ORIGINAL ARTICLE

Effect of Liver Cirrhosis on Thyroid Hormone Levels in Patients Presenting in a Tertiary Care Hospital

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ABSTRACT

Aim: To assess the mean thyroid hormone levels in patients presenting with liver cirrhosis in local population.
Place and duration of study: Research was conducted at Department of Medicine, Shaikh Zayed Hospital, Lahore, from 6 months, done between 21-08-2016 to 20-02-2017.
Methodology: It was a cross-sectional study. This study involved 214 patients of both genders aged between 20-70 years diagnosed to have liver cirrhosis. Thyroid function tests were done in these patients.
Results: The age of the patients ranged from 35 years to 70 years with a mean of 52.93±9.17 years. Majority 119(55.6%) of the patients were aged between 53-70 years. There were 131(61.2%) male and 83(38.8%) female patients in the study group with a male to female ratio of 1.6:1. Duration of disease ranged from 8 months to 4 years with a mean of 25.80±11.93 months. 63(29.4%) patients belonged to Child Class-B while 15 (70.6%) patients belonged to Child Class-C. Serum TSH level ranged from 3.5µU/ml to 5.8µU/ml with a mean of 4.65±0.65µU/ml while the serum FT_3 level ranged from 1.2pg/ml to 2.9pg/ml with a mean 1.87±0.38pg/ml. Serum FT_4 level ranged from 0.6 pg/ml to 2.5pg/ml with a mean of 1.70±0.51pg/ml.
Conclusion: Mean serum levels of FT_3 and FT_4 were lower in patients with liver cirrhosis. Mean serum TSH level was however raised among such patients. It was particularly raised among patients with more severe liver disease while no significant difference was observed across age, gender and duration of disease groups.
Keywords: Liver Cirrhosis, Thyroid Dysfunction, Serum TSH, NAFLD & hypothyroidism

INTRODUCTION

The liver has an important role in metabolism of thyroxin-binding globulin. More than 99% of thyroid hormones are bound to thyroxin-binding globulin, thyroxin-binding pre-albumin and albumin in plasma. Thyroid function is dependent on a normally functioning liver axis. Liver is the main organ in the body responsible for peripheral conversion of tetra-iodothyronine (T_4), tri-iodothyronine (T_3) and Thyroid stimulating hormone (TSH) & conjugation of thyroid binding proteins[1,2,3]. Liver diseases and endocrine disorders have a bidirectional and complex relationship[4].

Abnormalities of thyroid gland in patients with liver cirrhosis range from alterations in thyroid size, morphology, thyroid hormone metabolism and regulation. The volume of the thyroid gland is reported to increase by up to 17% in cirrhosis patients compared with non-cirrhotic controls, as measured using ultrasonography[5]. The prevalence of thyroid hormone abnormalities ranged from 13% to 61%. In patients with cirrhosis, hypothyroidism was more frequently seen, and hyperthyroidism has been also reported[6]. The most consistent thyroid hormone profile in patients with cirrhosis is euthyroid sick syndrome or low T_3 syndrome. There is in an increase in conversion of T_4 to T_3 and an increase in the rT_3: T_3 ratio. T_3:rT_3 ratio binds to the same plasma proteins; the T_3:rT_3 ratio provides a parameter of liver function & correlates negatively with severity of liver disease[7].

As the liver plays a role in regulating metabolism, these endocrine abnormalities also play a role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Thyroid hormone has significancy prognostic effect on liver cirrhosis. TSH and total T4 level in serum may serve as additional indicators of severity of liver disease.[8] In patients with hepatitis B related to acute-on-chronic liver failure, serum TSH levels may be a useful indicator for assessing severity and prognosis[7]. Regarding the association between severity of cirrhosis and thyroid function, low T_4 levels may be related with decreased short- and long-term survival of patients with liver cirrhosis[7]. Low T_3 levels are a good indicator of disease severity in cirrhosis[9].

Hypothyroidism play an essential role in the pathogenesis of NAFLD. Prevalence of NAFLD is negatively correlated with free T_4 levels and decreased free T_4 levels contribute to the risk of NAFLD Hypothyroidism is common in patients with autoimmune liver diseases and its prevalence has recently increased in those with hepatitis C and NAFLD[10]. Hypothyroidism is associated with cholestatic jaundice due to bilirubin and bile excretion. Hypothyroidism should be considered in patients with portal hypertension with refractory ascites, and thyroxine therapy can make them sensitive to diuretics[10]. Conversely, hyperthyroidism Liver injury caused by thyrotoxicosis is hepatic or cholestatic injury due to thyrotoxicosis induced relative hypoxia[11].

