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Factors predicting abnormal liver function tests induced by Hyperthyroidism

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Abstract: Abnormal liver function tests (LFTs) are often found in patients with hyperthyroidism and delay medication therapy. There are few data demonstrating the factors or biochemical factors contributing to LFT abnormalities. The aim of this study was to investigate predicting factors for abnormal LFTs induced by hyperthyroidism and observe the changes of liver function test after 6-months of antithyroid drug therapy. In this single-institution retrospective cohort study, patients received medical care at a regional hospital between January 2010 and December 2020 with a diagnosis of hyperthyroidism before any medical therapy. Inclusion criteria were a serum thyroid stimulating hormone [TSH] concentration < 0.35 mIU/L and free thyroxine (FT4) concentration> 1.48 ng/dL. The biochemical liver tests assessed were serum aspartate transaminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)and total bilirubin. Serum levels of anti-thyroid peroxidase (anti-TPO) antibody, TSH receptor antibody (TRAb) were also recorded. All patients were divided into abnormal LFTs (group A) and normal LFTs (group B). Cox regression and multiple linear regression were used to determine the factors predicting abnormal LFTs. There were 839 consecutive cases of newly diagnosed and untreated patients enrolled. The overall incidence of any biochemical liver test abnormality within 6 months of hyperthyroidism was 50.8%. The frequencies of ALT, AST, ALP and TBIL abnormalities were 52.7%, 21.5%, 65.6% and 22.2%, respectively. In the univariate analysis, patients in group A had significantly higher FT4 concentration (HR: 1.680, 95% CI: 1.411~1.870, P< 0.001) and TRAb, (HR: 1.590, 95% CI: 1.311~1.770, P< 0.001) and male gender (HR:1.300, 95% CI: 1.204~1.483, P = 0.020) when compared with those in group B. Logistic regression analysis revealed higher FT4 levels, higher TRAb value and male gender to be independent risk predicting factors. The liver function test recovering rate were 80% in ALT, 85% in AST, 72% in ALP and 70% in TBIL after 6 months of antithyroid drug therapy. This study revealed that abnormal liver function tests in patients with new onset of hyperthyroidism were common but mild. Higher serum levels of FT4,TRAb and male gender may be the predicting risk factors of liver function abnormalities. Most abnormal liver function tests were recovery after antithyroid drug therapy.

Keywords: Hyperthyroidism, Abnormal liver function, Free thyroxine, Thyroid-stimulating hormone receptor antibody, Antithyroid drug therapy.

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I. INTRODUCTION

Long-term hyperthyroidism has direct toxicity on the liver, influences liver glycogen and protein decomposition, then induces liver cell degeneration [1-2]. A hypermetabolic state may also increase in organic energy consumption and liver burden, which causes hepatocellular anoxia and free radical damage [3]. Autoimmune mechanisms may play a role in the process of hepatocyte injury and hyperthyroidism induced heart failure may cause hepatic ecchymosis and hepatocyte necrosis [4-5].

Previous studies have shown that both hyperthyroidism and hypothyroidism can alter liver biochemical tests. It was first described in 1874 [6]. Patients may be a carrier of hepatitis virus (hepatitis B virus, hepatitis C virus), with chronic or active or chronic hepatitis, drug-induced liver injury, alcoholic hepatitis, heart failure induced congestive hepatopathy, autoimmune liver disease or fatty liver disease. The previous medical history always alert clinical physician to follow patients' liver function before and after antithyroid drug administration. However, most patients with hyperthyroidism do not have the previous medical history of these disease and apparent clinical symptoms of abnormal liver function, except few patients with serious liver injury and liver failure due to severe thyrotoxicosis or with antithyroid drugs induced liver toxicity [7-9]. The American Thyroid Association also recommends careful initiation of antithyroid drugs if the values of liver function test are above five times of upper limit [10]. Initiating antithyroid drugs in patients with hyperthyroidism complicated with poor liver function may be a challenge for clinical physician. Therefore, liver function tests interpretation in thyroid dysfunction should

be careful in the patients without previous hepatic disease history.

