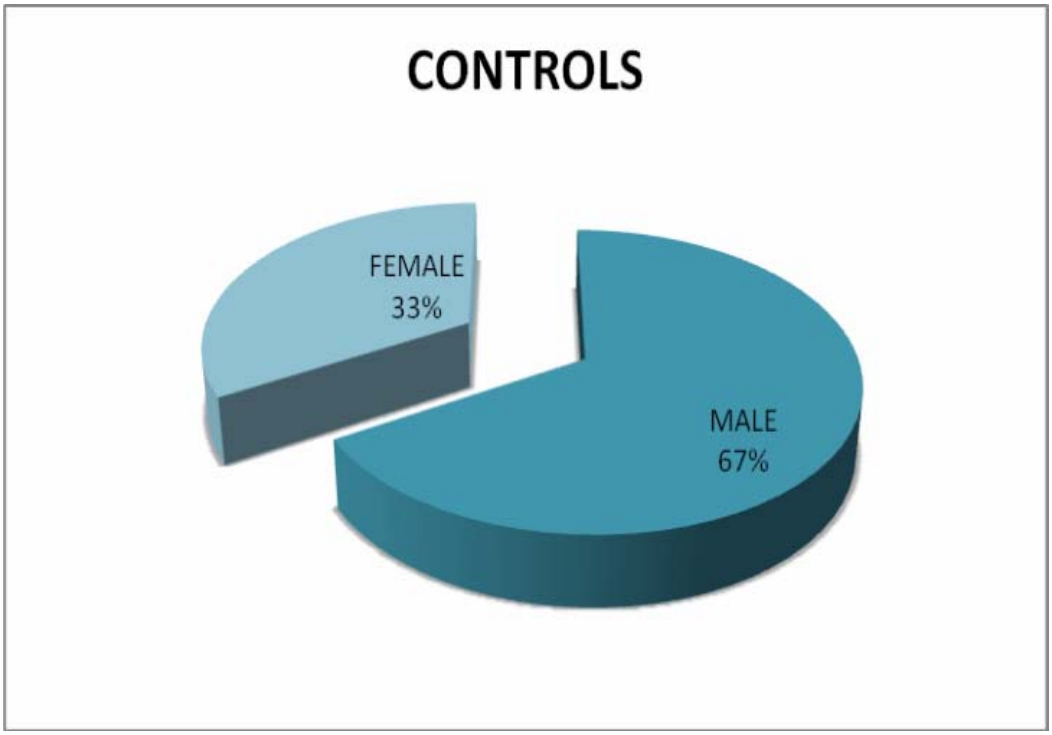


Figure 5 control sex distribution

Comparison of thyroid function variables

The comparison between the thyroid function tests of the three groups was carried out using ANOVA test. Among the thyroid function tests TSH and FT4 failed to show any statistically significant difference among them (p value of 0.67 and 0.35 respectively). The most statistically significant difference was in the comparison of TT4 and FT3 (p value -0.0001). The p value for the comparison of TT3 among the three groups was 0.033.

Thyroid variable	TSH[1] Mean-std dev	TT4[2] Mean-std dev	TT3[3] Mean-std dev	FT4[4] Mean-std dev	FT3[5] Mean-std dev
CLD	2.3788-4.01	6.5778 - 1.77	102.64-38.0	1.1632-0.362	1.8728-0.650
ALD	1.7330 - 1.04	9.9930-2.52	108.70 - 35.8	1.2720 - 0.279	2.3090-0.644
CONTROL	2.7440-1.56	7.4693 - 1.46	124.17-29.0	1.2630-0.292	2.8850 - 0.582

[1] P value- 0.67
[2] P value- .0001
[3] P value- 0.033
[4] P value- 0.35
[5] P value- .0001

The comparison of liver function abnormalities

There was no significant difference between the acute and the chronic disease groups in case of total or direct bilirubin. Among the enzymes both AST and ALT differed significantly between the two groups. Serum alkaline phosphatase did not vary significantly between the two groups. Markers of hepatic synthetic function like albumin and prothrmbin time varied significantly between the two groups. Among the sonologic parameters liver size did not show any significant difference while the difference in spleen size was significant. The comparison between the various liver function values and the level of significance is given in the table below.

Liver function variable	CLD Mean-std dev	ALD Mean-std dev	P value Mean-std dev
Total bilirubin	7.74 -5.69	7.78-4.46	0.98
direct bilirubin	4.33-3.44	4.34- 3.33	1.00
AST	125- 89.4	317- 219	.0001
ALT	129- 117	326- 230	0.0002
ALK PO4	198- 59.8	208- 38.1	0.62
Albumin	3.30- 0.446	3.69- 0.224	.0001
Prothrombin time	24.1- 6.34	16.3- 2.12	0.0003
Liver size	11.2-1.86	12.2-1.38	0.11
Spleen size	10.9- 2.68	7.60 - 0.745	0.0003

Correlation between the thyroid function and liver function

Correlation between the thyroid function and liver function in CLD

The correlation between various thyroid function variables and liver function variables was calculated using Pierson's coefficient of correlation method. The results are shown in the table below. There was no significant relation between the thyroid function and the level of liver enzymes (AST, ALT). Among the thyroid function tests FT3 showed the highest level of correlation with the liver function indices. TSH did not show any correlation with the liver function indices except total bilirubin. The correlation was significant with a p value of less than 0.05. All other thyroid function indices showed relationships with the liver indices (excluding the enzyme levels) that were significant with a p value less than 0.01. Serum albumin showed a significant positive correlation with TT4, TT3, FT4 and FT3. Both prothrombin time and child-Pugh score showed a significant negative correlation with TT4, TT3, FT4 and FT3. The best correlation was between FT3 and Child-Pugh score.

	T B	D B	AST	ALT	ALB	P T	CPS
TSH	+0.304[a]	+0.189	-0.072	-0.014	-0.178	+0.366[b]	+0.222
TT4	-0.405[b]	-0.515[b]	+0.261	+0.231	+0.427[b]	-0.595[b]	-0.651[b]
FT4	-0.446[b]	-0.432[b]	+0.137	+0.132	+0.412[b]	-0.564[b]	-0.481[b]
TT3	-0.580[b]	-0.575[b]	+0.110	+0.050	+0.486[b]	-0.626[b]	-0.535[b]
FT3	-0.599[b]	-0.582[b]	+0.117	+0.028	+0.505[b]	-0.726[b]	-0.682[b]

[a] correlation significant at 0.05 level (2 tailed)

[b] correlation significant at 0.01 level (2 tailed)

