Serial Changes in Liver Function Tests in Patients with Thyrotoxicosis Induced by Graves’ Disease and Painless Thyroiditis

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Context: When the liver function tests are aggravated after starting antithyroid drugs (ATDs) in Graves’ hyperthyroidism, discontinuation of ATDs is generally considered. However, a question arises whether such aggravation constitutes an adverse effect of the drugs or not.

Objective: The aim of this study was to clarify the influence of thyrotoxicosis on liver function tests, comparing the results with those in thyrotoxicosis induced by painless thyroiditis.

Design: We prospectively studied liver biochemical tests in 30 patients with Graves’ disease and in 27 patients with painless thyroiditis.

Main outcomes: Twenty-three (76.7%) untreated Graves’ disease patients and 14 (51.9%) untreated painless thyroiditis patients were found to have at least one liver function test abnormality. One month after starting ATD therapy in patients with Graves’ disease, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations from initial values were observed in 16 (53.3%). Similar elevations of AST and ALT from initial values at 1 month were observed in 10 (37.0%) and 7 (25.9%) patients with painless thyroiditis, respectively. Alkaline phosphatase (ALP) increased gradually after starting ATD therapy and maintained an elevated value for 3–5 months in Graves’ disease. In painless thyroiditis, ALP also increased gradually, similarly to that in Graves’ disease, but changes were mild. Elevation of ALT after 1 month of ATD therapy in Graves’ disease was significantly higher in patients whose estimated disease duration was 6 months or more compared to those with duration of less than 6 months. Elevated AST and ALT at 1 month after ATD therapy decreased to normal ranges, even though patients were receiving the same ATDs in Graves’ disease.

Conclusion: Similar serial changes in liver function tests in both Graves’ disease and painless thyroiditis strongly suggest that increases of AST and ALT after starting ATD therapy may not be due to ATD side effects but may be induced by changes in thyroid function.

Introduction

It is well known that liver biochemical abnormalities have been shown in untreated patients with thyrotoxicosis (1–3). These abnormalities are thought to be induced by the metabolic effects of excess thyroid hormone and hepatic tissue hypoxia, which occur as a result of enhanced splanchnic oxygen consumption and an increase in the hepatic requirement for oxygen (1,4). In Graves’ disease, abnormalities of liver function tests are not only observed in the untreated condition but also frequently found after starting antithyroid drugs (ATDs). Liver biochemical abnormalities after propylthiouracil (PTU) administration are thought to represent PTU-induced liver injury, and previous reports suggest that treatment should be stopped in these patients with “PTU hepatitis” (5–10). On the other hand, several studies reported that the discontinuation of PTU is not necessarily required unless overt hepatitis develops, because transient mild asymptomatic “PTU hepatitis” frequently occurs in patients with PTU-treated Graves’ disease (11–13).

To clarify the influence of thyrotoxicosis it may be helpful to compare the liver function tests in thyrotoxicosis induced by painless thyroiditis, since thyrotoxicosis spontaneously resolves without any medication (14). However, there have been no reports on the serial changes in liver function tests in patients with painless thyroiditis. In the present work, we
prospectively studied liver biochemical tests before and after starting ATD therapy in patients with Graves' disease and in patients with painless thyroiditis to compare the parameter changes in both diseases.

Materials and Methods

Subjects

We prospectively recruited 30 patients with newly diagnosed Graves' disease and 27 patients with painless thyroiditis in 2006. Graves' hyperthyroidism was diagnosed on the basis of diffuse goiter, thyrotoxicosis, elevated 3- or 24-hour radioiodine uptake (RAIU) of the thyroid, and/or positive anti-thyroid-stimulating hormone (anti-TSH) receptor antibodies. Painless thyroiditis is defined by thyrotoxicosis, nontender goiter, and markedly decreased RAIU of the thyroid. Patients who had evidence of cardiovascular complications or past histories of hepatobiliary disorder, and excess alcohol consumption were excluded from this study. Patients who had changed from methimazole (MMI) to PTU or vice versa during treatment were excluded, and all patients received the same drug during the study period. Patients who were positive for hepatitis B surface antigen and antihepatitis C virus antibodies were also excluded. We selected 35 healthy age- and sex-matched persons as normal controls. The durations of Graves' disease before starting ATD therapy were estimated from the clinical histories of patients. Informed consent was obtained from every subject. Protocols were approved by the ethics committee of our hospital.