Hyperthyroidism is common to induce liver function test abnormalities in patients with untreated hyperthyroidism. The prevalence ranged from 37% to 78% in previous studies [11-15]. Abnormal liver function tests in patients with hyperthyroidism were mild in Biscoveanus at al's study [13]. Elevated TSH receptor antibody (TRAb) and thyroid function levels may contribute to hepatic dysfunction in patients with hyperthyroidism [12, 16]. In the present study, I excluded non-thyroidal conditions induced liver function abnormality. Thyrotoxicosis includes clinical symptoms and biochemical thyroid function elevation. However, clinical symptoms not completely recorded in the retrospective chart review analysis, so all patients with biochemical thyroid function elevation were enrolled. I retrospectively collected patients with hyperthyroidism to investigate the incidence of hyperthyroidism induced liver function test abnormalities and the risk factors of liver function abnormality induced by hyperthyroidism. I also observed the changes of liver function test after 6-months of antithyroid drug therapy.

II. Results & Discussion

Comparison of Demographic, Clinical and Biochemical Characteristics

Table 1 summarizes the baseline demographic and clinical data of the study patients who had divided into abnormal LFTs (group A, n=426) and normal LFTs (group B, n=413). The female / male patient ratio was 2.8 (in group A, male 26.3%, female 73.7%; in group B, male 26.6%, female 73.4%). There were no apparent differences between group A and group B regarding age, gender distribution, BMI, WBC, T3, TSH, anti-TPO antibody, and anti-Tg antibody. Comparing to normal LFTs group (group B), the patients with abnormal liver function had marginally lower neutrophil (51±24 % vs. 54±30%, p = 0.05) and significantly higher FT4 (4.14 ± 4.12 ng/dl vs. 3.44 ± 3.67 ng/dl, p = 0.004) and TRAb (28.9±19.2 IU/L vs. 19.5±19.0, p =0.001).

Table 1: Comparison of Demographic, Clinical and Biochemical characteristics:

Parameter	Group A (n=426)	Group B (n=413)	p
Gender			0.01
Male	112 (26.3%)	110 (26.6%)	
Female	314 (73.7%)	303 (73.4%)	
Age (years)	38.5±15.1	39.3±14.3	ns
Body weight (Kg)	55.6±16.3	54.1±17.1	ns
BMI (kg/m^2)	22.2±2.2	23.7±3.1	ns
WBC (cells)	7450±1323	7930±1445	ns
Neutrophli (%)	51±24	54±30	0.050
T3 (ng/ml)	4.25±1,90	4.19±2.16	ns
FT4 (ng/dl)	4.14 ± 4.12	3.44 ± 3.67	0.004
TSH (μIU/ml)	0.020 ± 0.014	0.021± 0.015	ns
Anti-TPO (IU/mL)	290.9±161.9	295.7±182.7	ns
Anti-Tg (IU/L)	363.2±156.3	370.0±112.6	ns
TRAb (IU/L)	28.9±19.2	19.5±19.0	0.001

Incidence of biochemical liver test abnormality

Any one abnormality of LFTs including ALT,AST, ALP, and TBIL was 50.8% in all enrolled patients. Because ALP elevations may correlate with increasing in the bone isoenzyme in patients with hyperthyroidism, any one abnormality of ALT, AST,or TBIL after excluding ALP was 40.9%. In this cohort, the prevalence of abnormality ALT, AST, ALP, and TBIL in group A were 52.7% (76±32 U/L; value range:45-132 U/L), 21.5% (56±15 U/L;value range:36-70 U/L), 65.6% (180±48 U/L;value range:131-225 U/L) and 22.2% (1.8±0.4ng/dl; value range:1.3-2.1 ng/dl) respectively. (Figure 1).

