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Original Article

Biochemistry Section

Thyroid Hormone Levels in Chronic Alcoholic Liver Disease Patients Before and After Treatment

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ABSTRACT

Introduction: Alcoholic liver disease affects almost all aspects of the thyroid gland including the thyroid hormone levels and the thyroid gland size. The altered thyroid hormone levels in alcoholic liver disease may affect alcohol abstinence in withdrawal period by changing hormone milieu in brain, increasing withdrawal dysphoria and increasing craving.

Aim: The aim of the present study was to assess and compare the levels of thyroid hormones- free T3, free T4, Thyroid Stimulating Hormone (TSH) and Gamma Glutamyl Transferase (GGT) in chronic alcoholic liver disease patients before and after treatment.

Materials and Methods: This study was conducted on 70 alcoholic liver disease patients. Two serum samples were taken from the patient once at the time of admission and the other at the time of discharge after atleast ten days of treatment. Serum free T3, free T4, TSH and GGT were assessed on auto analyzer Beckman Coulter. Statistical analysis is done by paired t-test and Pearson's Correlation test.

Results: In present study, serum GGT levels decreased significantly (before treatment-207.46±66.90 U/L; after treatment-78.47±19.71 U/L) and free T3 levels increased significantly with treatment (before treatment-2.54±0.48 pg/mL; after treatment-2.88±0.37 pg/mL). Free T4 levels are also increased with treatment (before treatment-0.78±0.19 ng/dL; after treatment-0.88±0.13 ng/dL) and TSH levels are not altered significantly with treatment (before treatment-3.34±1.62 µIU/mL; after treatment-3.32±1.51 µIU/mL). Additionally, free T3 showed a significant correlation with GGT before (p-value<0.001) and after treatment (p-value-0.003) and free T4 and TSH showed a significant correlation with GGT after treatment (free T4: p-value<0.001) (TSH: p-value <0.001) and a suggestive significance exists before treatment (free T4: p-value= 0.098) (TSH: p-value=0.062).

Conclusion: Thyroid hormones levels, particularly free T3 and free T4, need to be evaluated in chronic alcoholic liver disease patients. Free T3 could be used as a marker of alcoholism and is very useful in assessing the treatment efficacy in chronic alcoholic liver disease. Also, assessing free thyroid hormones is necessary during the withdrawal and abstinent periods as decreased hormone levels may increase withdrawal effects and craving for alcohol.

Keywords: Free T3, Free T4, Gamma Glutamyl Transferase, Thyroid Stimulating Hormone

INTRODUCTION

Alcohol is one of the world's largest risk factor for disease and disability. Alcohol consumption can lead to dependence, also increases the risk to develop more than 200 diseases including liver cirrhosis and cancer. Globally, 3.3 million deaths in 2012 are due to the harmful effects of alcohol. Worldwide, 7.6% of men's deaths and 4% of women's deaths are alcohol related. In India, an age-standardized death rate for liver cirrhosis is 39.5/100,000 in males and 19.6/100,000 in females [1]. In view of magnitude of the problem, it becomes necessary for us to understand the effect of alcohol on various body systems and need to implement a prompt way to treat the patients accordingly.

Alcohol affects almost all organs and systems of the human body [2]. Alcohol has multiple effects on the hypothalamo-pituitary-thyroid axis as well as functioning of the thyroid gland. The involvement of hypothalamo-pituitary axis is present in development of dependence for addicting substances and therefore various effects are present on hypothalamo-pituitary-thyroid axis by these addicting substances [3].

The malfunction of liver due to alcohol affects most of the thyroid gland including the hormone levels as well as the gland size. The changes observed are: alteration of thyroid hormone levels and toxicity of thyroid cells [4]. This chronic alcoholic liver disease also destroys the thyroid cells and reduces their volume due to continued toxicity for a long time [5,6]. Alcohol causes a moderate suppression of serum thyroxine (T4) levels with more significant suppression of triiodothyronine (T3) levels in chronic alcoholics. In addition, alcohol-dependent individuals may present with a "euthyroid sick syndrome," evidenced by low levels of T3, high levels of reverse T3 (rT3), and normal levels of T4 [7,8].

Additionally, acute withdrawal from alcohol or long term soberity after alcohol dependence has seen reduction of hormone levels of thyroid. This suppression of peripheral hormones levels of thyroid during the soberity period has been in correlation to the severity of withdrawal phenomenon [6]. This phenomenon is clinically interesting as thyroid suppression may accentuate the withdrawal dysphoria [5-9] and therefore increases the relapse risk in alcoholism [10] and also the person's craving for alcohol. Therefore, the effect on thyroid gland may initiate a vicious circle making the patient to drink more alcohol and increased alcohol drinking causes furthermore thyroid dysfunction.