Graphical representation of the data

Plot between FT3 and liver variables

Free T3 - albumin

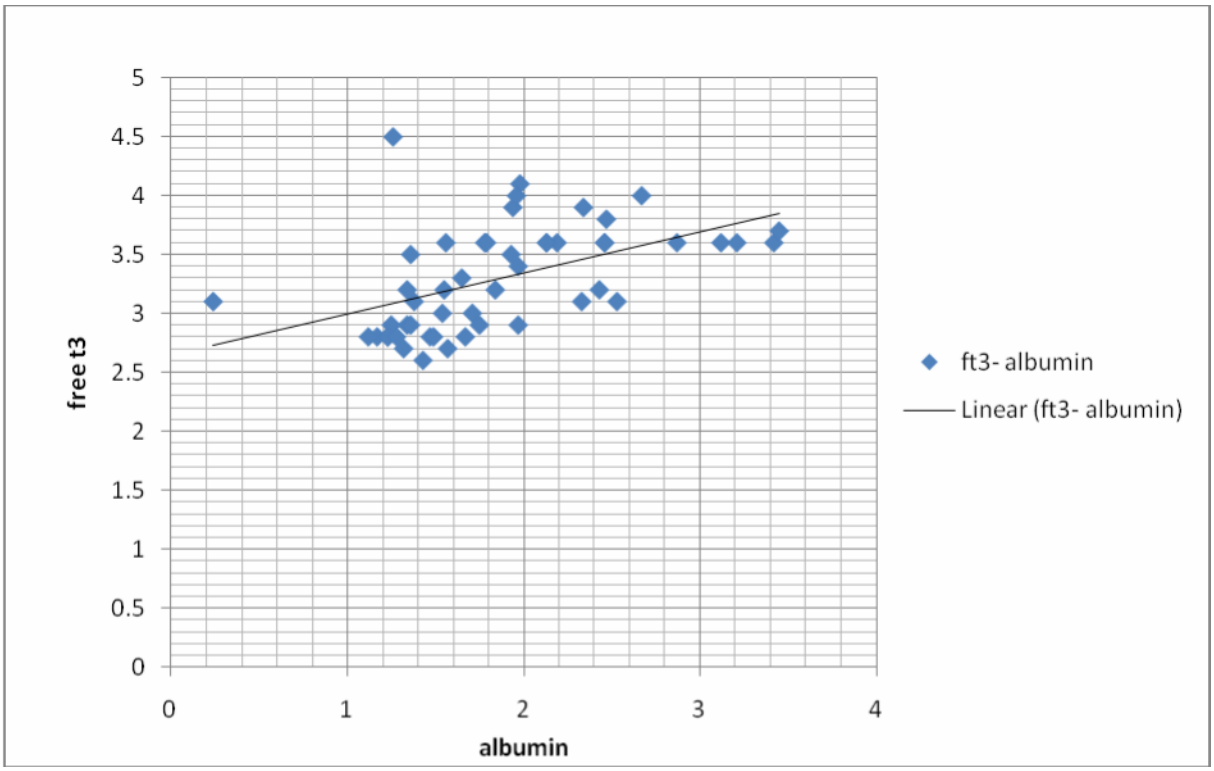


Figure 6 free T3- albumin

The coefficient of correlation – 0.505
Correlation significant at 0.01 level.

Plot between free T3 and prothrombin time

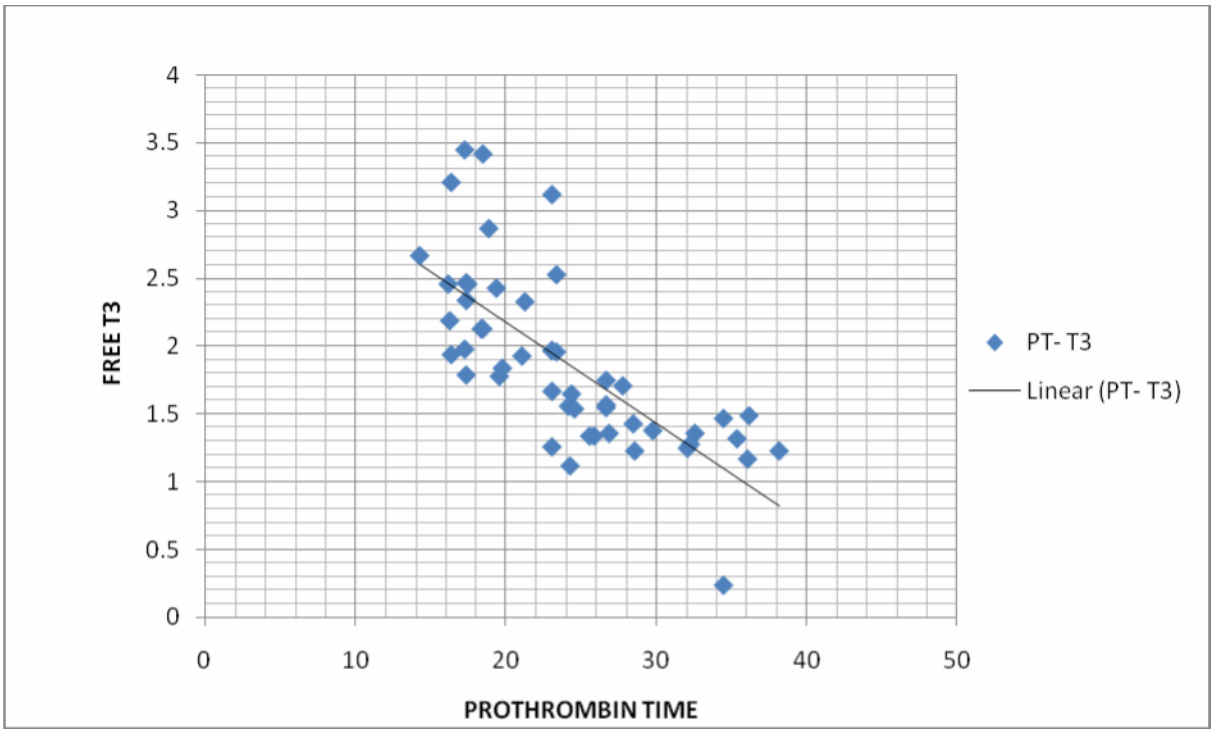


Figure 7 free T3- prothrombin time

The coefficient of correlation between free T3 and prothrombin time – -0.626
Correlation significant at 0.01 level.