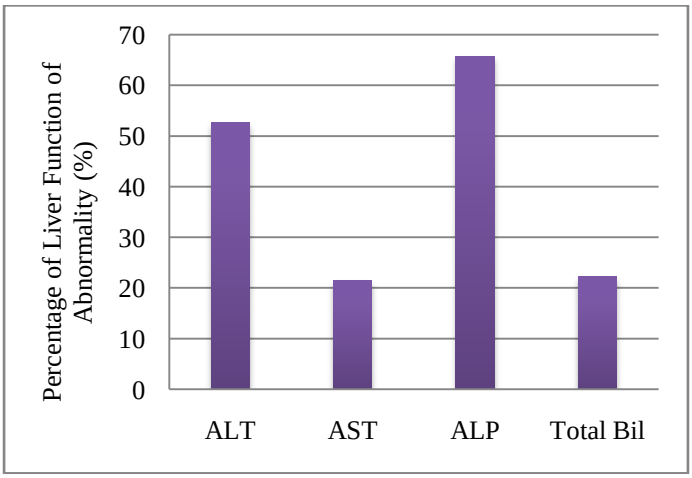

Figure 1: The relative distribution of different LFT abnormalities in patients with abnormal LFT (Group A).

Predictors of liver function test abnormalities induced by hyperthyroidism

To assess the effects of different markers on abnormal LFT, I performed the multivariate Cox

proportional-hazards models analyses. The serum levels of free T4 (HR: 1.680, 95% CI: 1.411~1.870, *P*< 0.001) and TRAb, (HR: 1.590, 95% CI: 1.311~1.770, *P*< 0.001) and male gender (HR:1.300, 95% CI: 1.204~1.483, *P*= 0.020) were significant positive predictors for a biochemical liver abnormality (Table 2).

Table 2: Cox regression model predicting initial liver function abnormality:

Variables	HR	95% CI	P value
Age (years)	0.977	0.888~1.008	0.644
Gender	1.300	1.204~1.483	0.020
BMI (kg/m^2)	1.020	0.9892~1.110	0.757
WBC (cells)	1.050	1.001~1.187	0.190
Neutrophil (%)	1,077	0.790~1.387	0.091
T3 (pmol/l	1.009	0.990~1.022	0.667
FT4 (ng/dL)	1.680	1.411~1.870	<0.001
TSH (Miu/l)	1.100	0.999~1.201	0.085
Anti-TPO (IU/L)	1.100	1.204~1.483	0.090
Anti-Tg (IU/L)	1.010	0997~1.003	0.354
TRAb (IU/L)	1.590	1.311~1.770	<0.001

After excluding ALP, the free T4 (HR:1.624, 95% CI: 1.251~1.702, *P* = 0.002) and TRAb (HR:1.314, 95% CI: 1.192~1.500, *P* = 0.005) were still the apparent predictors for abnormal LFT. Multiple linear regression analyses were also performed to investigate which markers predicted any one abnormal LFT (Table 3). Both free T4 (OR: 1.042 95% (CI: 1.025–1.068, *P* = 0.002) and TRAb, (OR: 1.031, 95% CI: 1.0153–1.054, *P* = 0.004) were still the apparently positive predictors for a biochemical liver abnormality, even after excluding ALP (free T4 with OR: 1.051, *P* = 0.001; TRAb with OR: 1.027, *P* = 0.005).

Table 3: Predictors of Liver Function Test abnormalities induced by Hyperthyroidism:

Parameter	OR	95% CI	P
FT4 concentration (per 1 ng/dL increment	1.042	1.025–1.068	0.002
TRAb value (per 1 IU/L increment)	1.031	1.0153–1.054	0.004

ROC curves were performed to proof the accuracy of FT4 and TRAb in predicting LFT abnormalities. It revealed acceptable discrimination and optimal cutoff value for FT4 was 3.92 ng/dL, at which the sensitivity and specificity were 77.0% and 70.5%, respectively (AUC: 0.760; 95% CI: 0.677–0.811, P<0.001, Figure 2). The optimal cutoff value for TRAb was 22.1IU/L, at which the sensitivity and specificity were 80.21% and 77.4%, respectively and excellent discrimination (AUC: 0.837; 95% CI: 0.684–0.811, P<0.001, Figure 3).

