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Association among liver biochemical parameters, thyroid gland hormones, and TNF-Alpha in hypothyroid patients compared to euthyroid subjects

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Abstract

Background: Tumor necrosis factor alpha (TNFα) is a 17 kDa, an important soluble pro-inflammatory cytokine, which is involved in some tissue dysfunctions, including thyroid and liver tissue. In spite of its role in thyroid and tissue damage separately, the relationship between this factor and these two disorders has not been clarified. The aim of the present study was to evaluate liver biochemical parameters and TNFα in hypothyroid patients compared to euthyroid subjects.

Methods: To achieve this purpose, samples were transferred into tubes without anticoagulants and then centrifuged immediately to separate the serum. All markers in the serum were measured using commercial kits, including T3, T4, TSH, and TNFα, which were detected using the ELISA method. Liver function tests, including albumin, total bilirubin, and total protein were measured by spectroscopy and the colorimetric method, respectively. In addition, AST, ALT, ALP, and GGT were detected using enzymatic methods.

Results: Our results showed that the level of TNFα in hypothyroid patients was significantly higher than that in normal individuals (P = 0.009). TNFα had a significantly positive correlation with TSH and T3 but a negative correlation with T4. Furthermore, AST, ALT, and GGT had a positive correlation with TSH and a negative correlation with albumin, total protein, and total bilirubin. These correlations were insignificant (P < 0.05).

Conclusion: According to our data, the positive correlation of TSH with both TNFα and liver function tests may indicate a relationship between thyroid and liver function with each other.

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Introduction

Hyperthyroidism is one of the endocrine system diseases in which the thyroid gland does not produce thyroid hormones. One of the risk factors for this disorder is liver dysfunction (1-5).

Investigations into the relationship between thyroid dysfunction and liver damage have demonstrated that patients suffering from thyroid disorders for more than ten years are more prone to Hepatocellular Carcinoma (6,7).

TNFα is a 17 kDa soluble pro-inflammatory cytokine that mediates the activation of several signaling pathways to regulate processes including inflammation and cellular apoptosis (8-10).

Recent studies have shown that normal thyroid function is necessary to maintain liver metabolism, while thyroid disease has a significant effect on the clinical severity of liver disease (11-13). In contrast to the role of thyroid hormones on liver function, the liver plays an important role in the metabolism of thyroid hormones, being the most critical organ for converting T4 to T3. Serum concentrations of thyroid hormones vary in patients with hepatic disorders, especially liver cirrhosis (14-16).

There are highly contradictory studies about the relationship between thyroid and liver disorders. Some studies have reported that lower thyroid hormone levels could lead to liver damage, including non-alcoholic fatty liver disease and liver fibrosis. Others have demonstrated that hypothyroidism was not correlated with the occurrence of liver injury (17-21).

In the normal physiological state, TNFα is an essential factor for liver cell proliferation by inducing the transcription factor nuclear factor-κB, which has protective functions during liver regeneration (15). However, in pathological conditions such as liver damage, the upregulation of numerous inflammatory cytokines like tumor necrosis factor-α (TNFα) is significantly induced. These factors then lead to the production of inflammation and repair as part of the physiological process (22-24).

Previous studies have all suggested the necessity of clarifying the relationship between thyroid hormones and liver function, but no study has examined the relationship among liver biochemical parameters, thyroid hormones, and TNFα. The aim of the present study was to evaluate liver biochemical parameters and TNFα in hypothyroid patients compared to euthyroid subjects.

Methods

This case-control study was carried out on 45 patients with hypothyroidism and 45 healthy subjects referred to Deziani Hospital in Gorgan, Iran. Consent forms were completed by all participants who met the inclusion criteria. The case and control groups were matched for age and sex to assess the mentioned parameters. Five cc of blood was obtained from individuals in both the case and control groups in tubes without anticoagulant and was immediately centrifuged to collect serum for measuring the levels of all parameters.

All markers were measured using commercial kits. T3, T4, TSH, and total protein (TP) were detected using the ELISA method. Albumin and total protein were measured by spectroscopy and the colorimetric method using fully automated systems. AST, ALT, ALP, and GGT were detected by enzymatic methods. Albumin, total bilirubin (BIL.T), and TP were determined by spectroscopy and the colorimetric method, respectively. TNFα serum levels were evaluated using a commercial kit and the ELISA method according to the manufacturer's instructions.