Treatment

All patients with Graves' disease were treated with ATDs. Initially, 15-30 mg/day of MMI or 100-300 mg/day of PTU was administered, and tapered gradually to maintain a euthyroid state. MMI was used for 25 patients, and PTU was used for 5 patients. Patients with painless thyroiditis were observed without medication.

Follow-up

We measured serum levels of albumin (ALB), total bilirubin (BIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gammaglutamyl transpeptidase (γ-GTP), lactic dehydrogenase (LDH), creatinine phosphokinase (CK), TSH, free thyroxine (FT4), and free triiodothyronine (FT3) before and 1, 2, and 3-5 months after starting ATD therapy in patients with Graves' disease. Identical parameters were measured at the time of diagnosis and 1, 2, and 3-5 months after the initial visit in untreated thyrotoxic patients with painless thyroiditis. CK levels were measured to clarify the effect of the hypermetabolic state on serum enzymes and to compare changes in hepatic enzymes.

Laboratory methods

Serum levels of ALB (normal range: 3.8–5.2 g/dL), BIL (normal range: 0.2–1.0 mg/dL), AST (normal range: 5–40 IU/L), ALT (normal range: 5–35 IU/L), ALP (normal range: 105–340 IU/L), γ-GTP (normal range: 0–40 IU/L), LDH (normal range: 105–215 IU/L), and CK (normal range: 50–180 IU/L) were measured using a routine automated analyzer (Hitachi 7170S Clinical Analyzer, Tokyo, Japan). Hepatitis B surface antigen and antihepatitis C virus antibodies were assayed using immunoassay kits (ARCHITECT HBsAg QT [Abbott Japan, Tokyo, Japan] and Ortho HCVAb IRMA test 3 [Ortho-Clinical Diagnostics, Tokyo, Japan], respectively). TSH, FT4, and FT3 concentrations were measured by chemiluminescent immunoassays (ARCHITECT TSH, ARCHITECT FREE T4, and ARCHITECT FREE T3 [Abbott Japan], respectively). Anti-TSH receptor antibodies were measured as TSH-binding inhibitor immunoglobulin (TBI) by a TSH receptor antibody ELISA assay kit (Cosmic, Tokyo, Japan).

Statistics

The baseline characteristics and results (serum levels of AST, ALT, and ALP) between each patient and control group were compared using the Mann–Whitney U-test. Correlation analyses were performed using the Spearman's rank correlation test. Differences were considered to be significant at $p < 0.05$.

Results

The initial laboratory results of all cases are summarized in Table 1. Serial changes in values of serum AST, ALT, and ALP in the patients with Graves' disease and painless thyroiditis are shown in Table 2. Individual changes in values of serum AST, ALT, and ALP in the patients with Graves’ disease and painless thyroiditis are also shown in Figure 1.

Graves' disease

The initial mean values of ALT, ALP, and γ-GTP of patients were significantly higher than those of normal controls, but AST was not. On the other hand, the initial mean values of ALB, BIL, LDH, and CK of patients were significantly lower than those of normal controls. Serum AST, ALT, γ-GTP, and ALP elevations above the upper limit of the normal range were observed in 2 (6.6%), 8 (26.7%), 8 (26.7%), and 18 (60.0%) patients, respectively. Twenty-three (76.7%) untreated pa-