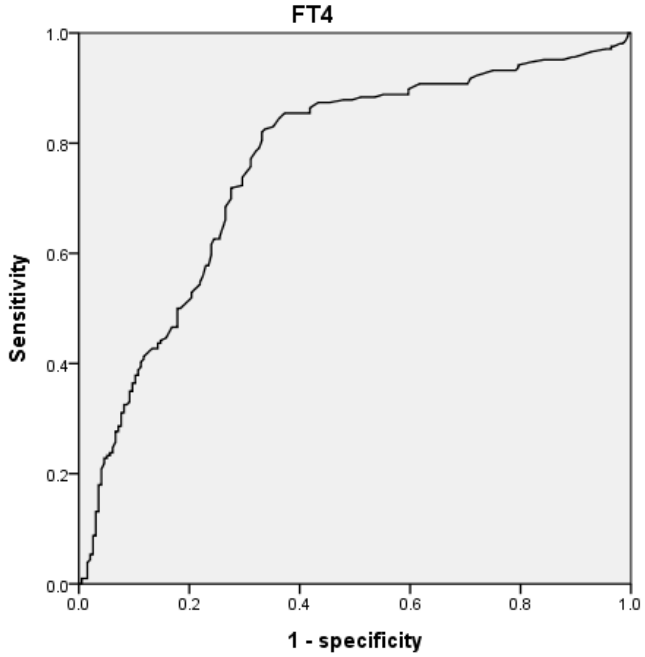

Figure 2: Receiver Operating Characteristic (ROC) curves predictors of LFT abnormalities. AUC: 0.760 (acceptable discrimination).

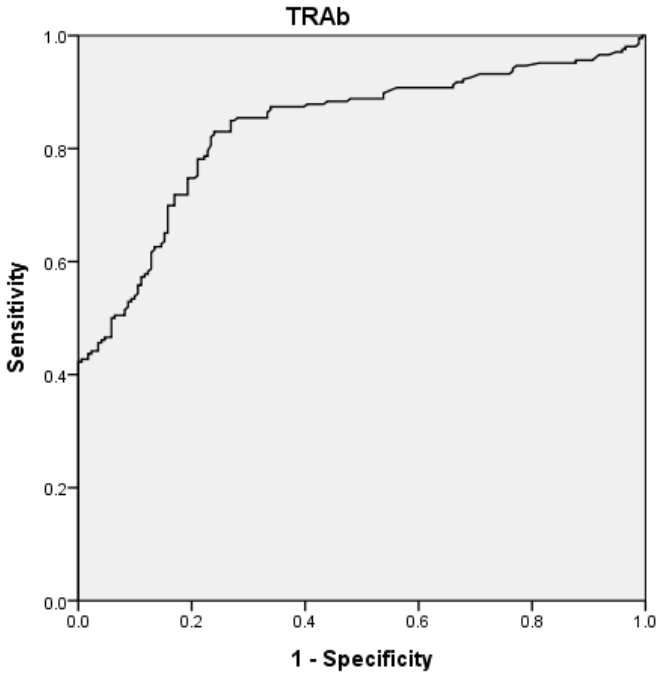

Figure 3: Receiver Operating Characteristic (ROC) curves predictors of TRAb abnormalities. AUC: 0.837 (excellent discrimination).

Recovery rate of abnormal LFT after 6-month medical therapy

In the group A, 402 patients completed treatment more than 6 months and FT4 < 1.48 ng/dL after 6-month medical therapy. ALT, and AST with valuable data were in 373 patients; ALP wasin 343 patients; Total Bil was in366 patients. The relative distribution of different LFT still abnormalities in Group A after 6 months of medication treatment were: ALT:10.6%, AST 3.3%, ALP18.4% and Total Bil6.6%. The liver function test recovering rate were 80% in ALT, 85% in AST, 72% in ALP and 70% in TBIL (figure 4).

