Abnormal Liver Function Test in Graves' Disease: A Prospective Study of Comparison between the Hyperthyroid State and the Euthyroid State

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Background: *Abnormal liver function test is sometimes seen in hyperthyroidism but no study had been carried out to compare liver function test in the hyperthyroid state and the euthyroid state.*
Objective: *This study aimed to find the prevalence of abnormal liver function test in Graves' disease and compare liver function test result in the hyperthyroid state with the euthyroid state.*
Material and Method: *This is a prospective study of 112 patients who had Graves' disease. These patients were new cases or recurrent cases of Graves' disease whose medication had been discontinue for more than 3 months. We followed-up 86 patients received treatment with antithyroid drugs up to the euthyroid state and compared liver function test at diagnosis and in the euthyroid state.*
Results: *An abnormal level of serum globulin was the most abnormal liver function test results in Graves' disease at 30.4%, followed by an abnormal level of serum alkaline phosphatase of 25.0% and gamma-glutamyl transpeptidase (GGT) of 23.3%. The trend of GGT levels returned to normal but there was an increased in serum alkaline phosphatase after treatment until the euthyroid state in the follow-up group.*
Conclusion: *Abnormal liver function tests in Graves' disease are common, after treatment until the euthyroid state, experienced an improvement in GGT level but also an increase in serum alkaline phosphatase level.*

Keywords: *Abnormal liver function test, Graves' disease, Hyperthyroid, Euthyroid*

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Graves' disease is a common form of endocrine disease. The symptoms of the patients are palpitation, weight loss, tremor, sweating and diarrhea. Some studies have found that there were abnormal results of liver function test in Graves' disease. The mechanisms are the direct effects of the thyroid hormone on the liver, organ damage such as congestive heart failure, autoimmune hepatitis associated with Graves' disease[1] and the effect of antithyroid drugs[2,3]. The result of autopsies in untreated cases of Graves' disease show inflammation, steatosis, necrosis and cirrhosis[4]. There is vacuolization of hepatocytes, ballone degeneration, portal inflammation from microscopic examination and hyperplasia of the smooth endoplasmic reticulum, as well as increase size and number of mitochondria from electron microscopic examination[5]. The effects of the thyroid hormone on liver are increased oxygen consumption by the liver[6] caused by increase Na-K ATPase activity and increase metabolism with no corresponding increase in blood flow to the liver[7]. Relative hypoxia may cause central necrosis of the liver in cases of thyroid storm. In Biscoveanu's study of 30 cases of Graves' disease, 37.0% of cases had at least one abnormal liver function test, increased serum alkaline phosphatase of 33.0%, alanine aminotransferase (ALT) of 17.0%, aspartate aminotransferase (AST) of 26.0%, gamma-glutamyl transpeptidase (GGT) in 6 from 25 cases and bilirubin in 2 from 24 cases[8]. But the change of liver function after the euthyroid state was not followed-up in this study.

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Material and Method

Research question

The study was approved by the research

ethics committee of the Rajavithi Hospital. The primary research question is to find the prevalence of abnormal liver function test in cases of Graves' disease. The second research question is to compare liver function test between the hyperthyroid state and the euthyroid state.

Study design

This was a prospective analytical study. The samples in this study were outpatient cases of Graves' disease at Rajavithi Hospital. The patients were new cases of Graves' disease or recurrent cases whose antithyroid drugs had been discontinued for more than 3 months in order to exclude the effect of antithyroid drugs on the liver.

Inclusion criteria were new cases or recurrent cases of Graves' disease after discontinuation of antithyroid drugs for more than 3 months. Exclusion criteria were patients who had: 1 a history of underlying liver disease; 2 thyroid crisis; 3 a history of allergy to antithyroid drugs; 4 pregnancy or lactation.

These patients with Graves' disease were treated with antithyroid drugs. The choice of the type of antithyroid drugs (either PTU or methimazole) depended on the primary physician. All of these patients had a thyroid function test and liver function test at diagnosis and most cases had follow-up treatment up to the euthyroid state. We had repeated the thyroid function test to confirm the euthyroid state and also repeated the liver function test. The definition of the euthyroid state was normal free or total thyroid hormone. The liver function tests that we used to measured albumin, globulin, AST, ALT, serum alkaline phosphatase and GGT.

Statistical analysis

Descriptive results of continuous variables were expressed as mean, range and standard deviation (SD). Statistical analysis was performed using Chi-square or Fisher exact tests to compare the number of cases of abnormal liver function test and a paired t-test to compare liver function test between the hyperthyroid state and the euthyroid state. The p-value of less than 0.05 was set for statistically significant.

Results

There were 112 patients with Graves' disease in this study. There was only 1 case of Graves' disease in this study that had clinical jaundice from physical examination, the result of liver function test showed cholestasis and clinical jaundice was improvement after treatment until the euthyroid state. The results of the baseline characteristic of the patients are shown in Table 1.