Statistical analysis was performed using SPSS software, version 18, and the differences in parameters between the case and control groups were compared. The analysis was calculated based on the Shapiro-Wilk test to determine the normal distribution of the data. In addition, other statistical tests, including the Chi-squared test, analysis of variance (ANOVA), Spearman's rho, and Pearson's correlation coefficient, were used to determine the relationships among the study parameters. General correlation analysis (Mann-Whitney U and Spearman's rho) was performed to assess correlations and comparisons between serum TNFα levels and other parameters in the two groups. All results were presented as mean ± standard deviation, and the significance of the data was indicated by a P-value < 0.05.

Results

Results showed a significant difference in the levels of thyroid hormones between the hypothyroid patients and 45 healthy subjects, with the level of TSH in hypothyroid subjects being significantly higher than its level in normal individuals (P < 0.05). T3 and T4 levels in subjects suffering from hypothyroidism were significantly lower than their levels in the control group. The mean values of TSH, T3, and T4 levels were compared in both groups. TNFα in hypothyroid patients was significantly higher than in normal individuals (P = 0.009).

This table shows some biochemical liver markers are different between hypothyroid patients and normal individuals. The levels of all parameters were presented as median, and significance was calculated as P < 0.05 (Table 1).

This table shows the serum levels of TNFα in the case and control groups. Statistical significance was indicated by P-value < 0.05 (Table 2).

Table 1. Comparison of biochemical liver function parameters between case and control

Variables	Number	Case Median (Interquartile)	Control Median (Interquartile)	P-value
GGT (U/L)	45	19 (13.75, 29.05)	22.4 (15.65, 42.95)	0.247
ALB (U/L)	45	5.19 (5.03, 5.34) *	5.28 (5.08, 5.48) *	0.452
T.P (gr/dl)	45	7.7 (6.85, 7.9)	7.9 (7.25, 8.4)	0.093
BIL.T (mg/dl)	45	0.6 (0.4, 0.08)	0.7 (0.5, 0.9)	0.053
ALP (U/L)	45	151 (126, 181)	149 (119.5, 172.5)	0.294
ALT (U/L)	45	21 (18, 25)	22 (17, 28)	0.671
AST (U/L)	45	17 (12, 20)	20 (13.5, 32.5)	0.012

Table 2. TNF-α level in case and control

Variable	Number	Case Median (Interquartile)	Control Median (Inter-quartile)	P-value
TNF-α (ng/ml)	45	37.97 (35.715, 40.225)	36.08 (33.15, 38.13)	0.009

This table shows the correlation between TNFα, thyroid hormones, and TSH. Statistical significance of all results was indicated by P-value < 0.05.

TNFα had an insignificant positive correlation with TSH and a negative correlation with T3 and T4 in healthy subjects (P-value < 0.05) (Table 3).

Table 3. Correlation between TNF-α and thyroid hormones and TSH in hypothyroid patients

Parameters	TNF-α (ng/ml)		
	r	P-value	N
T3	0.009	0.954	45
T4	- 0.079	0.604	45
TSH	0.214	0.158	45

In this table, the correlation coefficient between variables and significance was indicated by P-value < 0.05.

TNFα had an insignificant positive correlation with BIL.T and ALT and a negative correlation with GGT, ALB, TP, ALP, and AST in healthy subjects (P-value < 0.05) (Table 4).

Table 4. Correlation between TSH, thyroid panel hormone and LFTs in hypothyroid patients

Groups / Parameters		GGT (U/L)	ALB (U/L)	T.P (gr/dl)	BIL.T (mg/dl)	AL. P (U/L)	ALT (U/L)	AST (U/L)
T3	r	0.109	0.196	0.280	0.032	0.055	- 0.150	0.085
	P-value	0.477	0.198	0.063	0.834	0.720	0.327	0.580
	N	45	45	45	45	45	45	45
T4	r	0.094	0.139	0.044	- 0.027	0.012	0.193	0.275
	P-value	0.537	0.361	0.776	0.859	0.935	0.204	0.068
	N	45	45	45	45	45	45	45
TSH	r	0.005	- 0.084	- 0.118	- 0.197	- 0.111	0.233	0.043
	P-value	0.972	0.584	0.441	0.194	0.469	0.123	0.780
	N	45	45	45	45	45	45	45

Discussion

This study describes the evaluation of liver biochemical parameters and TNF-alpha in hypothyroid patients compared to euthyroid subjects. Serum levels of liver biochemical parameters and TNF-alpha were measured, and their relationship with thyroid hormones was calculated in patients suffering from hypothyroidism compared to the control group. Our results showed a significant difference in thyroid hormone levels between hypothyroid patients and healthy subjects, with TSH levels in hypothyroid subjects being significantly higher than in normal individuals. We observed that the level of TNFα was significantly higher in hypothyroid patients than in normal individuals. The components of the liver function test, including GGT, ALB, BIL.T, AST, and ALT, were insignificantly higher in hypothyroid subjects than in normal individuals, while ALP levels were lower in people suffering from hypothyroidism than in controls.

