Internet Journal of Medical Update

Journal home page: http://www.akspublication.com/ijmu

Original Work

Influence of thyroid hormones on biochemical parameters of liver function: a case-control study in North Indian population

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(Received 11 January 2012 and accepted 11 July 2012)

ABSTRACT: Normal level of thyroid hormones is important for normal hepatic function and thyroid dysfunction may modulate metabolic function of liver. The purpose of this study is to determine whether liver function is associated with subclinical and overt hypothyroidism. Thyroid and liver function tests were evaluated in 47 patients with overt (TSH ≥10.0 mIU/L) and 77 patients with subclinical hypothyroidism (TSH 6.0-9.9mIU/L) and compared with 120 age-matched euthyroid controls. Subjects with overt hypothyroidism had significantly raised serum ALT, AST, ALP and total protein levels as compared to controls whereas subclinical hypothyroid patients had significantly increased levels of serum ALT, ALP and total protein. Further, TSH showed significant positive correlation with AST and ALP values whereas fT3 and fT4 had a negative correlation with AST in overt hypothyroidism. Thus, overt hypothyroid state is associated with significant derangement in biochemical parameters of liver function. Hence, liver function should be regularly monitored in hypothyroid patients.

KEY WORDS: ***Hypothyroidism; Liver function tests; Free T3 and T4; TSH; AST***

INTRODUCTION

Hypothyroidism is the disease state caused by insufficient production of thyroid hormones by the thyroid gland. Thyroid hormones are essential for normal organ growth, development and function.[1,2] The major secretory product of the thyroid is a prohormone (T4), which is activated in peripheral tissues by outer ring deiodination to T3. There are three homologous iodothyronine deiodinases which catalyses these reactions.[3,4] Type I deiodinase is located in liver, kidney, and thyroid. In addition to the deiodination to activate and deactivate thyroid hormones, the liver has an important role in thyroid hormone transport and metabolism.[5] Thyroid hormones regulate the basal metabolic rate of all cells, including hepatocytes, and in this way they modulate hepatic functions; metabolism of the thyroid hormones occurs in the liver, so it regulates their systemic endocrine effects.[5,6]

The liver extracts 5–10% of plasma T4 during a single passage, as shown by studies using [131I] T4. 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 protein-bound T4 is available for uptake.[7] An active stereospecific transport mechanism has been identified for transporting T4 and T3 across the hepatocyte membrane. The intracellular concentrations of the free hormone are higher than the plasma levels, and the process is energy-dependent.[8]

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

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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.[9]

Normal thyroid function is essential for normal growth, development and regulation of energy metabolism within cells and depends on a normally functioning thyroid and liver axis. Thyroid dysfunction may affect liver function and liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs. Therefore, this study was done in subjects attending the hormone lab, with a view to evaluate changes in liver function in hypothyroid subjects.

METHODOLOGY

Study population

The present study was carried out in the hormone laboratory of a tertiary care hospital of north India after being approved by institutional review board. Subjects coming for thyroid screening were enrolled. A total of 244 subjects of age group 20-50 years were enrolled after informed consent. Brief clinical history and examination were done to rule out diabetes mellitus, liver disorder, persons already on thyroxin supplements, and any other acute inflammatory disease within 4 weeks and any major illness. Among these, 124 hypothyroid patients and 120 healthy controls with no evident disease were included in the study.

The study has been approved by institutional ethical committee and was in accordance with the world Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

6 ml venous blood sample was drawn between 7:00 and 9:00 AM from all study participants after 12-14 h overnight fasting. All the blood analyses were done on the day of blood collection. Thyroid function tests and liver function tests were evaluated by two different investigators and both the investigators were unaware of the findings of the other investigator. The analysis of the results was carried out by an independent investigator.

Serum TSH, free T4 (ft4) and free T3 (ft3) were assayed by using Access 2 immunoassay chemiluminescence analyzer by Beckman and Coulter (USA). The normal ranges for TSH, ft4 and ft3 values were 0.34-5.60 μIU/mL, 0.6-1.12ng/dL, and 2.5-3.9pg/mL respectively. Patients having TSH 6-10 μIU/mL with normal ft3 and ft4 were considered as subclinical hypothyroid. Overt hypothyroid was defined when fT3 and fT4 levels were low but had high TSH value (>10 μIU/mL).