MATERIALS AND METHODS

It was a cross-sectional study, conducted at Department of Medicine Shaikh Zayed Hospital, Lahore, conducted over a period of 6 months from 21-08-2016 to 20-02-2017. 214 patients of chronic liver disease, from both genders between 20-70 years were included in the study. Patients with history of I^{131} treatment, thyroid surgery or those who are on treatment for thyroid disorder were excluded. 214 individuals fulfilling selection criteria presenting in Medical

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OPD, SZH Lahore. Informed consent was obtained. Demographic information (including name, age, gender, duration of cirrhosis) was also recorded. Then venous blood sample was obtained under aseptic measures at the time of presentation using 5cc BD syringe. The blood sample was converted in vial containing ringer solution & sent to lab. for assessment of TSH, T_3 and T_4. All the patients were managed according to the hospital protocol. The data were collected on a specially designed patient proforma. All the collected data was entered and analyzed through SPSS v20.0. Numerical variables; age, duration of cirrhosis and thyroid hormone levels (TSH, FT_3, FT_4) were recorded as mean±SD. Categorical variables; Gender and grade of liver cirrhosis were recorded as frequency and percentage. Data has been stratified for age, gender and duration and grade of cirrhosis to address affect modifiers. Post stratification independent sample test has been applied taking P ≤0.05 as significant.

RESULTS

The age of the patients ranged from 35 years to 70 years with a mean of 52.93±9.17 years. Majority 119(55.6%) of the patients were aged between 53-70 years. There were 131 (61.2%) male and 83 (38.8%) female patients in the study group with a male to female ratio of 1.6:1. Duration of disease ranged from 8 months to 4 years with a mean of 25.80±11.93 months. 63(29.4%) patients belonged to Child Class-B while 151(70.6%) patients belonged to Child Class-C as shown in Table 1. Serum TSH level ranged from 3.5µU/ml to 5.8µU/ml with a mean of 4.65±0.65µU/ml while the serum FT_3 level ranged from 1.2pg/ml to 2.9pg/ml with a mean 1.87±0.38 pg/ml. Serum FT_4 level ranged from 0.6 pg/ml to 2.5 pg/ml with a mean of 1.70±0.51pg/ml as shown in Table 2. There was no significant difference in the mean levels of TSH, FT_3 and FT_4 across age, gender and duration of disease groups. However, mean serum TSH was significantly higher in Child Class-C as shown in Tables 3-5.

Table 1 Baseline Characteristics of Study Sample (n=214)

Characteristics	Participants
Age (years)	52.93±9.17
• 35-52 years	95 (44.4%)
• 53-70 years	119 (55.6%)
Gender	
• Male	131 (61.2%)
• Female	83 (38.8%)
Duration of Disease (months)	25.80±11.93
• <2 years	100 (46.7%)
• 2-4 years	114 (53.3%)
Child-Pugh Class	
• Class-B	63 (29.4%)
• Class-C	151 (70.6%)

Table 2 Thyroid Profile of Patients with Liver Cirrhosis

Parameter	Value
TSH (µU/ml)	4.65±0.65
FT_3 (pg/ml)	1.87±0.38
FT_4 (pg/ml)	1.70±0.51

Table 3 Thyroid profile of pts with liver cirrhosis across age groups

Parameter	Age Groups		P value
	35-52 yrs (n=95)	53-70 yrs (n=119)	
TSH(µU/ml)	4.707±0.5296	4.600±0.7381	0.234
FT_3 (pg/ml)	1.867±0.4072	1.870±0.3590	0.964
FT_4 (pg/ml)	1.676±0.6063	1.720±0.4110	0.525

Independent sample t-test, observed difference was statistically insignificant

Table 4 Thyroid profile of pnts with liver cirrhosis across gender groups

Parameter	Gender		P value
	Male (n=131)	Female (n=83)	
TSH (µU/ml)	4.616±0.6848	4.698±0.6045	0.376
FT_3 (pg/ml)	1.873±0.3853	1.861±0.3744	0.825
FT_4 (pg/ml)	1.662±0.5181	1.761±0.4838	0.161

Table 5 Thyroid profile of patients with liver cirrhosis across duration of disease

