

Prevalence of hypothyroidism in Liver Cirrhosis among Indian patients

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Abstract: *The liver has an important role in thyroid hormone metabolism its manufactures of protein that bind thyroid hormone such as thyroxin binding globulin (TBG), prealbumin and albumin, it's also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation of biliary excretion, oxidative deamination and extra thyroidal deiodination of thyroxin (T4) to triiodothyronine (T3) and reverse T3. The goal of the study is to assess the relationship and interconnection between hypothyroidism and chronic liver disease specially cirrhosis patients. This is a retrospective, cohort study design, in which the medical records of cirrhosis patient who had been enrolled in The Asian institute of gastroenterology hospital in Hyderabad from January 2013 to December 2013. All patients selected for this study were diagnosed as type of cirrhosis in the line with the criteria set up by WHO. The study is comparative study containing two groups (1) cases and (2) controls. The total number of case groups is 310 cirrhotic patients aged 20-80 years. Both genders included .Male are 211 and Female are 99. The control group comprised randomly selected non cirrhosis subjects. The total number of control subjects is 250 aged 20-80 years. Male are 145 and female are 105. The result showed that there was a significantly increased between cirrhotic patients and non-cirrhotic subjects for TSH and slightly decreased T3 and T4 where the p value is 0.039, 0.014 and 0.245 respectively. The mean of TSH levels of cirrhotic patients is higher than the mean of non-cirrhotic subjects and show significant difference. And also there is significant difference for T4 between two groups, but T3 seems no significant difference between two groups.*

Key words: Prevalence, hypothyroidism, liver cirrhosis.

1. Introduction

Cirrhosis and chronic liver failure are leading causes of morbidity and mortality in the whole the world –with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis or nonalcoholic fatty liver disease. Cirrhosis often is an indolent disease. Most patients remain a symptomatic unit the occurrence of decomposition, characterized by ascites, Spontaneous bacterial peritonitis, hepatic encephalopathy or variceal bleeding from portal hypertension.

The thyroid gland plays a pivotal role in tissue metabolism and development and in doing so effects various organ systems. The liver has an important role in thyroid hormone metabolism because its manufacture of protein that bind thyroid hormone such as thyroxine binding globulin (TBG), pre-albumin and albumin, it's also the major site of thyroid hormone peripheral metabolism and is involved in its conjugated biliary excretion ,oxidation deamination and extrathyroidaldeiodination of thyroxine (T4) to triiodothyronine (T3) and reverse T3 .

Thyroid hormone control the metabolism – the process by which oxygen and calories are converted to energy for use by the cells and organs .when the thyroid works normally it produces and secretes the amount of T4 and T3 necessary to keep various body function moving at their proper pace [1]. The degradation of thyroid hormones their excretion initiated by the liver and only harm happen to the liver will show it's eventuate effect on the thyroid hormone metabolism.

1.2. OBJECTIVES:

The general objective of this study is to assess the relationship and interconnection between hypothyroidism and chronic liver disease specially cirrhosis.

1. To determine thyroid hormone levels in the liver cirrhosis patients.
2. To study possible relation between hypothyroidism and liver cirrhosis.
3. To find out how Thyroid and liver interrelated in health and in disorder status.

2. Materials and Methods:

2.1 STUDY DESIGN:

This is a retrospective, cohort study design, in which the medical records of cirrhosis patient who had been enrolled in The Asian institute of gastroenterology hospital in Hyderabad from January 2013 to 30, December 2013. All patients selected for this study were diagnosed as type of cirrhosis in the line with the criteria set up by WHO. The study is comparative study containing two groups (I) cases and (II) controls.

GROUP I; 250 apparently healthy subjects aged 20-80 years. Males (n=145) and Females (n=105).

GROUP II; 310 cirrhotic patients aged 20-80 years. Males 211 and Females 99 .

The Inclusion Criteria for this study were males and females between the ages of 20-80 years old diagnosed as cirrhosis patients based on their medical record and without any other chronic condition.

2.2. EXCLUSION CRITERIA:

Patients with history of organ failure, Cancer, radio or chemotherapy and individuals with active infection such as bone and muscle disease, cardiac, pancreatic, diabetes and patients who had not meet up the inclusion criteria are excluded from this study.

2.3. BLOOD SAMPLING:

The data for this research was collected by accessing a data management System utilized by the Asian institute of gastroenterology, The HMS database. The sample was collected by phlebotomist at the sample collection point and analysis was done at the Biochemistry laboratory of the hospital. The research criteria were used to include patients with cirrhosis that had their levels of thyroid status determined, LFT levels and TFT determined within the study period. Liver Function test (LFT) was done by fully automated analyser of RandoxImola. the normal range of total bilirubin is up to 17µmol/l or up to 1.2 mg/dl, Direct bilirubin is up to 4.3µmol/l or 0.2 mg/dl, Indirect bilirubin is calculated by subtracting total bilirubin and direct bilirubin(TB - DB = INB),and is up to 0.6mg/dl . The normal range of the serum ALT is up to 40 U/L and AST level up to 40 U/L, ALP level from 30 to 120 U/L in both genders. The normal range of total protein in the serum is between (8-6gm/dl), and albumin level is (3.5-5.2 gm/dl), whereas globulin level was calculated by subtract between total protein and albumin (TP - ALB) and its normal range is between 2.3 to 3.5 gm/dl.

