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DERANGEMENT OF HEPATIC ENZYMES IN HYPOTHYROID PATIENTS WITH CLINICALLY INSIGNIFICANT HYPERBILIRUBINEMIA- A CROSS-SECTIONAL STUDY IN TRIBAL POPULATION OF BANKURA, WEST BENGAL, INDIA

Dr. Amrita Chatterjee	Senior Resident. Dept of Biochemistry, Medical College, Kolkata. 88, College Street, Kolkata, Pin- 700073.
Dr. Sumanta Banerjee	Medical Officer (Specialist- Biochemistry). Balurghat District Hospital & Multi-/Superspeciality Hospital, Balurghat, Dakshin Dinajpur, Pin- 733101.
Prof (Dr.) Pinaki Sarkar	Professor, Dept. of Biochemistry, I.P.G.M.E.R , Kolkata.
Dr. Subhayan Lahiri*	Demonstrator, Dept of Biochemistry, Medical College, Kolkata. *Corresponding Author

ABSTRACT This study was designed to find any association between hypothyroidism and liver function. It was a cross-sectional observational study. The study population consisted of 50 newly diagnosed hypothyroid participants from a tertiary care hospital in Bankura district, West Bengal. Two thyroid hormones (TSH, fT4) and few biochemical parameters of liver function (AST, ALT, ALP and Total & Direct Bilirubin) were measured on the study population. Depending on a cut off value of TSH and fT4, that study population was divided into two groups. A statistically significant difference was found in serum ALT level between those two groups, whereas no such finding was seen in case of serum AST and ALP level. TSH and fT4 was also having significant positive and negative correlation with AST, ALT, Total & Direct bilirubin respectively. It could be concluded that hypothyroidism and liver dysfunction might have an association. Accepting this scenario more extensive research work for LFT in hypothyroid patients is required to finalize the conclusion.

KEYWORDS : Bilirubin, Hypothyroidism, Liver function test, TSH.

Introduction:

Thyroid diseases are among the commonest endocrine disorders worldwide. Among Indian population also, they contribute a major burden on people's health. According to various studies, it is estimated about 42 million people in India suffer from thyroid diseases.[1] Thyroid gland secrets two iodine containing hormones, Thyroxine and Tri-iodothyronine, acts through nuclear receptors, part of nuclear superfamily group of receptors.[2] Thyroid disorders are grossly classified into two major categories, hypothyroidism and hyperthyroidism, where thyroid hormones decreased or increased respectively.[3] Hypothyroidism is the common thyroid dysfunction seen in India having the prevalence of 3.9%; sub-clinical hypothyroidism is even commoner than overt hypothyroidism with prevalence of 9.4%.[4] Thyroid hormones play a pivotal role in growth, development and function of different organs. They regulate the basal metabolic rate of all cells including the hepatocytes, so thyroid hormones are capable to modulate hepatic function. Along with this, liver is the site of organ for the metabolism of thyroid hormones, hence regulating the systematic endocrine effects of those hormones.[5] Thyroid hormone dysregulation may perturb liver function.[6] Liver disease modulate thyroid hormone metabolism and a variety of systemic diseases also affect both the organs; Liver and Thyroid gland.[5]

Missing loop between hypothyroidism and altered liver function has been emerging as a important tool, as few recent studies have shown that hypothyroidism associated hepatic dysfunction can be reversible with thyroxine replacement therapy without causing permanent liver damage.[7] Our present study was undertaken to evaluate few biochemical parameters of liver function test (three liver enzymes and bile pigments) and two thyroid hormones (TSH, fT4) among newly diagnosed hypothyroid patients and to find out any correlation between those parameters.