The altered thyroid hormone levels in alcoholic liver disease may affect alcohol abstinence in withdrawal period by changing hormone milieu in brain, increasing withdrawal dysphoria as well as craving for alcohol. Hence, this study was undertaken to know whether thyroid hormone levels could be used as markers of alcoholic liver disease and also to assess the changes in thyroid hormone levels with treatment for alcoholic liver disease.

MATERIALS AND METHODS

A prospective cohort study was conducted for the duration of one year (05/2014 to 04/2015) in Vydehi Institute of Medical Sciences,

Bengaluru, Karnataka, India, after obtaining the Ethical Clearance. Patient's consent for sample collection had been obtained before and after treatment. Statistically sample size was estimated as 70 patients by using sample size calculator Piface 1.72 with 90% power and effect *d as* = 0.3.

A total number of 70 male patients in the age group of 30-80 years who are chronic alcoholics with regular alcohol intake of more than 60-80 gm/day for the past 10 years [11] and having alcoholic dependence symptoms and admitted in Department of General Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru. A written informed consent was taken from the patients for the study. Patients with intrinsic thyroid disorders and other liver disorders due to any other cause (not caused by alcohol), patients with hypothalamus and pituitary gland dysfunction and patients on drugs that affect thyroid hormone levels such as inorganic iodine, iodide, amiodarone, cyanates, lithium, radio contrast material containing iodine, tyrosine kinase inhibitors, interferon alpha, interleukin 2 etc., were excluded from the study.

Method of Sample Collection and Preparation

Under aseptic conditions, venous blood sample of about 5 ml was collected by venepuncture and was used for the assessment of the free T3, free T4, TSH and GGT at the time of admission and also at the time of discharge after atleast ten days of treatment. Treatment mainly consisted of abstinence from alcohol and supplements like B-complex and folic acid and livopill (Exeltis India) as liver supplemental drug bd/tid for a period of atleast ten days and continued for one month depending upon the condition of the patient.

Patient's baseline data, clinical findings, basic investigation reports were obtained on a pre-structured proforma. A 5 ml of venous blood samples was collected from median cubital vein by venepuncture avoiding haemolysis into vacutainer, after overnight fasting. Samples were centrifuged at 3000 rpm for 10 minutes. The samples were aliquoted and kept at -20° C until analysis was done. All the analysis was carried on serum samples. Free T3 by competitive binding immunoenzymatic assay, Free T4 by two step enzyme immunoassay, TSH by two site immunoenzymatic (sandwich) assay and GGT by enzymatic rate method were performed, which are non invasive.

STATISTICAL ANALYSIS

Statistical analysis is done by Pearson's correlation test and paired 't' test to correlate between thyroid hormone levels and GGT at the time of admission and at the time of discharge. Pearson's correlation coefficient (r) is a measure of the strength of the association between the two variables. Positive correlation indicates that both variables increase or decrease together, whereas negative correlation indicates that as one variable increases, so the other decreases, and vice versa. Given two paired sets X and Y of n measured values, the paired t-test determines whether they differ from each other in a significant way under the assumptions that the paired differences are independent and identically normally distributed. The Statistical software namely SPSS 15.0 and MedCalc 9.0.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

A total of 70 subjects were included in our study, all were males with age group between 30-80 years with a mean age 44.74±10.3 [Table/Fig-1].

GGT levels decreased significantly with treatment in all the patients [Table/Fig-2].

Free T3 levels increased significantly with treatment. After treatment, the increase in free T3 is seen in 60 patients and in other 10 patients there is decrease in free T3 levels. We also found that all the patients in whom decrease in free T3 is observed after treatment, have free T3 levels in the normal range before treatment. Two patients who had free T3 levels in the lower normal reference range before treatment have free T3 levels slightly below the reference range after treatment. We had also observed that the decrease in free T3 levels is more in patients taking greater amounts of alcohol daily for more than ten years irrespective of their diet habits [Table/Fig-2].