Zhang et al. in 2020 evaluated the expressions of IL-17 and TNF-α and their role in prognosis in patients suffering from Hashimoto's disease in combination with thyroid cancer before and after surgery. Both IL-17 and TNFα at the protein and mRNA levels in the serum of HD subjects with thyroid cancer were higher than those of normal individuals (25). Díez et al. demonstrated that the serum level of TNFα was significantly higher in patients with HD than in healthy subjects (26).

Sinha et al. in 2018 investigated the association between hypothyroidism and both fatty liver disease caused by metabolic dysfunction and progressive hepatic fibrosis. They showed that a high level of TSH was associated with progressive hepatic fibrosis in both the hypothyroid and euthyroid states (27). Gou et al. in 2021 carried out a case-control study and revealed that fT4 and fT3 levels were significantly lower in individuals suffering from cirrhosis than in normal subjects (28). Anugwom et al. in 2021 showed that normal liver activity depends on the regulatory function of thyroid function, and reciprocally, the liver has an important effect on the metabolism of thyroid hormones (29). Bebars in 2021 studied the effect of acute and chronic liver disorders on thyroid function in children. They reported that both acute and chronic liver disorders had a positive effect on thyroid function in children, and this relationship was associated with the progression of the disease (14).

Mahaseth et al. in 2022 investigated TNFα as a biochemical inflammatory marker in subjects with hypothyroidism. They demonstrated that the level of TNFα is higher in patients suffering from hypothyroidism than in normal individuals (30). In 2016, Kalita and colleagues studied the role of TSH and thyroid function in the alterations of liver function biochemical markers in hypothyroidism. Their results were compared with normal thyroid control groups. Their findings revealed that the follow-up of liver enzymes in hypothyroid patients is necessary (31). In addition, in another study, Mane and his colleagues in 2011 evaluated serum levels of liver function tests in thyroid disorders. They found that serum ALP activity in hyperthyroidism is higher than in hypothyroidism and the control group. Furthermore, a small elevation in AST and ALT levels was observed in patients, indicating muscle dysfunction, while high levels of ALP in hypothyroidism can suggest a change in bone homeostasis (25,32). Arora et al. in 2009 investigated biochemical markers of liver function affected by thyroid hormones. This study indicated that serum levels of ALT, AST, and albumin had a positive correlation with TSH and a negative correlation in hypothyroid subjects. Hypothyroidism can lead to reversible liver injury (33). Sridevi and colleagues in 2017 examined the role of thyroid hormones in liver function changes. They explained that serum levels of AST, ALT, ALP, and total protein in people with primary hypothyroidism were higher than in the control group (34).

Yadav et al. in 2013 carried out a study on the effect of thyroid hormones on biochemical parameters of liver function in patients with overt and subclinical hypothyroidism. Their findings described that serum levels of ALT, AST, ALP, and total protein were significantly increased in patients with overt hypothyroidism compared to the control group (35).

Conclusion

According to our study, the TNFα level in hypothyroid patients was higher than in healthy subjects, but its correlation with TSH was insignificantly positive. According to our results, TNFα has an insignificantly positive correlation with BIL.T and ALT and a negative correlation with GGT, ALB, TP, ALK.P, and AST in healthy subjects. In addition, AST, ALT, and GGT have a positive correlation with TSH, while ALB, TP, and ALK.P have a negative correlation. The correlations between all variables were not significant.

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Ethical statement

This project is registered with Golestan University of Medical Sciences (Gorgan, Iran) under ethical code IR.GOUMS.REC.1401.568.

Conflicts of interest

All authors declare no conflicts of interest.

Author contributions

Noori Noha Alsharifi wrote the proposal and performed the experimental part of the project. Mahin Gholipur collaborated in designing and writing the proposal. Somayeh Ghorbani performed the analysis of results. Fatima Mohammad zadeh collaborated in sample collection. Safoura Khajeniazi designed the proposal and wrote the manuscript.

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