Thyroid Function tests (TFT) was done by Electrochemilumnesence by Roche Diagnostics ltd. The normal range of thyroid profile as a following: T3 is (0.8-2.0 ng/ml), T4 is (4.6-12.0 ug/ml), and TSH is (0.3- 4.2 mIU /ml). The bio data of the patient, sex, age and month, sample was analysed and result issued.

2.4. STATISTICAL ANALYSIS: All the statistical analysis was performed using SPSS software (21st version) and Microsoft excel 2007. The significant differences between two groups were used student (t) test and Chi-square test was used for categorical variables. Data were presented as mean ± S.D. A statistical value <0.05 was considered as significant. The results were expressed in the form of tables, etc.

2.5. ETHICAL ASPECTS: The protocol for the study was approved by the Ethical and Research Committee of the Hospital. Data were collected only after patient consent

3. Results:

CHARACTERISTICS OF THE STUDY POPULATION:

The present study is a cross sectional study, that included 310 cases and 250 controls. Overall the cases and controls were in the age range of 20-80 and mean age of case groups were 44 ±13.7 years and that of the control group were 45±15.7 years. Out of 310 patients were 211 (68.7%) males and females were 99 (31.9%). And the males included control groups were 145 (58%) and females were 105 (42%).

Table 1: General information of cirrhotic and non cirrhotic group

	Cases (n=310)	Controls (n=250)	P-Value
Age	44±13.7	45±15.7	0.231
Male (n %)	211 (68.7%)	145 (58%)	0.0177
Female (n %)	99 (31.9%)	105 (42%)	0.0177

Serum TB, DB and INB status in the study population:

Table (2) indicated that total bilirubin of the case groups of study population had elevated (>2mg/dl). And mean range is 2.89±1.65, whereas control groups were normal and mean range is 0.73±0.512, that given P value (significant). The direct bilirubin in case population also elevated (>1mg/dl), 1.39±1.43 compared to control subjects 0.71±0.046. The indirect bilirubin had arise (> 1mg/dl) compared control subjects. There is significant also.

Table 2: Serum bilirubin (Total, direct and indirect) status

	Cases (n=310)	Controls (n=250)	P-Value
TB (mg/dL)	2.89±1.65	0.73±0.512	0.0001
DB (mg/dl)	1.39±1.43	0.17±0.046	0.018
INB (mg/dl)	1.39±1.43	0.41±0.14	0.0001

Serum enzymes: ALT, AST and ALP status in the study population

The table 3 indicated that serum ALT in patients of the population had elevated its level and mean range is 109±103. Serum AST also elevated and its mean range 84.9± 86.4 and serum ALP had elevated more than normal range, the mean is 159±139, compared to the control subjects that all enzymes are normal range .and there is significant.

Table 3: Serum enzymes: ALT, AST and ALP status in the study population

	Cases (n=310)	Controls (n=250)	P-Value
ALT (U/L)	109±103.38	25.6±10.01	0.0001
AST (U/L)	84.9±86.42	26.7±11.18	0.0001
ALP (U/L)	159.6±139	81.1±23.45	0.0001

Serum Total protein, Albumin and Globulin in the study population

The serum total protein, albumin and globulin in the study population are shown in table no. There was no significant difference in the mean range levels of total protein 7.57±5.58, albumin 4.12±2.53. But the mean range level of serum globulin

is 3.23 ± 0.48 and significantly increased in cirrhosis patients compared non cirrhosis subjects.

Table 4 shown that serum total protein were normal, and serum albumin also normal ,but serum globulin there was found little highly significant, compared the control subjects.

Table 4: Serum Total protein, Albumin and Globulin in the study population

	Cases (n=310)	Controls (n=250)	P-Value
TP (gm/dl)	7.57±5.58	8.04±7.2	0.378
ALB (gm/dl)	4.12±2.53	4.2±0.39	0.61
GLB (gm/dl)	3.23±0.48	3.01±0.37	0.0001

p>0.05: not significant, p<0.05: significant

Thyroid profile in the study population

The mean of thyroid hormone in the cirrhosis patients as well as control subjects are shown in table no 5. The mean level of serum T3 is 1.06 ± 0.29 and was not found any significant compared control subject. The mean level of T4 was 8.47 ± 2.33 and was found significantly lower than that control one. And the mean level of TSH was 5.12 ± 11.67 that indicated significantly higher than control subjects.

Table 5: Serum thyroid profile of cases and control.