Plot between free T3 and total bilirubin

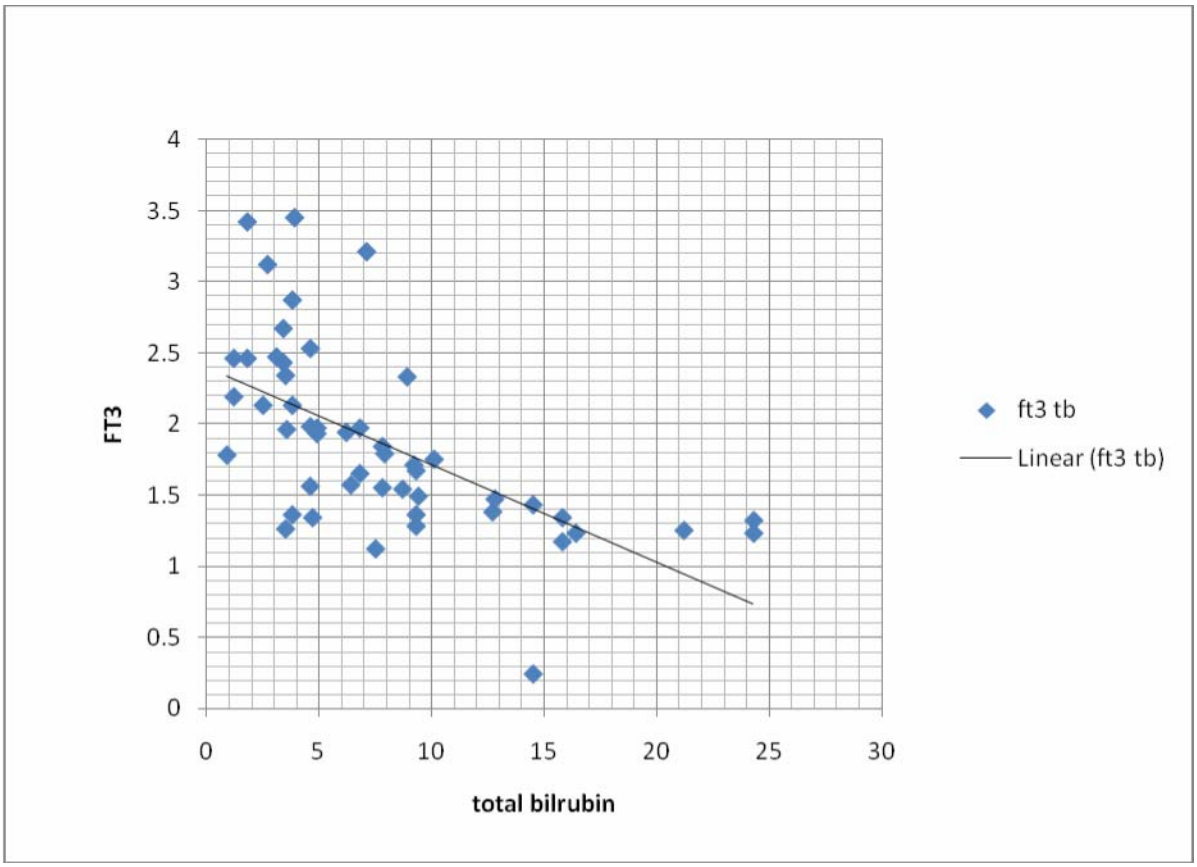


Figure 8 FT3 - total bilirubin

The coefficient of correlation between free T3 and prothrombin time – -0.599
Correlation significant at 0.01 level.

Plot between free T3 and Child-Pugh score

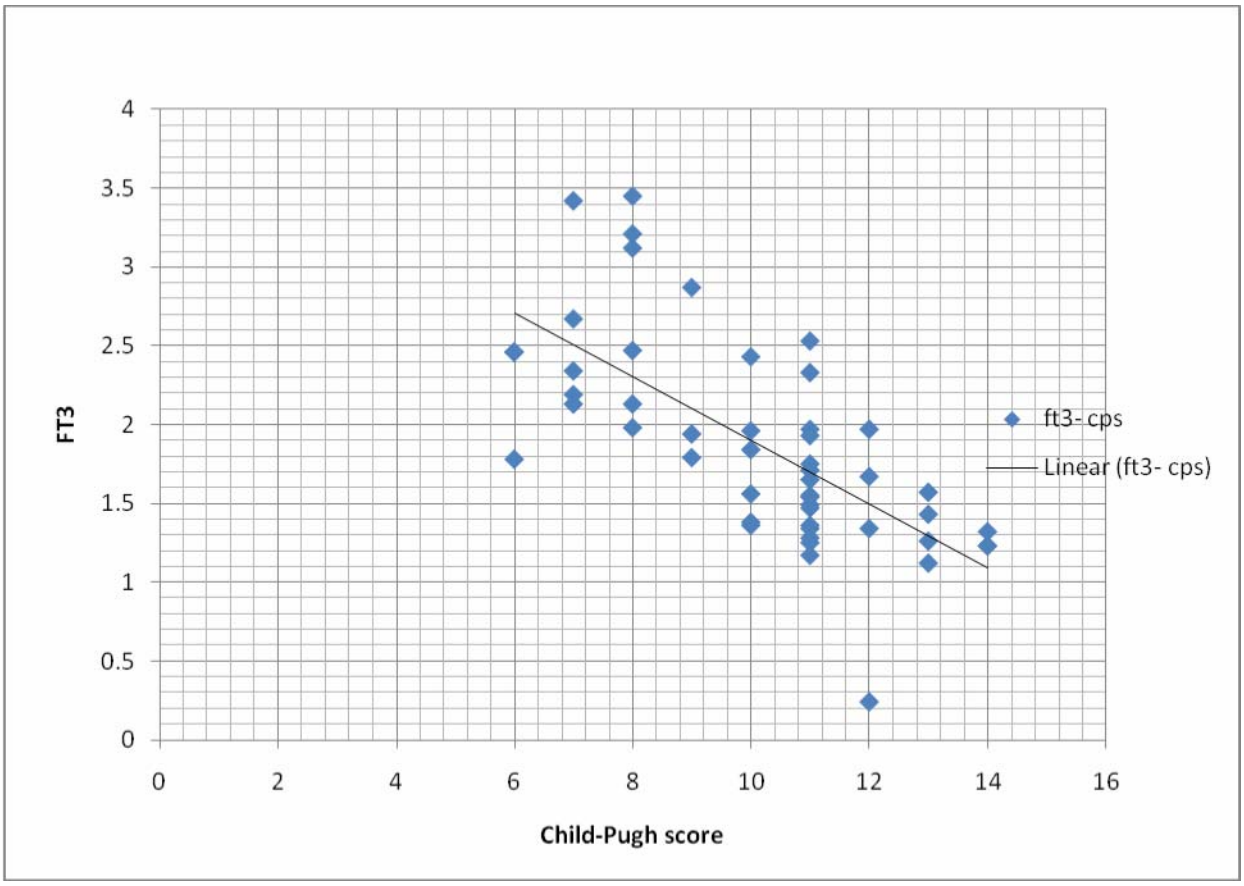


Figure 9 FT3-Child-Pugh score

The coefficient of correlation between free T3 and Child-Pugh score – -0.599
Correlation significant at 0.01 level.

Correlation between the thyroid function and liver function in ALD

The correlation between various thyroid function variables and liver function variables was calculated using Pierson's coefficient of correlation method. The results are shown in the table below.

There was no significant relation between the thyroid function values and the level of liver enzymes (AST, ALT). Among the thyroid function tests FT3 showed significant negative correlation with prothrombin time while the p value for the correlation with other variables did not reach level of significance, probably due to the small number of patients. TSH did not show significant correlation with any of the liver function indices. Total t4 showed a significant positive correlation with total bilirubin and a significant negative correlation with serum albumin levels. Total T3 showed significant negative correlation with AST levels. The level of correlation between other thyroid variables and various liver function values did not reach significant level.

	T B	D B	AST	ALT	ALB	P T
TSH	-0.192	-0.274	+0.444	+0.357	+0.028	-0.180
TT4	+0.857[a]	+0.890	+0.466	+0.433	-0.862[a]	+0.355
FT4	+0.408	+0.438	-0.214	-0.108	-0.222	+0.171
TT3	-0.587	-0.588	-0.644[b]	-0.559	+0.444	-0.485
FT3	-0.605	-0.611	-0.129	-0.057	+0.282	-0.730[b]

[a] correlation significant at the 0.01 level (2 tailed)
[b] correlation significant at the 0.05 level (2 tailed)