Free T4 levels also increased with treatment. The increase in free T4 levels is seen in 56 patients and in other 14 patients free T4 levels decreased to a slight extent. Majority of the patients in whom

Age in Years	Number of patients	%
<30	1	1.4
31-40	29	41.4
41-50	26	37.1
51-60	8	11.4
61-70	3	4.3
71-80	3	4.3
Total	70	100.0

[Table/Fig-1]: Age distribution of patients studied.
Mean ± SD: 44.74±10.33
Percentage calculation done to divide patients into various groups

Parameters		Before treatment	After treatment
GGT	<50 U/l	0	6
	50 – 150 U/l	13	64
	>150 U/l	57	0
Free T3	<2.5 pg/ml	34	8
	2.5-3.5 pg/ml	34	54
	>3.5 pg/ml	2	8
Free T4	<0.61 ng/dl	15	0
	0.61-1.12 ng/dl	53	69
	>1.12 ng/dl	2	1
TSH	<0.4 µlU/ml	0	0
	0.4-4.2 µlU/ml	48	48
	>4.2 µlU/ml	22	22

[Table/Fig-2]: GGT, Free T3, Free T4, TSH levels of patients before and ten days after treatment.

Para-meters	Before treatment	After treatment	Difference	't' value	p-value
GGT	207.46±66.90 U/l	78.47±19.71 U/l	128.986	16.927	<0.001**
Free T3	2.54±0.48 pg/ml	2.88±0.37 pg/ml	-0.344	-8.055	<0.001**
Free T4	0.78±0.19 ng/dl	0.88±0.13 ng/dl	-0.097	-6.659	<0.001**
TSH	3.34±1.62µlU/ml	3.32±1.51µlU/ml	0.017	0.476	0.636

[Table/Fig-3]: Comparison of GGT, FT3, FT4 and TSH before and after treatment by paired 't' test in patients studied.
** Strongly significant (p-value : p<0.001)
#Paired t-test is used to compare GGT, free T3, free T4 and TSH before and after treatment.
*pg/ml – picogram/milliliter; ng/dl – nanogram/deciliter.

Pair	Before treatment		After treatment		p-value
	r-value	p-value	r-value	p-value	
GGT vs free T3	-0.776	<0.001**	-0.346	0.003**	0.011*
GGT vs free T4	-0.199	0.098+	-0.378	0.001**	0.342
GGT vs TSH	0.224	0.062+	0.411	<0.001**	0.311

[Table/Fig-4]: Pearson correlation of GGT with FT3, FT4 and TSH in before and after treatment
+ Suggestive significance (p value: 0.05<p<0.10)
* Moderately significant (p value:0.01<p < 0.05)
** Strongly significant (p value : p<0.01)
# Pearson Correlation was used to correlate GGT with free T3, free T4 and TSH parameters before and after treatment

decrease in free T4 levels is observed have free T4 levels in the higher normal reference range [Table/Fig-2].

TSH levels did not vary significantly with treatment. Fifteen patients have TSH levels more than normal (normal range: 0.4-4.2 μIU/ml) before and after treatment. One patient who is having TSH levels more than normal before treatment had TSH level in the normal reference range after treatment. Twenty eight patients have increased TSH levels and 42 patients have decreased TSH levels after treatment when compared to before treatment levels. But the difference between TSH levels before and after treatment is not significant in majority of the patients; the reason most probably is that it takes longer time for the TSH levels to fluctuate after treatment with the feedback affect from increased free T3 and free T4 levels [Table/Fig-2].

There is a significant decrease in GGT levels after treatment when compared to those before treatment as well as free T3 and free T4 levels increased significantly with treatment [Table/Fig-3].

There is a significant correlation between free T3 and GGT before and after treatment. There is a significant correlation between free T4 and GGT after treatment and there exists a suggestive correlation between free T4 and GGT before treatment. Similarly, a significant correlation exists between TSH and GGT after treatment and also a suggestive correlation is present between TSH and GGT before treatment [Table/Fig-4].

DISCUSSION

In our present study, we found that GGT levels decreased significantly with treatment in all the patients. Free T3 and free T4 levels increased significantly with treatment and there was no significant change in TSH levels with treatment. There was a significant correlation between free T3 and GGT before (p-value < 0.001) and after treatment (p-value=0.003). There was a significant correlation between free T4 and GGT after treatment (p-value<0.001) and there existed a suggestive correlation between free T4 and GGT before treatment (p-value=0.098). Also, a significant correlation was present between TSH and GGT after treatment (p-value<0.001) and a suggestive correlation was present between TSH and GGT before treatment (p-value=0.062).