	Cases (n=310)	Controls (n=250)	P-Value
T3(ng/ml)	0.62±0.26	1.09±0.23	0.024
T4(ug/ml)	8.47±2.33	8.91±1.83	0.014
TSH(mIU/ml)	5.12±11.67	3.63±4.57	0.039

p>0.05: not significant, p<0.05: significant

4. Discussion:

The prevalence of hypothyroidism in chronic liver disease especially liver cirrhotic patients was found at this present study. The result of this study indicated that the case groups were significantly increased the total, direct, and indirect bilirubin levels compared to control groups. And also found serum enzymes have been elevated more than their normal reference levels compared control subjects. In the study it was found the thyroid hormone profile in patients with cirrhosis are slightly low T3, normal T4 and elevated TSH as shown table 5. In this study revealed that decrease total T3 probably reflects a decrease in deiodinase1 activity in the liver of cirrhotic patients [2]-[4]. 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 proteins stores. Indeed, a recent study in cirrhotic patients showed that onset of hypothyroidism from intrinsic thyroid disease of various etiologies during cirrhosis resulting in a biochemical improvement in liver function (e.g. coagulation profile) as compared to controls [5]. Hypothyroidism has also associated with lesser degree of decomposition in cirrhosis [6]. This thyroid dysfunction accompanied with simultaneous liver disorder due to excessive overload of iron storage inside the liver tissues itself. The iron storage within the body either of primary as in genetic diseases or through excessive iron therapy, are behind many hormonal

dysfunction including thyroid leaving the affected person into hypothyroidism due to untreated iron storage within the thyroid gland.

All these scenarios are happened at the time in which the body itself engaged with anaemia and hypoxia as result of hypothyroidism due to iron deposition within thyroid leaving thyroid with all the consequences of the hypothyroidism not for the liver but also for entire body as whole [7]. The liver has important role in thyroid hormone metabolism because it is the manufacturer of protein that bind thyroid hormone, such as thyroid-binding globulin (TBG), pre-albumin and albumin. It also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation biliary excretion, oxidative deamination and the extra thyroidal deiodination of thyroxin (T4) to triiodothyronine (T3) and to reverse T3 [8]. On the other hand the level of thyroid hormone is also important to normal hepatic function and bilirubin metabolism [9], [10]. Conceivably, the disorders of these two organs would interact or influence each other. As liver abnormalities worsen the T3 production from T4 is also reduced. It is believed this reduction of T3 which mainly correspond to even lower basic metabolism rate, economically can be useful due to preventing extra energy waste and keep it for the onset of liver disease or any other related syndrome which consume further energy. Free T3 concentration corresponding with the state of liver disease and it seems the serum T3 concentration directly related to liver abnormalities progress. Other studies indicated that during various phase of liver disease the serum T4 concentration altered accordingly and related also to the disease progression. T3 can be used as good laboratory index in the evaluating the status of liver disease, also the serum T3 concentration and those liver factors, such as bilirubin are now can be regarded as valuable index in the following the trends in thyroid-liver path physiology. It is vital to measure the free and T4 thyroid Stimulating Hormone (TSH) and any other laboratory test which may be in any help to avoid misdiagnosis of a hypothyroid patients suffering from liver diseases. It can be stated that in the initial state of acute liver diseases the total T4 production increases and subsequently as liver function is worsen it will reduced due the higher and low concentration of TBG, respectively . It was found that liver is one of main site of deiodinase enzyme activity for T3 production from T4. Liver also plays an important role in the production of potent hormone T3 but other biological pathways for T4, T3 metabolism and their transportation in the liver and blood circulation is the sole responsibility of liver function. It seems in addition to a healthy thyroid, liver can play an important role in the basic metabolic rate, growth and development of the human body in general due to its ability to transfer the thyroid hormone within circulation and in target tissue intracellular due to thyroid hormone transporting system which is mediated through. Thyroxin Binding Globulin (TBG), pre albumin and albumin, all are synthesized within liver.

Hypothyroidism may have features that mimic liver disease (pseudo-liver disease); example include myalgias, fatigue and muscle cramps in the presence of an elevated aspartate aminotransferase from a myopathy [11], coma associated with hyperammonaemia in Myxoedema coma [12] and Myxoedema ascites [13]. There is also evidence that hypothyroidism may directly affect the liver structure or function. The liver is the major sites of cholesterol and triglyceride metabolism, and the thyroid hormones play an integral part in hepatic lipid homeostasis. The thyroid hormones increase the expression of

LDL receptors on the hepatocytes [14] and increase the activity of lipid lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels [15]. Thyroid hormones also increase the expression of Apo lipoprotein A1, a major component of high density lipoprotein [16]. Clearly, the above effects of the thyroid hormones could be beneficial in the reducing the onset of the atherosclerosis if they were elicited without the deleterious effects, particularly cardiac effects such as arterial arrhythmias [17], [18].

5. Conclusion:

In this present study was found that a complex relationship exists between the thyroid gland and liver in both health and disease. The present study revealed that cirrhotic patients were more prevalence thyroid dysfunction specially hypothyroidism because of many reasons. It was found that liver is one of the main sites of deiodinase enzyme activity for T3 production from T4. And other biological pathways for T4, T3 metabolism and their transportation in the liver and the blood circulation that is sole responsibility of the liver function. Other reason is liver can play an important role for transport thyroid hormones within circulation and in target tissue intracellular due to thyroid transport system which mediated through Thyroxine – Binding Globulin (TBG), prealbumin and albumin ,all are synthesized within liver.

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