Plot between total T4 and serum albumin levels

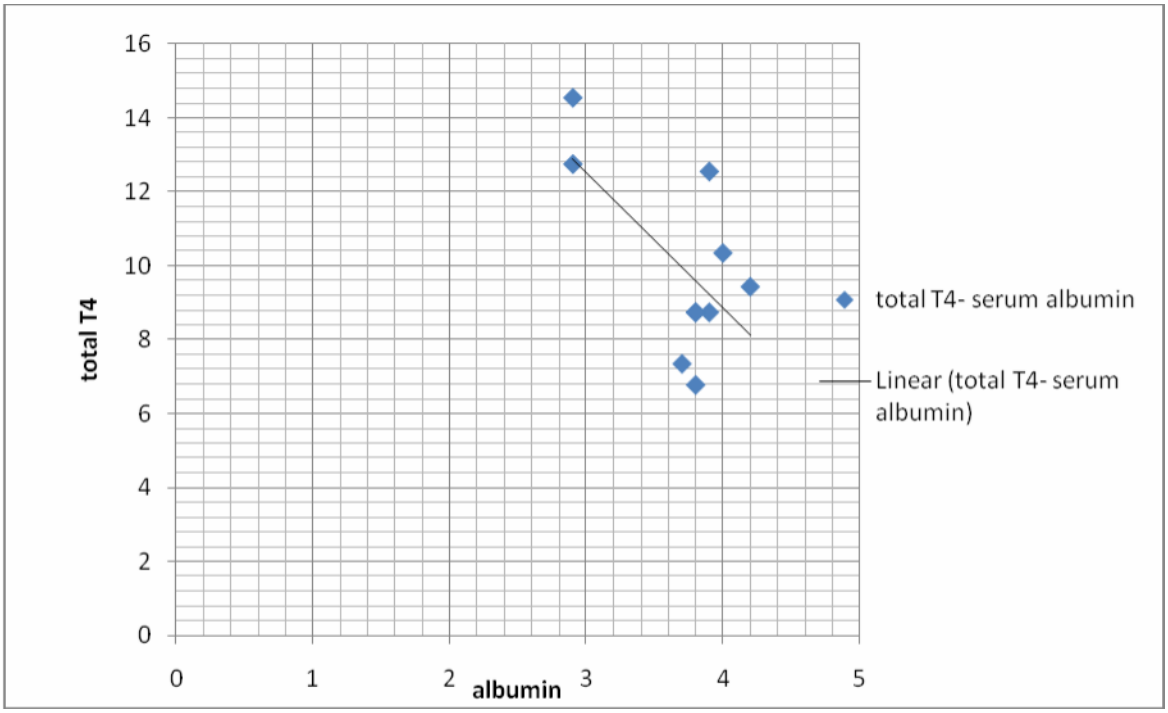


Figure 10 total t4- serum albumin

The coefficient of correlation between total T4 and serum albumin – 0.857
Correlation significant at 0.01 level

Plot between total T4 and total bilirubin levels

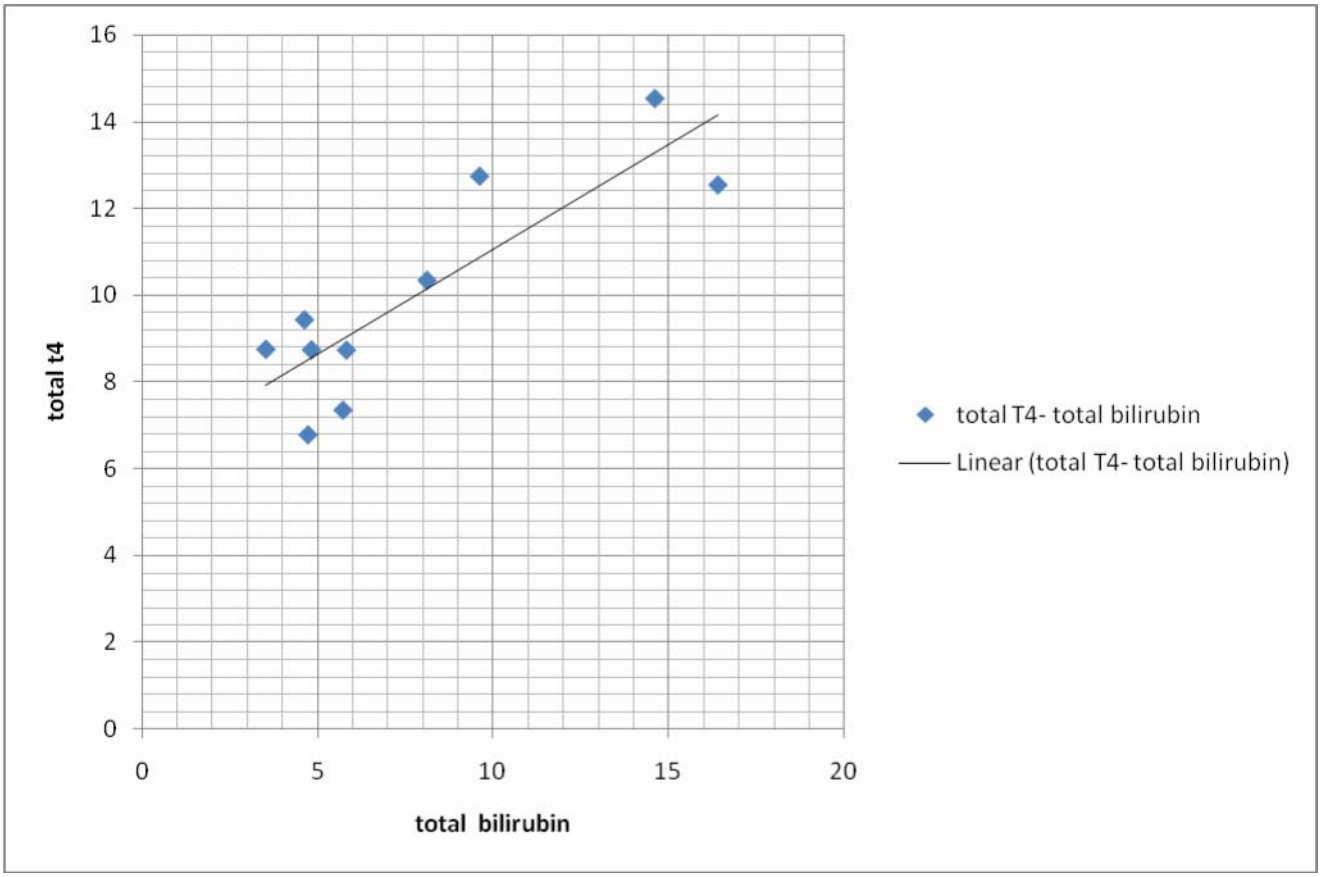


Figure 11 total T4- total bilirubin

The coefficient of correlation between total T4 and total bilirubin - +0.862
Correlation significant at 0.01 level