| Table 1. Liver Function Tests in Untreated Patients with Graves’ Disease and Painless Thyroiditis and Healthy Controls |
|-----------------|----------------|----------------|
| No. of patients | 30             | 27             | 35             |
| Female/male     | 25/5           | 24/3           | 31/4           |
| Age (years)     | 40.3 ± 13.6    | 38.8 ± 17.3    | 43.7 ± 12.2    |
| ALB (g/dL)      | 4.1 ± 0.2b     | 4.1 ± 0.3a     | 4.7 ± 3.0      |
| BIL (mg/dL)     | 0.5 ± 0.3b     | 0.6 ± 0.4      | 0.7 ± 0.3      |
| AST IU/L        | 23.7 ± 9.5a    | 30.6 ± 16.5b   | 20.3 ± 5.4     |
| ALT IU/L        | 30.8 ± 11.3a   | 47.2 ± 42.1a   | 17.4 ± 7.3     |
| ALP IU/L        | 368.7 ± 140.6a | 206.1 ± 78.4   | 187.7 ± 58.7   |
| γ-GTP IU/L      | 38.4 ± 36.4b   | 28.5 ± 30.0    | 26.3 ± 27.1    |
| LDH IU/L        | 147.8 ± 25.0b  | 154.9 ± 35.3   | 161.8 ± 28.7   |
| CK IU/L         | 51.4 ± 21.3a   | 70.5 ± 82.2a   | 98.6 ± 32.7    |

*Significantly different from healthy controls at $p < 0.01$ and $p < 0.05$.

Data indicate mean ± SD. ALB: albumin; BIL: bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γ-GTP: gammaglutamyl transpeptidase; LDH: lactic dehydrogenase; CK: creatinine phosphokinase.
### Table 2. Serial Changes in Values of Serum AST, ALT, and ALP in Patients with Graves’ Disease and Painless Thyroiditis

<table>
<thead>
<tr>
<th></th>
<th>Months after first visit</th>
<th>Healthy controls</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
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<tr>
<td><strong>Graves’ disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>23.7 ± 9.5</td>
<td>27.8 ± 15.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>30.8 ± 11.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40.7 ± 29.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>368.7 ± 140.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>438.7 ± 171.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FT&lt;sub&gt;4&lt;/sub&gt; (ng/dL)</td>
<td>3.23 ± 0.86&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.56 ± 0.53&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td><strong>Painless thyroiditis</strong></td>
<td></td>
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<tr>
<td>AST (IU/L)</td>
<td>30.6 ± 16.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32.7 ± 17.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>47.2 ± 42.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48.4 ± 35.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>206.1 ± 78.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>283.4 ± 127.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FT&lt;sub&gt;4&lt;/sub&gt; (ng/dL)</td>
<td>2.82 ± 0.73&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.56 ± 1.12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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Significantly different from healthy controls at *p < 0.05 and *<sup>a</sup>p < 0.001.

Data indicate mean ± SD. Normal range of FT<sub>4</sub>: 0.7–1.6 ng/dL. AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; FT<sub>4</sub>: free thyroxine.

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**FIG. 1.** Individual serial changes in values of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) in patients with Graves’ disease and painless thyroiditis.
patients with Graves’ disease were found to have at least one liver function test abnormality. Serum CK reductions below the lower limit of the normal range were observed in 17 (56.7%) patients.

The mean values of AST and ALT increased 1 month after starting ATD therapy and then decreased to the normal range in 3–5 months. One month after starting ATD therapy, serum AST and ALT elevations from initial values were observed in 16 (53.3%) and 16 (53.3%) patients, respectively. Serum AST and ALT were normalized in all and 27 (90.0%) patients, respectively, at 3–5 months after starting ATD therapy. On the contrary, ALP increased gradually after commencing ATD therapy, and maintained an elevated value for 3–5 months.

We performed correlation analyses between initial values of ALT or ALP and FT4, FT3, or TBI; however, there were no significant correlations. Serum ALT elevations shown 1 month after starting ATD therapy were significantly higher in the patients whose estimated duration of disease was 6 months or more compared to those with duration of less than 6 months (Fig. 2). The changes in liver function tests were similar in both PTU-treated patients and MMI-treated patients, and showed no significant difference.