This study found abnormal liver function test results as follows: increased total bilirubin of 5.4%, direct bilirubin of 1.8%, AST of 11.6%, ALT of 11.6%, serum alkaline phosphatase of 25.0%, GGT of 23.2%, globulin of 30.4% and decreased serum albumin of 8.9%. There were 79 patients who were new cases and 33 patients who were recurrent cases. Comparing the liver function test results in the new cases and the recurrent cases, the percentage of abnormal liver function test results in the new cases was lower than in recurrent cases with regard to AST and ALT but there were not statistically significant ($p > 0.05$). The results of abnormal serum alkaline phosphatase and GGT are shown in Fig. 1.

Fig. 1 shows that there were 28 patients with increased serum alkaline phosphatase but 14 patients had both increased serum alkaline phosphatase and GGT. It is possible that the source of abnormal serum alkaline phosphatase is 50.0% from the liver and 50.0% from bone.

There were 86 patients with Graves' disease who had followed treatment up to the euthyroid state. The durations of hyperthyroidism until the euthyroid state were reached varied between 4 weeks to 42 weeks and the mean duration was 16 weeks. We compared liver function test results in this group between the hyperthyroid state and the euthyroid state; the results are shown in Table 2.

From Table 2, it is clear that there were significant improvements in liver function test in albumin, AST, ALT, GGT but also an increase in serum alkaline phosphatase. There was no significant change in total bilirubin, direct bilirubin or serum globulin.

The number of cases of abnormal liver function test results in the hyperthyroid state and the euthyroid state are shown in Table 3.

Table 3 shows no statistical significance in the number of cases of abnormality in AST and ALT but a significant decrease in the number of cases of abnormal GGT ($p = 0.001$) and a significant increase in the number of cases of abnormal serum alkaline phosphatase ($p < 0.001$). The number of cases of abnormal serum alkaline phosphatase and GGT in the hyperthyroid state and the number in the euthyroid state are shown in Fig. 2.

Fig. 2 shows that the number of cases of isolated increased serum alkaline phosphatase rose from 10 to 27 but the number of cases of isolated elevated

Table 1. Baseline characteristic of the patients (n = 112)

Characters	Recurrent (n = 33)	New cases (n = 79)	Total (n = 112)
Sex			
Male	4 (12.2%)	5 (6.3%)	9 (8.0%)
Female	29 (87.8%)	74 (93.7%)	103 (92.0%)
Result of liver function test			
Albumin			
Mean ± SD	4.07 ± 0.36	3.90 ± 0.46	3.94 ± 0.43
Abnormal	2 (6.1%)	8 (10.1%)	10 (8.9%)
Globulin			
Mean ± SD	3.45 ± 0.53	3.27 ± 0.56	3.31 ± 0.55
Abnormal	13 (33.4%)	21 (26.6%)	34 (30.4%)
Total bilirubin			
Mean ± SD	0.84 ± 1.20	0.68 ± 0.54	0.72 ± 0.41
Abnormal	2 (6.1%)	4 (5.1%)	6 (5.4%)
Direct bilirubin			
Mean ± SD	0.19 ± 0.58	0.14 ± 0.32	0.16 ± 0.79
Abnormal	1 (3.0%)	1 (1.3%)	2 (1.8%)
AST			
Mean ± SD	23.82 ± 10.56	28.14 ± 14.06	26.40 ± 13.20
Abnormal	1 (3.0%)	12 (15.2%)	13 (11.6%)
ALT			
Mean ± SD	19.03 ± 15.81	22.42 ± 18.32	21.25 ± 17.59
Abnormal	2 (6.1%)	11 (13.0%)	13 (11.6%)
Alkaline phosphatase			
Mean ± SD	96.88 ± 57.32	105.77 ± 53.08	102.73 ± 54.17
Abnormal	8 (24.2%)	20 (25.3%)	28 (25.0%)
GGT			
Mean ± SD	34.76 ± 24.94	44.38 ± 36.36	41.14 ± 33.38
Abnormal	6 (18.2%)	20 (25.3%)	26 (23.2%)

Values were represented as n (%), Mean ± SD, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, GGT = Gamma-glutamyl transpeptidase

GGT decreased from 9 to 6; the number of cases of both elevated GGT and alkaline phosphatase decreased from 10 to 4.

Comparing the effects of antithyroid drugs (PTU and methimazole) on liver function test results, there was no statistical significance ($p > 0.05$) and the details are shown in Table 4.