Plot between free T3 and prothrombin

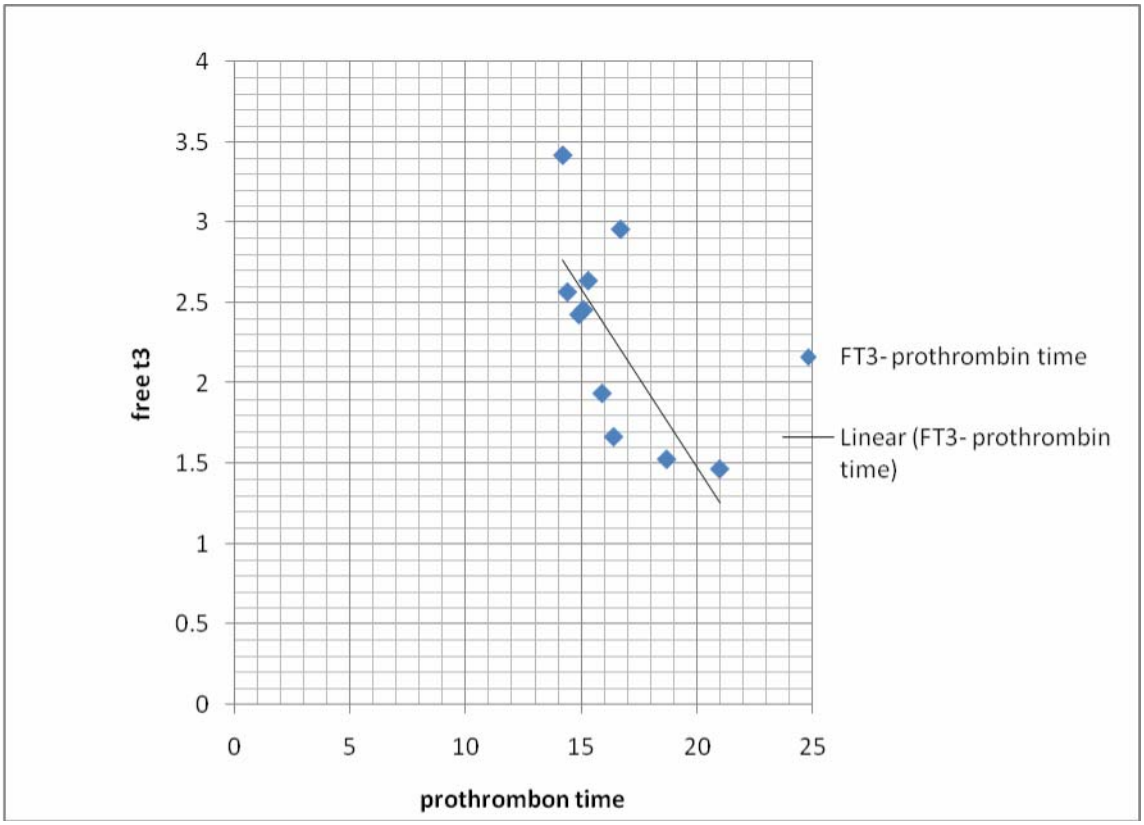


Figure 12 FT3- prothrombin time

The coefficient of correlation between total T4 and total bilirubin - -0.730
Correlation significant at 0.05 level.

Plot between total T3 and AST

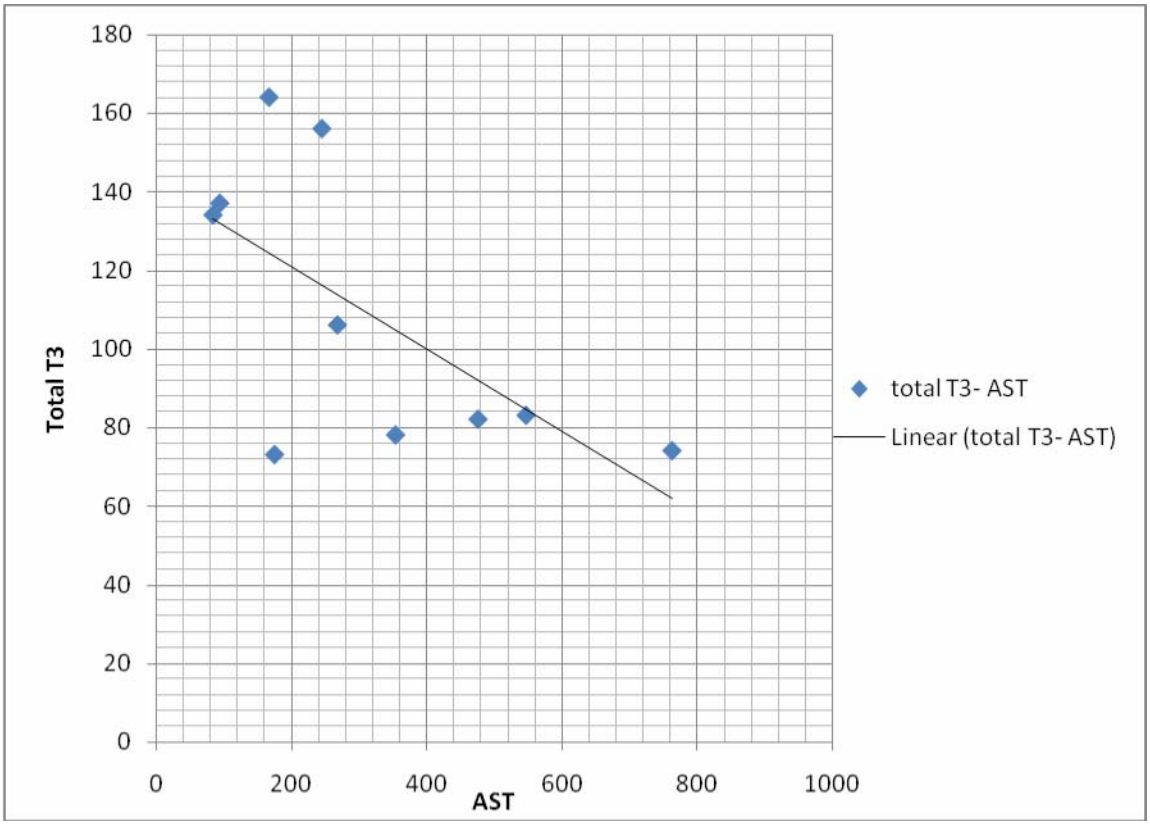


Figure 13 total T3- AST

The coefficient of correlation between total T3 and AST - -0.644
Correlation significant at 0.05 level.

Analysis of the difference between the various correlations

The significance of the difference between the various values of correlation was assessed by Z- transformation test. There was no significant difference between the statistically significant correlation values. The data obtained in the analysis is given in the following table.

CLD group								
	type	n	r	z	1/n-3	se(z1-z2)		**P-value**
PT	free_3	50	-0.726	-0.92022	0.021277			
	tot_t3	50	-0.626	-0.73481	0.021277			
				-0.18541	0.042553	0.206284	-0.89879	**0.369**
CP	free_3	50	-0.682	-0.83284	0.021277			
	tot_t3	50	-0.535	-0.59712	0.021277			
				-0.23572	0.042553	0.206284	-1.14269	**0.253**
ALD Group								
PT	free_3	10	-0.73	-0.92873	0.142857			
	tot_t3	10	-0.485	-0.5295	0.142857			
				-0.39923	0.285714	0.534522	-0.74688	**0.455**

Discussion

Baseline characteristics of the data show that the majority of the liver disease population is constituted by males, both in acute and chronic liver

disease groups. Among these two groups, males constituted a higher proportion (82%) in the chronic liver disease group. This probably reflects the high prevalence of alcohol abuse among males. Another reason could be greater exposure of the males to infectious agents due to their outdoor lifestyle.

Among the chronic liver disease patients only one patient had gross hypothyroidism, she also had clinical evidence of thyroid disease. Two other patients showed elevated TSH between 5 and 10 without clinical evidence of hypothyroidism. There were no other gross abnormalities in any of the other patients in chronic liver disease group or acute liver disease group. So it can be inferred that all chronic liver disease patients should be carefully examined for features of hypothyroidism and if it is present laboratory confirmation is warranted. The usefulness of routine screening for thyroid abnormalities in chronic liver disease patients is doubtful as there is uncertainty regarding the benefit of treating patients with subtle thyroid abnormalities. This concern is especially valid since many investigators have suggested that hypothyroidism may be an adaptive change liver cirrhosis patient.

On analysing the thyroid function variables, TSH did not vary significantly between the three groups (p value-0.67). Total T4 was significantly lower in the chronic liver disease group compared to controls and acute liver disease (p value .0001). The total T4 level was significantly elevated in acute liver disease group (p value .0001). This reiterates the fact that total T4 is an acute phase reactant and is elevated in any conditions causing systemic inflammation. Total T4 may emerge as a useful marker to differentiate between acute and chronic liver disease patents as the values go in different directions from normal in these two groups. A potential caveat to this approach would be chronic liver disease patients with significant inflammation.

Total T3 was significantly lower in both the disease groups compared to controls (p value .033) probably due to impaired peripheral conversion in liver disease groups. Free T4 did not vary significantly between the three groups. This was surprising given that earlier studies have demonstrated significant difference between these groups. It has previously been proposed that free T4 could be used as an indicator to differentiate acute and chronic liver disease patients as it is decreased only in chronic liver disease patients.

Free T3 differed significantly between all the three groups with chronic liver disease group having the lowest value. The difference between the acute liver disease group and controls was also significant (p value .0001). So free T3 may be used as a sensitive indicator to differentiate acute and chronic liver disease patients. For this separate normal limit of free T3 has to be established in both acute and chronic liver disease groups by large population studies.