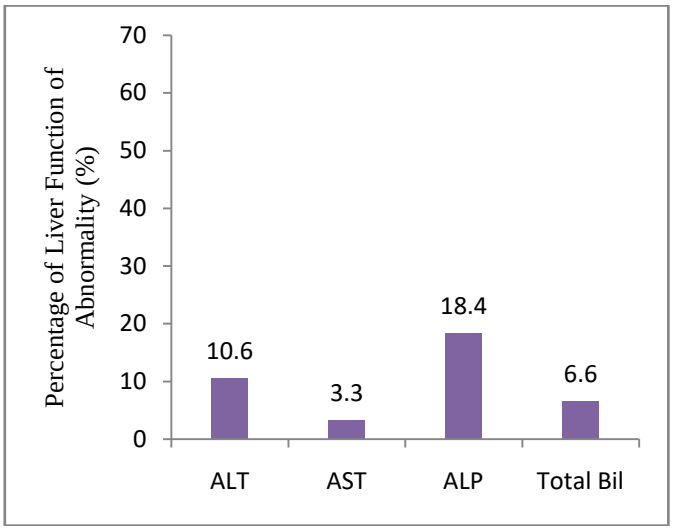

Figure 4: The relative distribution of different LFT abnormalities in Group A after 6 months of medication treatment.

Discussion

The interaction between the liver and thyroid gland could maintain homeostasis in both organs. Thyroid hormones are glucuronidated and sulfated in the hepatocytes and excreted into bile subsequently. Thyroid hormones also influence the metabolism of bilirubin. In this retrospective cohort study of patients at aTaiwan regional hospital, there was a 50.8% incidence of liver biochemical abnormalities at a new diagnosis of hyperthyroidism. A meta-analysis of 25 cohort studies (including 5 prospective and 20 retrospective) also revealed 55% liver biochemical abnormalities in patients with newly diagnosed hyperthyroidism before receiving antithyroid drugs therapy [17]. However, the heterogeneity of studies was significant with extremely high I^2 because differences in inclusion criteria and the assessment of liver function. In this meta-analysis, some studies measured either ALT or AST, but some assessed both. The variable follow-up duration may also result the heterogeneity. In my study, I have included AST, ALT, Total Bil and ALP as the markers of abnormal liver function test. Because the effect of bone turnover activity on ALP levels, I also excluded ALP to allowed me to elucidate the incidence of liver function abnormality due to hyperthyroidism only. After excluding ALP, the free T4 and TRAb were still the apparent predictors for abnormal LFT. The previous study also revealed that ALP may still be abnormal for several months even thyroid function returning to normal range [12]. In my study, 28% of patients had abnormal ALP levels after 6 months of antithyroid drug treatment, which more than other parameters of abnormal liver function tests.

Although measuring baseline liver function test is a weak recommendation at the 2016 guideline of The American Thyroid Association, abnormal liver function make physician hesitant regarding antithyroid drug therapy initiation [10]. After excluding other precipitating factors or concomitant liver disease for abnormal liver function test, hyperthyroidism induced abnormal liver function test is common and with high prevalence in patients with hyperthyroidism. In this study, abnormal liver function test was all less than three times of upper limit of normal range. Niculescu et al. had revealed that at less than two times of upper limit of normal range, antithyroid drugs may be safely administered in hyperthyroid patients [19]. Factors predicting abnormal liver function tests induced by hyperthyroidism should be investigated to decrease delay treatment of hyperthyroidism. Some previous studies have revealed that hepatic dysfunction is more likely to occur in patients with higher thyroid function or TRAb concentrations. Otherwise, the prognosis of abnormal LFT is closely associated with the outcomes of hyperthyroidism after treatment [12,16,20]. In this study, I also found increased risks of abnormal liver function test were observed in those with an initial serum free T4 concentration of ≥3.92 ng/dL, higher titer of TSH receptor antibody ≥ 22.1IU/L and in men. Therefore, even with liver function abnormality, early initiating antithyroid drug therapy may be considered in these patients.

Although, Graves' disease is predominant in female gender. In previous studies, the prevalence of liver biochemical abnormalities affected by gender were discordant [16,18]. In Zhang's study, patients with Graves' disease were enrolled and only FT4 and TRAb but not gender difference to predict abnormal liver function test. In a 14-year retrospective study, including all patients with hyperthyroidism including Grave's disease and hyperactive nodule, liver function abnormality within 6 months of thyrotoxicosis correlated with initial serum TSH concentration <0.02 mIU/L, and male gender [18]. Male gender play an important role to predict abnormal LFT. My study enrolled all patients with hyperthyroidism including patients with hyperactive

nodule, also indicates that male gender is a significant positive predictor for liver function test abnormalities.