Discussion

Comparing past studies[9,10], the incidence of hyperbilirubinemia in thyrotoxicosis in patients with congestive heart failure was 79.7%, but only 33.0% in patients who did not have congestive heart failure. In this study, however, the incidence of hyperbilirulinemia was only 5.4% because the people studied were outpatients and less severe cases; furthermore, there were no cases of congestive heart failure and cases of thyroid storm were excluded. Liver function test after treatment up to the euthyroid state showed significant improvement in AST, ALT, GGT but also an increase in the cases of increased serum alkaline phosphatase. In normal, serum alkaline phosphatase is produced from the liver and bone and the elevation of GGT confirms that increased serum alkaline phosphatase is caused by the liver. However, data from the group that had elevation of serum alkaline phosphatase and normal GGT may suggest that the source of serum alkaline phosphatase is bone. Cooper's study of the alkaline phosphatase isoenzyme pattern in hyperthyroidism showed that increased serum alkaline phosphatase was caused by bone and the liver in almost equal proportion. In 50.0% of cases, there was increased serum alkaline phosphatase alone and in the other 50.0% of cases, there was both increased serum alkaline phosphatase and GGT in hyperthyroid state[11]. The cause of increased serum alkaline phosphatase from

Table 2. Liver function test in the hyperthyroid state and the euthyroid state (n = 86)

Liver function test	Hyperthyroidism state	Euthyroid state	p-value
Total bilirubin	0.74 ± 0.87	0.60 ± 0.29	0.130
Direct bilirubin	0.17 ± 0.47	0.08 ± 0.60	0.090
Albumin	3.94 ± 0.46	4.06 ± 0.51	0.040
Globulin	3.33 ± 0.57	3.35 ± 0.55	0.770
AST	26.25 ± 13.42	20.38 ± 7.49	< 0.001
ALT	20.38 ± 18.31	14.18 ± 8.98	0.001
Alkaline phosphatase	99.60 ± 54.26	117.00 ± 63.78	0.001
GGT	39.02 ± 30.11	27.61 ± 23.15	< 0.001

Values were represented as Mean ± SD, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, GGT = Gamma-glutamyl transpeptidase

Table 3. Number cases of abnormal liver function test in 86 cases of Graves' disease in the hyperthyroid state and the euthyroid state

Liver function test	Number cases of abnormality in Hyperthyroidism	Number cases of abnormality in the euthyroid state
Total bilirubin	4 (4.7%)	4 (4.7%)
Direct bilirubin	2 (2.3%)	0 (0.0%)
Albumin	12 (14%)	13 (15.1%)
Globulin	28 (32.6%)	33 (38.4%)
AST	9 (10.5%)	2 (2.3%)
ALT	8 (9.3%)	1 (1.2%)
Alkaline phosphatase*	20 (23.3%)	31 (36%)
GGT**	19 (22.1%)	10 (11.6%)

Values were represented as n (%), *p < 0.001 , **p = 0.001

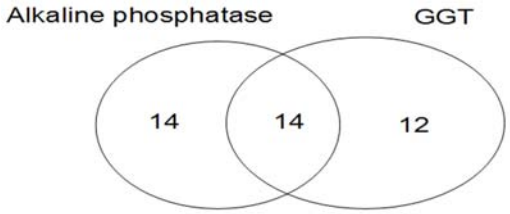

Fig. 1 Number of cases who had abnormal serum alkaline phosphatase or GGT in 112 cases of Graves' disease in the hyperthyroid state.

the liver is cholestasis, as confirmed by liver pathology[12] and the cause of increased bone alkaline phosphatase is the effect of stimulation of osteoblasts. Osteoblastic activity varies according to the severity of hyperthyroidism and serum alkaline phosphatase varies according to T3 levels; there will be increased serum alkaline phosphatase in 3-5 months and it will return to normal within 20 months of receiving treatment[13].

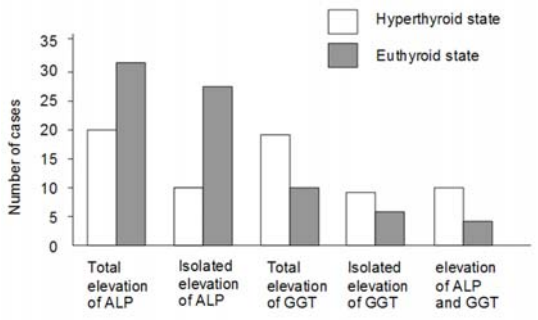

Fig. 2 The number of cases of abnormal serum alkaline phosphatase and GGT in the hyperthyroid state and the number in the euthyroid state

With regard to the effect of different types of antithyroid drugs on liver function test, in this study no difference was found between PTU and methimazole. In other studies, the incidence of liver toxicity caused by PTU was about 0.1-0.2%[14,15] and the figure for methimazole was very low although some fatality have

Table 4. Number of cases of abnormal Liver function test in the groups treated with PTU and methimazole.