Parameter	Duration of Disease		P value
	<2 yrs (n=100)	2-4 yrs (n=114)	
TSH (µU/ml)	4.705±0.6288	4.597±0.6750	0.231
FT_3 (pg/ml)	1.904±0.4285	1.838±0.3311	0.204
FT_4 (pg/ml)	1.673±0.5969	1.725±0.4119	0.459

DISCUSSION

Cirrhosis is the common end stage of acute and chronic liver damages.[12] Liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ responsible for the peripheral conversion of tetra-iodothyronine (T_4), tri-iodothyronine (T_3) and Thyroid stimulating hormone (TSH). Moreover it is involved in conjugation aid circulation of thyroid binding proteins[3]. Therefore, it is not surprising that thyroid dysfunction has been reported in patients with liver cirrhosis. However there was controversy in the existing literature[13-15] while there was no such local published material which necessitated the present study.

In the present study, the mean age of the patients was 52.93±9.17 years. Ali et al (2008) reported similar mean age of 52±9 years among such patients presenting at Muhammad Medical College Hospital, Mirpurkha[22] Similar mean age of 53.09±8.86 years has been reported by Almani et al (2008) among such patient presenting at Liaquat University Hospital Hyderabad.[16] Achakzai et al. in 2016 (54±11 years) and Hussain et al in 2014 (51.12±6.03 years) also reported comparable mean ages among such patients in local population.[17] Penteado et al reported similar mean age of 51.4±7.6 years among Brazilian patients with liver cirrhosis[18]. Mansour-Ghanaei et al (2012) also observed similar mean age of 55.03±12.05 years in Iranian such patients.[3] Tariq et al in 2015 reported much younger mean age of 41.1±6.1 years among such patients presenting at Civil Hospital, Karachi[19]. Bhattacharyya et al (2016) also reported similar mean age of 45.8±10.45 years in Indian patients of liver cirrhosis.[20] Mousa et al (2016) reported similar younger mean age of 45.6±11.3 years among Sudanese such patients[21]. Anastasiou et al (2015) reported much lower mean age of 40.4±1.7 years among such patients in Germany[22]. There were 131(61.2%) male and 83(38.8%) female patients in the study group with a male to female ratio of 1.6:1. A similar male predominance among such patients has been reported previously by Ali et al. who observed it to be 1.5:1 in local population.[23]

Achakzai et al (2016) however observed a female predominance among such patients presenting at Dow University Hospital, Karachi with a male to female ratio of 1:1.5[17]. Abdel-Fattah El-Feki et al. (2016) reported similar male to female ratio of 1.5:1 among Egyptian such patients.[24] Mansour-Ghanaei et al (2012) reported male to female ratio of 1.9:1 among Iranian such patients[3].

Serum TSH level ranged from 3.5µU/ml to 5.8µU/ml with a mean of 4.65±0.65µU/ml while the serum FT_3 level ranged from 1.2pg/ml to 2.9pg/ml with a mean 1.87±0.38pg/ml. Serum FT_4 level ranged from 0.6pg/ml to 2.5pg/ml with a mean of 1.70±0.51pg/ml. Our observation is similar to that of El-Kabbany et al who also reported similar lower mean serum FT_3 (1.9±0.2 pg/ml) and FT_4 (1.6±0.4pg/ml) levels with raised TSH level (4.05±1.4µU/ml) among Egyptian patients.[25] Deepika et al reported similar mean TSH (5.12±11.67µU/ml) levels among Indian cirrhotic patients. However, they observed much higher mean FT_4 (8.47±2.33pg/ml) levels with much lower mean FT_3 (0.62±0.26pg/ml) level.[26] There was no significant difference in the mean levels of TSH, FT_3 and FT_4 across age, gender and duration of disease groups. However, mean serum TSH was significantly higher in child Class-C. Our observation concedes with the observation of Abdel-Fattah El-Feki et al. (2016) who also observed significantly elevated level of TSH in patients with Child Class-C versus Class-B (18.1±14.3 vs. 3.3±3.1µU/ml; $p<0.001$)[24].

CONCLUSION

Liver diseases and endocrine disorders have a bidirectional and complex relationship. It is important that primary care physicians, endocrinologists, and hepatologists are aware of the scope of both diseases. Through this study we will be able to implement the practice that cirrhotic patients should be screened for thyroid functions tests in routine investigations conversely those with hypothyroid patients must have been evaluated for NAFLD

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