After six months of antithyroid drug therapy, more than 70% of all abnormal liver function tests recovered. Although antithyroid drug treatment may induce mild liver function test elevation, antithyroid drugs may be safely administered in hyperthyroid patients with less than two times of upper limit of normal range. [19]. In this study, I found more than 80% abnormal liver function test recovery. Therefore, hyperthyroidism induced liver function abnormality may almost recover after 6 months of antithyroid drug therapy. Further long-term follow-up may increase the recovery rate. Because this study focused on predictors of incident abnormal liver function test before receiving antithyroid drug therapy, I only observed the changes of liver function test after 6 months of antithyroid drug but not long-term time course of resolution of the abnormal liver biochemical tests after treatment, which is the limitation of this study.

III. Conclusions

This retrospective study revealed that abnormal liver function tests in patients with new onset of hyperthyroidism were common but mild. Higher serum levels of FT4 and antibody titers of TRAb and male gender may be the predicting risk factor of liver function abnormalities. Most abnormal liver function tests were recovery in this patient group. Therefore, we may not delay antithyroid drug for patents with hyperthyroidism induced mild liver function abnormality, but excluding other precipitating factors for abnormal liver function test and following liver function test after antithyroid drug administration are also indicated.

IV. Materials & Methods

This is a single-center, hospital-based, retrospective chart review analysis. No investigational or interventional medication was provided. The variables of all patient were recorded in electronic medical charts. The chart numbers were included by ICD10 codes for hyperthyroidism: E05, E05.0, E05.00, E05.1, E05.10, E05.11, E05.2, E05.20, E05.21, E05.3, E05.30, E05.31, E05.4, E05.40, E05.41, E05.8, E05.80, E05.81, E05.9, E05.90, E05.91.

Subjects

During index period from January 2010 to December 2020, we retrospectively reviewed 839 patients who were newly diagnosed with hyperthyroidism including Graves' disease, thyrotoxicosis, or hyperactive nodule (222 males, 617 females; age 39.0 ±14.5 years). Hyperthyroidism diagnosed including increased thyroid hormones (free thyroxine (FT4) > 1.48 ng/dL or total triiodothyronine (T3)>1.59 ng/ml) and decreased thyroid-stimulating hormone (TSH)< 0.35 mIU/L. Patients with positive hepatitis B surface antigen, C virus antibodies, drug-induced liver injury, alcoholic hepatitis (defined by 5 characteristics of the American Medical Association), heart failure induced congestive hepatopathy, autoimmune liver disease or fatty liver disease were excluded. Rather than investigating the effect of thyroid medications on liver biochemical patterns, patients who received anti-thyroid drug therapy (propylthiouracil or methimazole), or amiodarone for cardiac disease before enrolled were also exclude. Patients who had radioiodine131 therapy or partial thyroidectomy within 1 year remaining as potential confounding variables in this study were also excluded from this patient cohort. This study was conducted per the guidelines of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Pao Chien Medical Foundation on 2019/11/07. This is a retrospective study, so the need for informed consent was waived by the IRB.

Data collection and grouping

Gender, age, body weight and body height were collected. Liver function test including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (TBIL) were available within 6 months before hyperthyroidism noted. Abnormal liver function test was defined as: AST > 38 U/L, ALT > 44 U/L, ALP >130 U/L, or total bilirubin > 1.2 ng/dl. White blood cell, neutrophil count, serum levels of TSH, total T3, and free T4, titers of TSH receptor antibody (TRAb), anti-thyroglobulin (anti-Tg) antibody, and anti-thyroid peroxidase (anti TPO) antibody were also recorded. Depending on at least one liver function test (LFT) abnormality, all patients divided into abnormal LFTs (group A) and normal LFTs (group B).

Parameter assessments

Liver function indexes were measured using an autoanalyzer (Hitachi 7250 Special; Hitachi, Tokyo, Japan).Serum levels of thyroid function tests were measured by chemiluminescence immunoassays (ADVIA CENTAUR XP SIEMENS AG). TRAB and anti-TPO antibody were detected by enzyme-linked immunosorbent assay (MEDIPAN Germany).