Similar findings by Liappas I et al., where most of the hepatic enzymes (ALT, AST, GGT) and thyroid hormones (T3, T4, TSH) returned to normal after completion of alcohol detoxification program and there exists a significant correlation between hepatic enzymes and thyroid hormones after detoxification. Also, a significant correlation existed between the levels of thyroid hormones and the mood status scales [5]. It is clear from Loosen PT et al., observations that a normo or hypo rather than a hypermetabolic or hyperthyroid state is more common in chronic alcoholics [7].

In a study by Baumgartner A et al., free T3 and free T4 levels were found to be subnormal and their protein bound fractions were normal during the withdrawal period, it was observed that during the abstinence period there was increase in T4, T3 and thyroxine binding globulin levels and a decrease in free T3, reverse T3 levels and normal TSH levels and reduced T3 uptake. A direct effect of ethanol on intracellular thyroid hormone metabolism and/or function seems conceivable in their study [12].

Heinz A et al., found that levels of serum T4 and thyroxine binding globulin were significantly reduced in alcoholic patients compared to healthy controls before detoxification. During the entire observation period, free T4 and free T3 levels were slightly elevated in alcoholics when compared to healthy controls. T4 and TBG levels increased significantly during the first week of abstinence. Severity of withdrawal symptoms was negatively correlated with the total T4 levels after eight days of abstinence. Their findings suggest a different time course for T3 and T4 levels after detoxification in alcohol dependent patients, and indicate that T4 levels after detoxification interact with withdrawal symptoms [13].

Decreased thyroid hormones might result from the damage to thyroid gland or from alterations in the hypothalamo-pituitary-thyroid axis at the pituitary level caused by chronic alcohol intake as evidenced by blunted TSH response to thyrotropin releasing hormone. In addition, there are some studies reporting thyroid dysfunction in late withdrawal (20 days) [8] and during long-term abstinence. Loosen PT et al., have found decreased thyroid values even years after alcohol cessation (mean 5.8±1.1 years) [7]. In a study by Ozsoy S et al., free T3 and free T4 levels were low in late withdrawal period when compared to those of both controls and patients in early withdrawal phase [14]. Several previous studies [6,13] have also reported normal free thyroid hormone levels in acute withdrawal. The cause of normal hormonal levels in early withdrawal may be transient nor epinephrinergic over activity during the acute withdrawal, since hyperactivity of nor epinephrine leads to stimulation of basal thyroid hormones secretion. Thus, thyroid hormones might increase temporarily to normal levels, owing to enhanced nor epinephrinergic activity during the early withdrawal, and decrease again in late withdrawal.

An increase in level of TRH has been observed due to chronic alcohol consumption, which may lead to the rise of the down-regulation of the pituitary TRH receptors and, in turn lead to the reduced TSH response to TRH and a decrease in hormones levels of thyroid. Pienaar WP et al., (abstinent for 5–8 weeks) have showed blunted TSH response to TRH as compared with that of healthy controls [6]. It has also been observed that abnormal TSH response in the TRH test is noticeable even after few years discontinuation of alcohol. Chronic alcohol abuse leads to dysfunction of the thyroid gland causing decreased free T4 and free T3 levels, which by a feedback effect causes increased TRH levels leading to decreased TRH receptors in the pituitary gland and a blunted TSH response in the TRH test.

A post-mortem autopsy study has found decreased thyroid volume in alcoholics, and this damage was associated with the duration of excessive alcohol intake and dose dependent. Eight patients with autonomous thyroid nodules were given Percutaneous Ethanol Injections (PEIs) under guidance by means of Ultrasound (US). After therapy, symptoms subsided, hormonal levels became normal or reached the range of subclinical hypothyroidism and all nodules had shrunk [15]. These studies suggest that alcohol may have a direct toxic effect on the thyroid gland.

LIMITATION

Assessing the minerals, particularly iodine, could have been useful as there may be some nutritional factors involved in the disease.

CONCLUSION

Free T3 is a good marker of alcoholism and also very useful in assessing the treatment efficacy in chronic alcoholic liver disease. Thyroid hormone levels, particularly free T3 and free T4, need to be evaluated in all chronic alcoholic liver disease patients. The fluctuations in free T4 levels is not so significant because free T4 has a longer half life but free T3 (half life: few hours) has very short half life when compared to free T4 (half life: 5-7 days). Hence, free T3 levels fluctuation reflects the more recent adaptations happening in the body with treatment. Also, assessing free thyroid hormones is necessary during the withdrawal and abstinent periods as decreased hormone levels may increase withdrawal effects and craving for alcohol.

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