Liver function test	PTU (n = 20)		MMI (n = 66)	
	Hyperthyroidism n (%)	Euthyroidism n (%)	Hyperthyroidism n (%)	Euthyroidism n (%)
Total bilirubin	2 (1.0%)	0 (0.0%)	2 (3.0%)	0 (0.0%)
Direct bilirubin	1 (5.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)
Albumin	5 (25.0%)	5 (25.0%)	7 (10.6%)	8 (12.1%)
Globulin	7 (35.0%)	10 (50.0%)	21 (31.8%)	23 (34.8%)
AST	3 (15.0%)	1 (5.0%)	6 (9.0%)	1 (1.5%)
ALT	4 (20.0%)	0 (0.0%)	4 (6.0%)	1 (1.5%)
Alkaline phosphatase	3 (15.0%)	5 (25.0%)	17 (25.8%)	26 (39.3%)
GGT	5 (25.0%)	2 (10.0%)	14 (21.2%)	8 (12.1%)

Values were represented as n (%), AST = Aspartate aminotransferase, AST = Aspartate aminotransferase, GGT = Gamma-glutamyl transpeptidase, PTU = Propylthiouracil

been reported[3]. The result of this study showed that there was no liver toxicity after treatment with antithyroid drugs. This might due to the small sample sizes and the fact that it was not the objective of this study.

This was a prospective study that compared liver function test results between the hyperthyroid state and the euthyroid state. There were three limitations of the study, first the study could not follow-up all cases but there were no difference of the baseline liver function test in both groups. Secondly, follow-up of liver function tests were done when it was confirmed that the patients were in the euthyroid state but no serial liver function was done; consequently, it was not possible to establish when the elevated serum alkaline phosphatase would return to normal. Thirdly, there was no comparison of liver function tests in normal subjects with the hyperthyroid patients because the difference in liver function test at the baseline in hyperthyroid patients might caused by other factors such as fatty liver or other liver disease.

Acknowledgements

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Potential conflicts of interest

Rajavithi reserch fund.

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ความผิดปกติของการทำงานตับในผู้ป่วย Graves' disease การศึกษาไปข้างหน้า เพื่อเปรียบเทียบภาวะต่อมไทรอยด์เป็นพิษและปกติ

วีระศักดิ์ ศรินนภากร, พรชนก นภเวชวิชญ์, ทองคำ สุนทรเทพวรากุล, ชัยชาญ ดีโรจนวงศ์, สุพรรณี เงางามรัตน์

***ภูมิหลัง**: ความผิดปกติของการทำงานตับพบได้บางรายในผู้ป่วยไทรอยด์เป็นพิษแต่ไม่เคยมีการศึกษาการทำงานตับเปรียบเทียบช่วงไทรอยด์เป็นพิษและไทรอยด์ทำงานปกติ*

***วัตถุประสงค์**: จุดมุ่งหมายของการศึกษานี้เพื่อหาความชุกของความผิดปกติของการทำงานตับในผู้ป่วยไทรอยด์เป็นพิษและเปรียบเทียบการทำงานตับในช่วงไทรอยด์เป็นพิษและไทรอยด์ทำงานปกติ*

***วัสดุและวิธีการ**: การศึกษานี้เป็นการศึกษาแบบ prospective study โดยได้ศึกษาการทำงานตับในผู้ป่วยไทรอยด์เป็นพิษชนิด Graves' disease 112 ราย โดยเป็นผู้ป่วยใหม่หรือถ้าเป็นผู้ป่วยที่กำเริบซ้ำหลังจากหยุดยามากกว่า 3 เดือน ได้ติดตามผู้ป่วย 86 ราย ที่ได้รับการรักษาด้วยยาต้านไทรอยด์จนการทำงานปกติ และเปรียบเทียบกับผลการทำงานตับขณะเริ่มวินิจฉัยและช่วงไทรอยด์ทำงานปกติ*

***ผลการศึกษา**: ความผิดปกติของตับในผู้ป่วย Graves' disease ที่พบบ่อยที่สุดคือความผิดปกติของ serum globulin 30.4% ตามด้วยค่า serum alkaline phosphatase 25% และ GGT 23.2% ตามลำดับในกลุ่มที่ได้รับติดตามการรักษาผู้ป่วยจนอยู่ในภาวะไทรอยด์ทำงานปกติจะมีแนวโน้มค่า GGT กลับสู่ปกติขณะที่จะมีการเพิ่มขึ้นของค่า serum alkaline phosphatase*

***สรุป**: ความผิดปกติของตับพบได้บ่อยในผู้ป่วย Graves' disease หลังการรักษาจนกระทั่งการทำงานของไทรอยด์ปกติจะมีการเปลี่ยนแปลงของค่า GGT ที่ดีขึ้นแต่มีการเพิ่มขึ้นของค่า serum alkaline phosphatase*