Liver function tests were analyzed on fully automated analyzer Synchron CX4 and CX9 by Beckman and Coulter (USA) using standard reagent kits. Serum bilirubin was analyzed by Jendrassik modified method using diagnostic kit by FAR SRL (Verona, Italy). The normal range for total bilirubin was 0.2-1.2mg/dl. Serum alanine transaminases (ALT), aspartate transaminases (AST), alkaline phosphatase and albumin were estimated by using diagnostic kit from Centronic GmbH (Wattenberg, Germany). ALT and AST were done by using IFCC Fluid method. Their normal range was 0-41 IU/L and 0-38 U/L respectively. ALP was analyzed using SFBC method and its normal range was 0-117 IU/L. Albumin was estimated by bromocresol green method and normal range was 3.4-4.8g/dL. Serum total proteins were analyzed using biuret method using diagnostic kit from Randox Laboratories (Crumlin, United Kingdom). The reference range was 6.4-8.3 g/dL.

Statistics

Continuous variables were expressed as mean ± standard error of mean (S.E.M). Normality of the sample distribution of each continuous variable was tested with the Kolmogorov-Smirnov test. The Student's 't' or Mann-Whitney U test, depending on the shape of the distribution curves was used for evaluation of differences in continuous variables. Linear Pearson correlation (r) was applied for association between TSH, ft4, ft3 levels and liver function tests in both subclinical and overt hypothyroid subjects. Statistical analysis was carried out using SPSS for Windows 14.0 software (SPSS Inc. Chicago, IL, USA).

RESULT

Our entire study population included 244 women of age group 22-49 years. Out of these, 124 women were found to be hypothyroid (77 subclinical hypothyroid and 47 overt hypothyroid) and 120 were euthyroid. Both the groups were age-matched. The thyroid profile of all the study groups is presented in **Table 1**. A highly significant difference was observed in serum TSH between the study group and the control Group (2.43 ± 0.22 μIU/ml). The subclinical hypothyroid (7.61 ± 0.15 μIU/ml) patients showed significant increase in TSH levels and it was much more significant in overt hypothyroid cases (42.3 ± 4.55 μIU/ml). The levels of ft4 (0.84 ± 0.03 μg/dL) and ft3 (3.09 ± 0.07 ng/ml) decreased slightly in subclinical hypothyroid patients as compared to the ft4 and ft3 value of controls (0.94 ± 0.023 μg/dL and 3.20 ± 0.46 ng/ml respectively), which was statistically significant. In overt hypothyroid cases ft3 and ft4 (2.60 ± 0.75 ng/ml and 0.43 ± 0.23 μg/dL respectively) levels showed a statistically significant decrease in value as compared to the control group.

Table 1: Comparison between TSH, fT3, fT4 values obtained in controls, euthyroid and subclinical hypothyroid subjects

Parameter	Control (n=120)	Subclinical hypothyroid (n=77)	Overt hypothyroid (n=47)
TSH (μIU/ml)	2.428 ± 0.217	7.615 ± 0.148*	42.301 ± 4.546*
ft4 (μg/dL)	0.943 ± 0 .025	0.8453 ± 0.030	0.428 ± 0.228*
ft3 (ng/mL)	3.205 ± 0.040	3.088 ± 0.069	2.604 ± 0.745*

** denotes p value <0.001 vs. control*

The liver enzyme ALP showed statistically significant increase in subclinical hypothyroid patients (134.16 ± 5.75 IU/L) (p=0.017) and in overt hypothyroid cases (149.0 ± 11.31 IU/L) (p= 0.002) as compared to the controls (100.41 ± 5.69 IU/L) (**Table 2**). In comparison to control (32.93 ± 1.94 IU/L), there was rise in AST levels in subclinical hypothyroid cases (37.18 ± 1.49 IU/L) and a significant increase in overt hypothyroid cases (42.46 ± 2.53 IU/L) (**Table 2**). The changes in ALT value were also statistically significant when control (25.73 ± 1.89 IU/L) was compared with subclinical hypothyroid (32.81 ± 0.98 IU/L) (**Table 2**) and overt hypothyroid cases (42.15 ± 2.75 IU/L) (**Table 3**). A statistically significant increased value of serum total protein was observed in both subclinical (8.32 ± 0.18 g/dL) (table 2) and overt hypothyroid cases (8.29 ± 0.24 g/dL) as compared to control (7.05 ± 0.16 g/dL) (**Table 3**). The change in albumin and bilirubin levels in control and cases were not statistically significant.