Materials and Methods

An observational, cross-sectional, tertiary care hospital based study was conducted in Bankura Sammilani Medical College and Hospital, over a period of eight months (from October, 2017 to May, 2018) among fifty newly diagnosed hypothyroid patients, presenting at the out-patient department of Medicine, by systematic random sampling. After getting Ethical clearance from the Institutional Ethics committee a predesigned, pretested questionnaire was framed for history taking, giving information and taking written consent for each agreed participants.Thyroid stimulating hormone (TSH) and serum free tetra-iodothyronine (fT4) was assayed by sandwich enzyme-linked immunosorbent assay (ELISA) and competitive ELISA method, respectively. Total and Direct Bilirubin (T.Bil and D.Bil), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline phosphatase (ALP) were measured in XL-360 Automated Biochemistry Analyzer (ERBA).

Inclusion Criteria: Newly diagnosed hypothyroid patients.

Exclusion Criteria:

i. Critically ill and moribund patients.
ii. Patients suffering from malignancy.
iii. Patient on treatment for any thyroid disease.
iv. Pregnant, lactating and postmenopausal women.
v. Patient on treatment for any liver disease.
vi. Patient was on any therapy that might change thyroid, liver functions.

Data were compiled in MS excel sheet and codified accordingly. Statistical calculations were done by suitable statistical methods like central tendencies, correlation, cross-tabulations and chi-square tests etc. by software package (SPSS ver.20). Shapiro-Wilk test was done to check the distribution pattern of parameters and it was found that all parameters were skewed, hence nonparametric tests were mandate for statistical analyses.

Results

Total no of participants 50.
among them male: female ratio 1:1.174.
Statistical distribution of different attributes:

Table-1 :

Attributes	Age	TSH	fT4	T. BIL	D. BIL	AST	ALT	ALP
Mean	42.62	22.53	1.05	1.22	0.31	85.72	87.88	154.04
Std. Error of Mean	1.42	2.67	0.07	0.06	0.02	4.90	5.33	10.94
Median	42.00	15.71	1.02	1.10	0.30	74.50	78.00	128.00
Std. Deviation	10.03	18.884	0.52	0.43	0.12	34.66	37.69	77.34
Variance	100.57	356.60	0.27	0.18	0.01	1200.98	1420.39	5981.14

Minimum	25	6.12	0.09	0.60	0.0	44	34	56
Maximum	65	72.47	1.88	2.20	0.5	190	198	369

We assume the highest normal cut off limit of AST and ALT were 45 and 56 U/mL, respectively. It was noted from statistical analyses that ALT was elevated more in male population with respect to female population (95.7% vs 66.7%) but AST was elevated in all females and 94.4% of males.

Cross tabulation: TSH vs AST & ALT
Table-2 :

			AST Groups		ALT Groups	
			≤45	>45	≤56	>56
TSH Groups	≤10	Count (Total = 15)	2	13	9	6
		% within TSH Group	13.3%	86.7%	60%	40%
	>10	Count (Total = 35)	0	35	1	34
		% within TSH Group	0.0%	100.0 %	2.9%	97.1%
Total		Count	2	48	10	40
		% within TSH Group	4.0%	96.0%	20%	80%
Pearsons Chi Square		Value	4.861		21.429	
		Asymp. Significance (2-sided)	0.027		≤0.001	
Likelihood ratio		Value	5.014		20.768	
		Asymp. Significance (2-sided)	0.025		≤0.001	
Fisher's exact test		Exact Significance (2-sided)	0.086		≤0.001	

Cross tabulation: fT4 vs AST & ALT
Table-3 :

			AST Groups		ALT Groups	
			≤45	>45	≤56	>56
fT4 Groups	≤0.7	Count (Total = 14)	0	14	0	14
		% within TSH Group	0.0%	100.0%	0.0%	100.0 %
	0.7-1.9	Count (Total = 36)	2	34	10	26
		% within TSH Group	5.6%	94.4%	27.8%	72.2%
Total		Count	2	48	10	40
		% within TSH Group	4.0%	96.0%	20%	80%
Pearsons Chi Square		Value	0.810		4.861	
		Asymp. Significance (2-sided)	0.368		0.027	
Likelihood ratio		Value	1.346		7.5	
		Asymp. Significance (2-sided)	0.246		0.006	
Fisher's exact test		Exact Significance (2-sided)	1.000		0.045	

It was surprisingly found that the higher the level of TSH, higher the level of liver enzymes and the Pearsons chi-square was found to be significant and the lower the level of fT4, the higher the level of liver enzymes and the Pearsons chi-square was found to be significant.