**Painless thyroiditis**

The initial mean values of AST and ALT of patients were significantly higher than those of normal controls; however, ALB and CK were significantly lower than those of normal controls. Serum AST, ALT, γ-GTP, and LDH elevations above the upper limits of the normal range were observed in 5 (18.5%), 12 (44.4%), 5 (18.5%), and 2 (7.4%) patients, respectively. Fourteen patients (51.9%) were found to have at least one liver function test abnormality. Serum ALB and CK reductions below the lower limits of the normal range were observed in 3 (11.1%) and 16 (59.3%) patients, respectively. One month after the initial evaluation, serum AST elevations from the initial value were observed in 10 (37.0%). Similarly, serum ALT elevations from the initial value were observed in 7 (25.9%) at 1 month after the initial evaluation. The mean value of serum ALP increased gradually, and the peak of serum ALP occurred within 2 months of the initial evaluation. These ALP changes were similar but mild compared to those of Graves’ disease. We performed correlation analyses between initial values of ALT and FT4; however, there were no significant correlations.

There was no significant difference between Graves’ disease and painless thyroiditis in mean values of AST and ALT at all points. The mean values of ALP in Graves’ disease were significantly higher \((p < 0.001)\) than those in painless thyroiditis at all points.

**Discussion**

Liver biochemical abnormalities were marked in both untreated patients with Graves’ disease and painless thyroiditis in this study. In general, the duration of thyrotoxicosis induced by Graves’ disease is longer than that induced by painless thyroiditis, because thyrotoxicosis is transient in painless thyroiditis. A comparatively short duration of thyrotoxicosis seems to be able to increase serum AST and ALT levels. A major difference between these two diseases is the initial mean value of serum ALP, which is mainly of bone origin and sometimes helpful in the differential diagnosis of thyrotoxicosis \((11,12,15,16)\). The rise in serum ALP observed after the treatment of Graves’ hyperthyroidism related to heightened osteoblastic activity is well known \((16)\). The rise of serum ALP was observed not only in the treated patients with Grave’s disease but also in those with painless thyroiditis in this study. These data indicate that even the short duration of thyrotoxicosis influences bone metabolism.

Transient liver biochemical abnormalities after starting PTU therapy have been reported. In these reports, transient elevations of serum ALT were observed in 16–30% of PTU-treated patients 6–8 weeks after starting therapy, and the abnormalities were considered to be induced by PTU \((13,16,17)\). Interestingly, similar transient liver biochemical abnormalities were observed in patients with painless thyroiditis who did not receive any medication in this study. These results suggest that liver biochemical abnormalities observed after starting ATD therapy in this study may not be due to ATDs. Kim et al. reported that the incidence of symptomatic clinically overt hepatic injury due to PTU was 1.2% \((18)\). This supports our notion. We may say that we do not have to discontinue ATDs unless serum AST or ALT is elevated to more than 150 IU/L. Nonetheless, close observation of hepatic enzymes is necessary after starting ATD therapy in Graves’ disease.

One month after the initial evaluation, serum changes in AST and ALT varied in painless thyroiditis. Serum AST and ALT decreased after 1 month in the patients whose initial values were high. It is assumed that the variation was related to the phase of painless thyroiditis. The patients whose serum AST and ALT decreased after 1 month were possibly evaluated in the late phase of the disease; on the contrary, the patients whose serum AST and ALT increased were evaluated in the early phase.
We studied various factors that may influence transient serum AST and ALT elevations shown after ATD therapy in Graves’ disease to elucidate its mechanism. Only the estimated duration of Graves’ disease before starting therapy was related to the transient serum AST and ALT elevations. It is possible that a prolonged hypermetabolic state regarding liver function is responsible. Possibly, both the production and turnover rate of hepatic enzymes may be increased in the condition of hyperthyroidism, and if the turnover rate normalizes faster than production, serum hepatic enzymes may increase transiently.

In summary, similar serial changes in liver function tests were shown in both untreated patients with Graves’ disease and painless thyroiditis. Transient liver biochemical elevations were observed not only in ATD-treated patients with Graves’ disease but also in patients with painless thyroiditis who did not receive any medication. These results strongly suggest that liver biochemical abnormalities observed after starting ATD therapy may not be induced by ATDs but by the dynamic changes in thyroid function.

References


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