The chronic liver disease group was considerably older than the acute liver disease group. The acute liver disease group was less sick with better prothrombin time (p value-<0.0001). The enzyme levels, both AST and ALT differed significantly between the two groups (p value-<0.0001).among the ultrasound parameters spleen size varied significantly (p value-<0.0001) but there was no significant difference in liver size (p value-0.11). There was no significant difference between the total or direct bilirubin levels between the two groups (p value-0.98). These results were along the expected levels.

On assessing the correlation between thyroid and liver function variables in the chronic liver disease group, TSH showed significant correlation only with total bilirubin (p value of < 0.05). In the acute liver disease group TSH did not show any significant correlation with any of the liver function variables.

In chronic liver disease patients total T4 showed significant negative correlation with total bilirubin, direct bilirubin, prothrombin time and Child-Pugh score (p value of < 0.01). There was significant positive correlation between serum albumin levels and total T4 (p value of < 0.01). This was in contrast to the situation in acute liver disease group where there was significant positive correlation between total T4 levels and total bilirubin and direct bilirubin and significant negative correlation with serum albumin levels. There was no significant correlation between total T4 and other liver variables despite high coefficient of correlation value. This was due to the small number of subjects in the acute liver disease study group (10). It can be concluded that in chronic liver disease total T4 decreases as the severity of the disease worsens but in acute liver diseases total T4 increases as the disease severity worsens. This may be due to the fact that in acute liver disease group it acts as a marker of inflammation while in chronic liver disease group it is decreased probably due to direct suppression of the thyroid function in chronic liver disease group or abnormalities in pituitary thyroid axis.

Free T4 follows the same pattern of relationship with liver function variables as total T4 in chronic liver disease. It showed significant negative correlation with total bilirubin, direct bilirubin, prothrombin time and Child-Pugh score (p value of < 0.01). There was significant positive correlation between serum albumin levels and total T4 (p value of < 0.01). But when it came to acute liver disease it failed to show any statistically significant relationship. Moreover the relationship it showed was in inverse direction to the relationship with total T4 in case of enzymes. This again points to the fact that the elevation of total T4 in acute liver diseases is due to elevated thyroid binding globulin release from liver.

Total T3 showed significant negative correlation with total bilirubin, direct bilirubin, prothrombin time and Child-Pugh score (p value of < 0.01). There was significant positive correlation between serum albumin levels and total T4 (p value of < 0.01). When it came to acute liver diseases it showed significant relationship only with AST which was negative (coefficient of correlation -0.644 with p value 0.05). Though coefficients of correlations with other liver variables were numerically robust, it did not reach levels of statistical significance due to the small number of patients.

Free T3 showed the highest level of correlation with liver variables whenever the relationship was significant. Free T3 showed significant negative correlation with total bilirubin, direct bilirubin, prothrombin time and Child-Pugh score (p value of < 0.01). There was significant positive correlation between serum albumin levels and total T4 (p value of < 0.01). Among the different variables the highest correlation was between prothrombin time (-0.726) and then Child-Pugh score (-0.682). In acute liver disease patients free T3 showed significant negative correlation with prothrombin time (-0.730). This shows that free T3 could be a useful marker of severity and prognosis in chronic liver disease patients as it has consistent and significant relationship with prothrombin time and Child-Pugh score. Free T3 maintains this strong relationship with prothrombin time in acute liver diseases. Since prothrombin time is widely regarded as one of the best prognostic indicator in acute liver diseases free T3 can be used as another marker of severity and prognosis.

Among the thyroid variables free T3 showed the highest correlation with the liver function variables. But this did not turn out to be significant statistically (p value 0.369). Even then by virtue of the higher coefficients of correlations it can be said that free T3 deserves maximum attention as a marker of liver disease severity and prognosis. In acute liver disease patients total T4

showed the highest and most significant correlation. So total T4 may be used as a marker of acute diseases in which it increases in contrast to chronic diseases in which it deceases. Regarding prognosis and severity free T3 showed significant correlation with prothrombin time, total T3 with AST and total T4 with bilirubin. The difference between free T3 and total T3 in their relationship with liver variables were not statistically significant (0.455). So it will be hard to recommend one value among these as a better index, but free T3 probably deserves more attention because of its relationship with prothrombin time. All these variables require validation in prospective studies before they can be considered be useful markers of prognosis. Further more their relationship liver function has to be established in each of the etiologically different liver diseases.

Limitations of the study

There were many limitations to the study. The most important among them is that it was a cross sectional study without follow up of the patients. So the conclusions made regarding the prognosis of the patients are at best inadequate. Another major limitation of the study was the limited number of patients in the acute liver disease group. This was due partly to the pattern of hospital admission and to financial constrains. Assessment of reverse T3, reverse T4 and thyroid binding globulin (TBG) was not carried out as part of this study. Assessment of TBG levels would have made interpretation of T4 levels more meaningful.

Assessment of liver disease was limited by lack of histological diagnosis. Histological diagnosis would have permitted further refinement in interpretation of the results. Another major drawback was the lack of etiological classification of the liver disease patients. Most of these shortcomings were due to financial constrains.

Conclusions

Conclusions

1) Males constitute the majority of liver disease patients in govt general hospital and this is more prominent in the chronic liver disease group. The chronic liver disease patients are sicker and have more complications than acute liver disease patients.

2) Gross thyroid abnormalities are uncommon in liver disease patients if clinical features of thyroid dysfunction are absent. In every patient with liver disease signs of thyroid dysfunction should be looked for. Patients with features of thyroid dysfunction should promptly undergo laboratory evaluation. There is not enough evidence to suggest routine screening for thyroid dysfunction in liver disease patients in the absence of symptoms.

3) Different thyroid function parameters differ significantly between chronic liver disease patients, acute liver disease patients and controls. This can be utilized in differentiating acute liver disease patients from chronic patients. For this total T4 seems to be the most promising followed by free T3 and total T3.

4) Thyroid indices may be useful in assessing the prognosis of patients with liver disease since they show significant correlation with established markers of liver disease prognosis. In this regard free T3 seems to be the most promising in chronic liver disease patients. In acute liver disease there is nothing much to choose between total T4 and free T3.

5) Further prospective studies are required for validating and assessing the role of thyroid function tests as markers of prognosis in liver disease. Studies need to be carried out in each of the etiologically different liver diseases for better defining the role of thyroid hormones in each situation.

Thyroid abnormalities in liver disease

Performa

Name
Age
Sex
Date
History

- Thyroid illness-duration
- Treatment taken
- Duration of liver disease
- Complications
- UGI bleed
- Hepatic encephalopathy
- Ascites
- Bleeding tendencies
- Previous episodes of jaundice
- Bowel habits
- Features of hypothyroidism
- Features of hyperthyroidism
- Other clinical diagnosis

Clinical examination

- Icterus
- Edema
- Goiter
- Bleeding manifestations
- Ascites
- Liver
- Flapping tremor
- reflexes

Investigations

- Total T4
- Total T3
- Free T4
- Free T3
- TSH

LFT

- Total bilirubin
- Direct bilirubin
- AST
- ALT
- Alkaline phosphatase
- Total protein
- Albumin
- PT -INR

Ultrasound abdomen

- Liver size
- Texture
- Nodules
- Ascites
- Spleen size
- Portal hypertension
- Gall stone

Child-Pugh score

Diagnosis

- ❖ Liver disease
- ❖ Thyroid status

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L.Dis.No. 14597/MES/ EthicsDean/MMC/2009 Dated .09.2009