It was also found that TSH was significantly and directly correlated with total and direct bilirubin and AST, ALT but there was no significant correlation with ALP. fT4 was significantly and inversely correlated with TSH, total and direct bilirubin and AST, ALT but there was no significant correlation with ALP.

Correlations:
Table-4 :

SPEARMAN'S CORRELATION		Age	TSH	fT4	T. BIL	D. BIL	AST	ALT	ALP
TSH	Correlation Coefficient	-0.103	1.000	-0.476	0.827	0.560	0.894	0.845	0.267
	Sig. (2-tailed)	0.476	-	<0.001	<0.001	<0.001	<0.001	<0.001	0.061
fT4	Correlation Coefficient	0.014	-0.476	1.000	-0.623	-0.445	-0.549	-0.511	0.036
	Sig. (2-tailed)	0.925	<0.001	-	<0.001	0.001	<0.001	<0.001	0.805
T. BIL	Correlation Coefficient	-0.158	0.827	-0.623	1.000	0.723	0.866	0.753	0.218
	Sig. (2-tailed)	0.273	<0.001	<0.001	-	<0.001	<0.001	<0.001	0.129
D. BIL	Correlation Coefficient	-0.173	0.560	-0.445	0.723	1.000	0.704	0.532	-0.039
	Sig. (2-tailed)	0.229	<0.001	0.001	<0.001	-	<0.001	<0.001	0.787

Discussion :

Female preponderance is seen among hypothyroidism patients.[3,6] In our study, we got female to male ratio of 1.174 : 1. In our study a statistically significant difference is seen in serum ALT level between two groups – (one having TSH > 10 mIU/ml and another group having TSH < 10 mIU/ml), but no statistical significant difference is seen in case of other two liver enzymes AST and ALP. [Table 2]. Similar findings are also seen when two groups were divided on the basis of fT4 values. (One having fT4 values < 0.7 ng/dl and another group having fT4 values 0.7-0.9 ng/dl).[Table 3]. In corroboration with our study, Kalita N et al.[8], Yadav A. et al.[9], p.d Griffiths et al.[10]also found significant difference in serum ALT values,but unlike us they found difference in AST and ALP levels also.It is evident in present days that thyroid hormones are involved in regulation of lipid metabolism, insulin resistance.[11] Hypothyroidism causes increased LDL-cholesterol and triglycerides by decreasing LDL-receptor's activity.[12] Excess triglycerides accumulation leads to steatosis , a component of NAFLD.[13] NAFLD is nowadays considered as hepatic feature of metabolic syndrome.[14] Previous many studies has already been evaluated the association between hypothyroidism and NAFLD, as independent risk factor.[15]

In our study we also got a statistically significant correlation between TSH and fT4 with Total and Direct Bilirubin and AST, ALT levels. TSH got a strong positive correlation whereas fT4 having negative correlation with those parameters.TSH and fT4 is also negatively correlated. [Table 4].Our study findings of Bilirubin are in agreement with few case reports, where hypothyroidism has been shown to be associated with cholestatic jaundice.[16] In experimental hypothyroidism, decreased activity of UDP-glucuronyl transferase is seen, resulting in reduction in bilirubin excretion.[17] Incidence of Gallstone is high in hypothyroid patients, may be due to the triad of hypercholesterolemia, reduced bilirubin excretion and atonia of gallbladder seen in hypothyroidism.[18]

Limitations:

Further study with large sample size is required to avoid statistical bias and conclude to a confirmatory conclusion. And longitudinal cohort study has to be carried out to establish cause to effect relationship between thyroid and liver dysfunction.

Conclusion :

Our study identifies an intricate relation between thyroid hormones and liver function. Hypothyroid patients are shown to have few altered parameters of liver function. Hence patients suffering from hypothyroidism should undergo liver function test at a regular interval to early detect and prevent complication.

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