Statistical analysis

The variables were summarized descriptively as mean ± SD; categorical variables are presented as number (%). Differences in clinical and biochemical characteristics between groups were tested using an unpaired *t*-test. Cox regression and multiple linear regression were used to determine the factors predicting

abnormal LFTs. Receiver operating characteristic curve (ROC) and area under curve (AUC) were used to verify the accuracy for the prediction. A probability value of <0.05 was considered significant. All statistical operations were performed using SPSS for Windows (Version 11.5; SPSS, Chicago, IL).

REFERENCES

1. De Campos Mazo, Daniel Ferraz, et al. "Clinical spectrum and therapeutic approach to hepatocellular injury in patients with hyperthyroidism." *Clinical and experimental gastroenterology* 6 (2013): 9.
2. Eshraghian, Ahad, and Alireza Hamidian Jahromi. "Non-alcoholic fatty liver disease and thyroid dysfunction: a systematic review." *World journal of gastroenterology: WJG* 20.25 (2014): 8102.
3. Ashkar, Fuad, et al. "Liver disease in hyperthyroidism." *Southern medical journal* 64.4 (1971): 462-465.
4. Khemichian, Saro, and Tse-Ling Fong. "Hepatic dysfunction in hyperthyroidism." *Gastroenterology & hepatology* 7.5 (2011): 337.
5. Cui, Binglin, et al. "Autoimmune hepatitis associated with Graves' disease." *Internal medicine* 42.4 (2003): 331-335.
6. Habershon, S. O. "Exophthalmic goiter, heart disease, jaundice, death." *Lancet* 1 (1874): 510.
7. Choudhary, Adil M., and Ingram Roberts. "Thyroid storm presenting with liver failure." *Journal of clinical gastroenterology* 29.4 (1999): 318-321.
8. Regelmann, Molly O., et al. "Graves' disease presenting with severe cholestasis." *Thyroid* 22.4 (2012): 437-439.
9. Bhuyan, Ashok Krishna, et al. "Grave's disease with severe hepatic dysfunction: a diagnostic and therapeutic challenge." *Case reports in medicine* (2014).:790458.
10. Ross, Douglas S., et al. "2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis." *Thyroid* 26.10 (2016): 1343-1421.
11. Kubota, Sumihisa, et al. "Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis." *Thyroid* 18.3 (2008): 283-287.
12. He, K., et al. "Hepatic dysfunction related to thyrotropin receptor antibody in patients with Graves' disease." *Experimental and Clinical Endocrinology & Diabetes* 122.06 (2014): 368-372.
13. Biscoveanu, Michaela, and Stefan Hasinski. "Abnormal results of liver function tests in patients with Graves' disease." *Endocrine Practice* 6.5 (2000): 367-369.
14. Aydemir, S., et al. "Effect of hyperthyroidism and propylthiouracil treatment on liver biochemical tests." *International journal of clinical practice* 59.11 (2005): 1304-1308.
15. Gürlek, Alper, Veli Çobankara, and Miyase Bayraktar. "Liver tests in hyperthyroidism: effect of antithyroid therapy." *Journal of clinical gastroenterology* 24.3 (1997): 180-183.
16. Zhang, Ruiguo, et al. "Factors predicting abnormal liver function tests induced by Graves' disease alone: a retrospective cohort study." *Medicine* 94.19 (2015).e839
17. Lee, Sun Y. "Liver Enzymes Are Commonly Elevated in Untreated Hyperthyroidism and Improve after Correction of the Hyperthyroidism." *Clinical Thyroidology* 33.2 (2021): 70-73.
18. Lin, Tiffany Y., et al. "Incidence of abnormal liver biochemical tests in hyperthyroidism." *Clinical endocrinology* 86.5 (2017): 755-759.
19. Niculescu, Dan Alexandru, et al. "Serial changes of liver function tests before and during methimazole treatment in thyrotoxic patients." *Endocrine Practice* 22.8 (2016): 974-979.
20. Wang, Renfei, et al. "Risk factors of hepatic dysfunction in patients with Graves' hyperthyroidism and the efficacy of 131iodine treatment." *Medicine* 96.5 (2017) e6035.