Title of the work : "Spectrum of thyroid abnormalities in liver disease"

Principal Investigator : Dr. C. Anwar varghese, p.g - M.D General medicine

Department : Madras medical college - ch-3

The request for an approval from the Institutional Ethical Committee(IEC) was considered on the IEC meeting held on 23rd September 2009 at 2.00P.M. in Madras Medical College, Deans, Chamber, Chennai-3/pharmacology seminar hall/madras medical college ch-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearnance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s).
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC MMC CHENNAI

21/10/09

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Data chart

serial no C LD	age	sex	duration	ug bleed	encephlthy grade	ascites	feat hypo	hyper	icterus	edema	tot t4	free t4	free t3	tot t3
1	60	m	2	1	2	2	0	0	1	1	3.07	0.84	1.26	72
2	61	m	1	0	0	1	0	0	1	1	6.11	1.03	1.34	99
3	45	m	12	1	1	1	0	0	1	1	6.87	1.34	1.36	122
4	44	m	12		0	0	1	0	0	0	6.51	0.95	1.78	88
5	46	m	24	1	1	2	0	0	1	1	4.4	0.97	1.55	72
6	56	f	24	0	0	1	0	0	1	1	4.6	1.08	1.65	97
7	46	m	1	0	2	0	0	0	1	0	6.75	1.43	1.79	124
8	57	f	30	0	0	1	0	0	1	1	7.4	1.22	2.33	175
9	25	m	1	0	0	0	0	0	1	0	11.8	1.26	2.34	123
10	46	m	24	1	0	2	0	0	1	1	4.32	1.02	1.34	67
11	64	m	18	0	0	0	0	0	1	0	6.88	1.67	1.38	98
12	58	m	36	1	2	2	0	0	1	1	4.78	0.79	1.23	86
13	34	m	24	0	0	0	0	0	1	0	6.78	1.54	2.67	145
14	45	m	15	1	0	1	0	0	1	1	5.43	1.21	1.71	76
15	54	m	48	1	1	1	1	0	1	1	2.33	0.32	0.24	23
16	38	f	24	1	0	1	0	0	1	0	6.79	1.45	1.97	103
17	68	m	36	0	0	1	0	0	1	1	4.78	1.02	1.47	57
18	58	m	4	1	0	1	0	0	0	0	8.76	1.56	2.46	135
19	42	m	6	0	0	0	0	0	1	0	6.78	0.94	3.12	104
20	39	m	12	1	0	0	0	0	1	1	4.85	0.83	1.17	64
21	63	f	9	1	0	1	0	0	1	0	6.92	0.94	1.25	38
22	38	m	4	1	0	0	0	0	1	0	8.42	1.24	1.98	102
23	56	m	6	1	1	1	0	0	1	1	5.71	0.87	1.43	59
24	44	m	12	0	0	1	0	0	1	1	6.83	1.42	1.94	84
25	35	m	8	0	0	1	0	0	1	1	7.43	0.97	1.96	134
26	49	m	6	1	2	2	0	0	1	1	4.75	0.85	1.23	45
27	72	f	24	0	0	1	0	0	1	1	6.74	1.23	1.84	85
28	59	m	6	0	0	1	0	0	1	1	7.85	2.53	2.87	186
29	57	m	14	1	0	1	0	0	1	1	5.42	0.94	1.36	83
30	43	m	6	1	0	1	0	0	0	1	5.42	0.84	2.19	89
31	76	m	3	0	0	1	0	0	1	1	8.74	1.56	1.56	169
32	37	m	36	1	0	1	0	0	1	1	6.7	0.83	1.49	68
32	68	f	48	1	0	0	0	0	0	0	8.91	1.34	2.46	146
34	29	f	12	1	0	1	0	0	1	0	7.92	1.26	2.53	153
35	58	m	12	0	0	1	0	0	1	1	4.78	0.86	1.75	78
36	21	m	12	0	0	1	0	0	0	0	9.87	1.53	3.42	168
37	46	m	3	1	1	2	0	0	1	1	4.32	0.77	1.32	57
38	53	m	4	0	0	1	0	0	1	0	6.78	1.23	2.43	79
39	39	m	3	0	1	1	0	0	1	1	5.78	1.02	1.12	123
40	64	m	12	0	0	0	0	0	1	0	9.67	1.78	3.45	176
41	40	m	6	1	0	0	0	0	0	0	7.41	1.04	2.13	124
42	75	m	1	0	1	0	0	0	0	1	5.42	0.87	1.67	72
43	34	m	3	0	0	0	0	0	1	0	6.34	1.45	2.13	123
44	37	f	12	0	0	1	0	0	1	1	6.73	0.83	1.54	73
45	46	m	6	1	1	1	0	0	1	1	5.87	0.83	1.57	98
46	47	m	3	0	0	0	0	0	1	0	7.89	1.46	3.21	143
47	54	m	6	1	0	0	0	0	0	0	8.34	1.54	2.47	124
48	54	m	48	1	1	1	0	0	1	1	7.32	1.65	1.97	103
49	38	m	12	1	0	1	0	0	1	0	8.23	0.99	1.93	124
50	32	f	24	0	0	1	0	0	1	1	6.39	1.02	1.28	96