Table 2: Comparison between the laboratory values obtained in euthyroid and subclinical hypothyroid subjects

	Control (n=120)	Subclinical Hypothyroid (n=77)	p value
T. Bilirubin (mg/dL)	0.684± 0.0491	0.7579 ± .0618	0.662
ALT (IU/L)	25.731 ± 0.899	32.808 ± 0.980	0.005
AST (IU/L)	32.929 ± 1.940	37.1786 ± 1.495	0.163
ALP (IU/L)	100.41 ± 5.689	134.162 ± 5.745	0.017
Total serum protein(g/dL)	9.046 ± 0.0943	10.317 ± 0.1831	0.002
Albumin (g/dL)	4.626 ± 0.525	4.965 ± 0.127	0.472

Table 3: Comparison between the laboratory values obtained in control and overt hypothyroid (OH) subjects

	Control (n=120)	Overt hypothyroid (n=47)	p value
T. Bilirubin (mg/dL)	0.684± 0.0491	0.800 ± .07473	0.185
ALT (IU/L)	25.731 ± 0.899	42.154 ± 2.753	0.003
AST (IU/L)	32.929 ± 1.940	42.464 ± 2.528	0.033
ALP (IU/L)	100.41 ± 5.689	149.00 ± .235	0.002
T. serum protein(g/dL)	9.046 ± 0.0943	10.288 ± .159	0.000
Albumin (g/dL)	4.626 ± 0.525	4.877 ± 1.061	0.107

When subclinical and overt hypothyroid cases were compared, ft3, ft4, TSH and ALT showed a statistically significant change in the values while other parameters were not significant statistically (**table 4**).

Table 4: Statistical significance between subclinical and overt hypothyroid cases

	Subclinical Vs Overt Hypothyroidism (p value)
TSH	0.000
ft4	0.00
ft3	0.005
Total Bilirubin	0.903
ALT	0.004
AST	0.243
ALP	0.219
Total serum protein	0.728
Albumin	.702

Further, in the subclinical hypothyroid group, serum TSH levels showed a significant negative correlation with bilirubin (**Table 5**). ft4 showed a negative correlation with ALP and a positive correlation with albumin while ft3 did not show any correlation with other parameters (Table 5). For the overt hypothyroid cases, TSH correlated well with AST and ALP and both ft3 and ft4 showed a positive correlation with albumin and a negative correlation with AST values (**Table 6**).

Table 5: Correlation (p values) of liver function tests in subclinical hypothyroid cases

	TSH		ft4		ft3	
	r values	p value	r values	p value	r value	p value
Total Bilirubin	-0.386	0.010	0.129	0.272	-0.157	0.187
ALT	0.042	0.786	0.004	0.975	0.067	0.585
AST	-0.132	0.387	0.002	0.985	0.197	0.108
ALP	0.037	0.807	-0.247	0.036	0.132	0.275
Total serum protein	-0.022	0.889	-0.214	0.083	0.083	0.513
Albumin	-0.223	0.155	-0.308	0.011	0.226	0.071

Table 6: Correlation (p values) of liver function tests in overt hypothyroid cases

	TSH		ft4		ft3	
	r value	p value	r value	p value	r value	p value
Total Bilirubin	-0.092	0.547	-0.066	0.667	-0.023	0.883
ALT	0.199	0.200	-0.256	0.097	-0.295	0.054
AST	0.317	0.034	-0.443	0.002	-0.372	0.012
ALP	0.326	0.031	-0.139	0.369	-0.171	0.267
Total serum protein	0.122	0.442	0.086	0.588	0.138	0.384
Albumin	0.088	0.575	0.346	0.023	0.406	0.007

DISCUSSION

Thyroid hormone influences the function of all body organs and cells. The data presented here clearly indicates how biochemical markers of liver may be affected by alteration in the thyroid hormone levels in the body. The hypothyroid cases in the present study were mainly the referral cases from different outpatient departments of the hospital. In the present study, significant difference was seen in liver function tests when subjects in hypothyroid groups were compared with euthyroid subjects.