serial no CLD	t b	d b	ast	alt	alk po4	t p	alb	pt	C P S	liver size	texture	ascites	spleen	gall stones	thy status
1	3.5	2.3	67	45	93	7	4.5	23.1	13	9.3	1	1	11	0	1
2	15.8	10.4	51	55	80	5.6	2.9	25.9	11	9.8	1	1	10.4	0	1
3	3.8	2	71	86	123	6.4	3.5	26.9	10	11.1	1	1	8.6	0	1
4	0.9	0.3	20	24	116	7.6	3.6	19.6	6	14.4	1	0	13.8	0	1
5	7.8	4.5	98	120	198	7.5	3.2	26.7	11	10.4	1	1	12.4	0	1
6	6.8	4.1	124	213	214	7.3	3.3	24.4	11	10.6	1	1	13.4	0	1
7	7.9	4.3	342	543	198	6.9	3.6	17.4	9	13.2	1	0	7.8	0	1
8	8.9	3.9	124	231	204	7.1	3.1	21.3	11	10.2	1	1	11.3	0	1
9	3.5	2.3	445	564	235	7.3	3.9	17.4	7	13.4	1	0	6.7	0	1
10	4.7	2.6	76	86	176	6.4	3.2	25.6	12	9.8	1	0	10.2	1	2
11	12.7	7.6	112	142	189	6.7	3.1	29.8	10	11.2	1	0	8.7	0	1
12	24.3	14.5	76	86	193	6.4	2.8	38.2	14	8.9	1	1	13.4	0	2
13	3.4	1.6	56	76	87	7.3	4	14.3	7	10.3	1	0	7.5	0	1
14	9.2	6.4	98	134	192	6.4	3	27.8	11	11.2	1	1	13.2	0	1
15	14.5	5.7	94	104	187	6.8	3.1	34.5	12	12.3	1	1	12.5	1	3
16	6.8	3.2	234	346	243	7	3.4	23.1	11	11.3	1	1	8.9	0	1
17	12.8	7.8	94	98	178	6.4	2.8	34.5	11	10.2	1	1	12.4	1	1
18	1.2	0.7	68	84	142	7.2	3.6	16.2	6	9.7	1	1	14.2	0	1
19	2.7	1.4	58	73	188	6.8	3.6	23.1	8	14	1	0	8.5	0	1
20	15.8	9.2	143	165	245	6.4	2.8	36.1	11	9.3	1	0	14.5	0	1
21	21.2	8.9	92	143	241	6.7	2.9	32.1	11	11.4	1	1	13.4	0	1
22	4.6	2.4	86	78	286	7.3	4.1	17.3	8	12.4	1	0	12.4	0	1
23	14.5	9.3	94	128	194	6.8	2.6	28.5	13	11.3	1	1	17.8	0	1
24	6.2	3.5	223	246	256	7.4	3.9	16.4	9	12.4	1	1	13.2	0	1
25	3.55	1.3	245	78	423	7.3	4	23.4	10	12.7	1	1	10	0	1
26	16.4	10.3	145	85	204	7.1	2.8	28.6	14	10.2	1	1	12.4	0	1
27	7.8	4.5	254	346	178	7.2	3.2	19.8	10	12.2	1	1	12.4	0	1
28	3.8	2.1	78	46	204	6.9	3.6	18.9	9	11.3	1	1	9.7	0	1
29	9.3	7.4	168	67	196	7.2	2.9	32.6	11	9.7	1	1	8.7	0	1
30	1.2	0.5	34	27	102	6.7	3.6	16.3	7	11.2	1	1	7	0	1
31	4.6	1.9	87	56	213	6.9	3.6	24.2	10	14.5	1	1	8.5	0	1
32	9.4	5.4	56	74	186	6.4	2.8	36.2	11	13.4	1	1	14.5	0	1
32	1.8	0.8	54	46	201	6.8	3.6	17.5	6	9.7	1	0	15.7	0	1
34	4.6	2.3	88	67	235	6.7	3.1	23.4	11	9.2	1	1	13.2	0	1
35	10.1	6.7	178	132	321	6.4	2.9	26.7	11	11.5	1	1	9.8	0	1
36	1.8	0.9	56	75	198	7.2	3.6	18.5	7	8.7	1	1	12.4	0	1
37	24.3	14.5	134	67	234	6.4	2.7	35.4	14	7.8	1	1	10.1	0	1
38	3.4	1.6	57	46	198	6.8	3.2	19.4	10	10.7	1	1	8.7	0	1
39	7.5	3.7	87	76	234	6.4	2.8	24.3	13	8.8	1	1	9.4	0	1
40	3.9	1.6	246	134	214	7.1	3.7	17.3	8	12	1	0	6.8	0	1
41	2.5	1.1	57	54	253	6.9	3.6	18.4	7	14.5	1	0	13.2	0	1
42	9.3	5.4	87	75	188	6.4	2.8	23.1	12	9.4	1	0	7.6	0	1
43	3.8	2.1	93	75	276	6.9	3.6	18.5	8	14.3	1	0	7.9	0	1
44	8.7	4.6	75	64	167	6.7	3	24.6	11	8.6	1	1	12.3	0	1
45	6.4	4.5	192	84	248	6.5	2.7	26.7	13	8.3	1	1	8.9	0	1
46	7.1	3.7	346	243	154	7.2	3.6	16.4	8	13.2	1	0	7.4	0	1
47	3.1	1.6	49	65	134	7.1	3.8	17.4	8	11	1	0	7.2	0	1
48	4.9	2.1	146	89	172	6.4	2.9	23.1	12	12.2	1	1	13.2	0	1
49	4.9	1.4	58	64	154	6.9	3.5	21.1	11	9.9	1	1	8.6	0	1
50	9.3	5.8	246	342	168	6.4	2.8	32.3	11	15.4	1	1	13.2	0	1

acute liver d.	age	sex	duration	ug bleed	encephlthy	ascites	feat hypo	hyper	icterus	edema	goitre	tot t4	free t4	free t3	tot t3
1	24	m	0.5	0	0	0	0	0	1	0	0	10.34	1.04	1.47	78
2	56	m	0.25	0	0	0	0	0	1	0	0	12.54	1.32	1.67	73
3	35	f	0.25	0	0	0	0	0	1	0	0	8.75	0.94	2.46	83
4	21	m	0.25	0	0	0	0	0	1	0	0	9.43	1.43	3.42	164
5	36	f	0.5	0	0	0	0	0	1	0	0	7.35	1.46	2.96	156
6	43	f	0.33	0	0	0	0	0	1	0	0	14.53	1.79	1.53	82
7	34	m	0.25	0	0	0	0	0	1	0	0	8.74	0.93	2.57	137
8	29	m	0.5	0	1	2	0	0	1	0	0	12.74	1.04	2.64	74
9	18	m	0.33	0	0	0	0	0	1	0	0	6.78	1.32	1.94	106
10	37	m	0.5	0	0	0	0	0	1	0	0	8.73	1.45	2.43	134

acute liver d.	t b	d b	ast	alt	alk po4	t p	alb	pt	liver size	texture	ascites	spleen	gall stones	thyroid status
1	8.1	4.5	354	265	156	7.1	4	21	14.2	2	0	6.8	0	1
2	16.4	10	175	169	193	7.2	3.9	16	12.4	2	0	7.8	0	1
3	3.5	1.6	547	674	234	7	3.8	15	11.2	2	0	8.4	0	1
4	4.6	2.6	167	231	178	7.3	4.2	14	12.5	2	0	7.4	0	1
5	5.7	2.3	245	268	159	6.9	3.7	17	13.2	2	0	7.3	0	1
6	14.6	10	476	563	246	6.8	2.9	19	12.4	2	0	7.4	0	1
7	4.8	2.1	94	84	231	7.2	3.9	14	13.2	2	0	7.3	0	1
8	9.6	5.3	763	682	254	7	2.9	15	9.2	2	0	9.3	0	1
9	4.7	1.9	268	258	183	6.9	3.8	16	12.3	2	0	7.4	0	1
10	5.8	2.6	84	62	246	6.4	3.8	15	11.2	2	0	6.9	0	1

controls	age	sex	tot t4 4.5-12.0	free t4 .70-1.80	free t3 1.7-4.2	tot t3 60-200	tsh .35-5.5
1	36	m	10.64	1.74	3.54	163	3.45
2	24	m	7.45	1.38	2.61	123	3.82
3	56	m	8.76	1.52	2.91	142	2.63
4	29	m	6.79	1.41	2.74	93	4.04
5	67	f	8.41	0.92	3.17	108	2.87
6	39	m	7.42	1.06	2.37	127	1.98
7	42	f	5.43	0.89	1.93	88	5.02
8	19	m	11.23	1.69	3.92	183	0.51
9	61	m	9.36	1.42	3.16	142	0.71
10	52	m	5.04	0.87	1.87	78	4.57
11	36	f	7.09	1.25	2.67	108	2.36
12	32	f	7.41	1.17	2.93	126	2.93
13	47	m	8.42	1.23	3.45	131	3.07
14	71	m	6.92	1.05	2.83	88	3.75
15	57	f	5.91	1.26	2.46	92	3.54
16	43	m	9.23	1.24	2.36	174	1.26
17	22	m	7.54	1.17	3.42	137	1.86
18	55	m	5.82	0.92	2.93	108	4.13
19	29	f	6.82	0.89	2.16	112	1.47
20	42	m	6.73	1.09	3.02	126	1.09
21	39	m	7.83	1.26	2.79	154	1.04
22	30	f	6.92	1.65	3.04	127	2.32
23	47	m	5.63	0.92	1.82	72	7.32
24	62	f	8.19	1.63	3.49	137	2.08
25	60	f	7.34	0.87	2.15	99	4.32
26	44	m	6.03	1.16	3.95	124	3.05
27	34	m	7.89	1.62	3.85	156	0.73
28	28	m	5.83	1.23	2.93	102	4.11
29	42	m	8.37	1.49	3.02	132	1.18
30	51	f	7.63	1.89	3.06	173	1.11