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.[10] In this study, the liver enzymes (AST) showed a significant positive correlation of serum TSH levels in hypothyroid subjects which may be because of myopathy associated with hypothyroidism. In few case reports hypothyroidism has been associated with cholestatic jaundice attributed to reduced bile excretion.[11] Though the average bilirubin levels were higher in the overt hypothyroid group but the values were not found to be clinically or statistically significant. This insignificant difference in bilirubin levels may be because of the selective data of the referral cases of outpatient department. However, a highly significant change was observed in serum ALP levels which showed a positive correlated with serum TSH levels in overt hypothyroid subjects. These observations may be explained on the basis that in hypothyroidism there is an increase in membrane cholesterol-phospholipid ratio and diminished membrane fluidity, which affect a number of canalicular membrane transporters and enzymes, including the Na+, K+-ATPase resulting in the change of ALP enzymes.[12]

Serum total protein demonstrated a statistically significant increase in hypothyroid subjects as compared to euthyroid subjects. However, the

difference in serum albumin was not found to be clinically or statistically significant. Albumin levels showed a significant positive correlation with ft4 levels in both subclinical and overt hypothyroid patients and with ft3 levels in overt hypothyroid subjects. This indicates that probably in hypothyroidism proteins other than albumin may be synthesized by the liver. The liver is known to synthesize a number of plasma proteins that bind the lipophilic thyroid hormones. Added to this, low-grade inflammation associated with even mild degrees of hypothyroidism may lead to a resultant increase in inflammatory proteins and immunoglobulins.[13]

CONCLUSION

Reduced liver function is associated with subclinical and overt hypothyroidism. Knowledge of the association between hypothyroidism and deranged biochemical markers of liver function is important for the clinician to consider an evaluation of thyroid function in the workup of the patient with altered liver function tests. It is also noteworthy that the levels of liver enzymes progressively increase with the degree of hypothyroidism. This emphasizes the need for monitoring liver enzymes in hypothyroid patients as declining liver function may be missed by single assessment. However, future studies are needed to determine the potential adverse effects of hypothyroidism on liver function.

REFERENCES

1. Michael Braun. The Breast In: Russel RCG, Williams NS, Bulstrode CJK, editors. *Bailey and Love's Short Practice of Surgery*. 24th ed. London: Hooldev Arnold Oxford Uni Press 2004:835-9.
2. Peter AM, Kathleen MB. Lipid Transport & Storage. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, editors. *Harper's Illustrated Biochemistry*. 28th ed. New Delhi: Lange Medical Books;2009:110-1.
3. Larsen PR, Berry MJ. Nutritional and hormonal regulation of thyroid hormone deiodinases. *Annu Rev Nutr*. 1995;15:323-52.
4. Visser TJ. Pathways of thyroid hormone metabolism. *Acta Med Austr*. 1996;23:10-11.
5. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. *Q J Med*. 2002;95:559-69.
6. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. *J Gastroenterol Hepatol*. 1995;10:344-50.
7. Mendel CM, Cavalieri RR, Weisiger RA. Uptake of thyroxine by the perfused rat liver: implications for the free hormone hypothesis. *Am J Physiol*. 1988;255:E110-19.
8. Hennemann G, Docter R, Friesema EC, et al. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. *Endocr Rev*. 2001;22:451-76.
9. Bianco AC, Salvatore D, Gereben B, et al. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23:38-89.
10. Laycock MA, Pascuzzi RM. The neuromuscular effects of hypothyroidism. *Semin Neurol*. 1991;11:288-94.
11. Van Steenbergen W, Fevery J, De Vos R, et al. Thyroid hormones and the hepatic handling of bilirubin. Effects of hypothyroidism and hyperthyroidism on the hepatic transport of bilirubin mono- and diconjugates in the Wistar rat. *Hepatology*.1989;9:314-21.
12. Inkinen J, Sand J, Nordback I. Association between common bile duct stones and treated hypothyroidism. *Hepatogastroenterology*. 2000;47:919-21.
13. Kvetny J, Heldgaard PE, Bladbjerg EM, et al. Subclinical hypothyroidism is associated with a low-grade inflammation; increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf)*. 2004;61:232-8.