Hypertriglyceridemia and Fatty Liver: Clinical Diagnosis of Fatty Liver and Lipoprotein Profiles in Hypertriglyceridemic Patients with Fatty Liver

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Fatty liver has prevailed by 14% in the healthy population of this country. The factors contributing genesis of fatty liver were gender (male), obesity, high alcohol consumption, glucose intolerance and hypertriglyceridemia. And hypertriglyceridemia seems to be the common underlying factor to all other causes. The mechanism for accumulation of triglycerides in the liver can be explained at least by increased HTGL activities and elevated apo A-II levels, a postulated co-factor of HTGL. And hypertriglyceridemic patients with fatty liver had the insulin resistance.

Key words: Fatty liver, Ultrasonography, Hypertriglyceridemia, Apolipoprotein A-II, Insulin resistance

In the past 40 years in Japan, fat intake and alcohol consumption have increased 4 and 6 times, respectively (1), and that a nationwide average in serum triglycerides has risen by about 30 mg/dl since 1970 (Fig. 1) (2). But, except acute pancreatitis due to chylomicronemia and coronary heart disease induced by type III hyperlipidemia, the clinical significance of hypertriglyceridemia is not clearly understood (3). Therefore, to evaluate the significance of triglycerides in health and disease, we studied about the relationship between serum triglycerides and fatty liver. In the meantime, a progress has been made in non-invasive techniques for detecting fatty liver. Today we can detect fatty liver by abdominal ultrasonography in daily practice.

I. Clinical Diagnosis of Fatty Liver

Methods

At first, we evaluated the accuracy of non-invasive techniques to diagnose fatty liver. We performed abdominal ultrasonography (US) and computed tomography (CT) simultaneously in 62 patients who underwent liver biopsy operations and we compared the findings of each examinations.

As the criteria of fatty liver, we used bright liver and the augmentation of hepato-renal contrast for US(4), liver CT number ≤ 50 HU and liver CT number/spleen CT number ≤ 0.90 for CT (5), fat infiltration occupying over one third of every liver lobule and no other significant abnormalities for pathology (6).

Furthermore, in order to assess the consistency of US findings, the same doctor performed US twice blindly in 228 outpatients at intervals of more than 6 months.

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Results and Discussion

Compared with liver biopsy findings (Fig. 2), US tended to overdiagnose fatty liver, and the rate of diagnostic coincidence was 93.5%. No patient, who did not possess fatty liver on US, had fatty liver pathologically. Four patients, once diagnosed fatty liver on US, proved to possess chronic hepatitis with fibrosis by pathology.

On CT, we found that liver CT number/spleen CT number correlated significantly with the percentage of cells stored large fat droplets in biopsy specimens. But, CT was relatively dull to diagnose fatty liver compared with US and the coincidence rate with pathology was 83.9%.

Assuming that the condition of every liver was steady in the study period, we found that the rate of consistency was 91.7% (Fig. 3).

Both the accuracy and consistency of US were over 90%, so that we could detect at least 80% of fatty liver by US.
The Incidence and Causative Factors of Fatty Liver

Methods

Under these situations, we investigated the incidence and factors causative for fatty liver in 2,358 healthy subjects (1,792 males and 566 females) who visited Keio Health Counseling Center for their health check (Table 1).

Results and Discussion

The overall incidence of fatty liver was 14.0% (16.8% for male and 5.1% for female) (7). Univariate analyses on physical and biochemical data revealed that the incidence of fatty liver correlated best with serum triglyceride levels. Multivariate analyses on the same data showed that principal components for fatty liver were summarized into 5 categories such as gender, nutritional states, alcohol consumption, glucose intolerance and lipid disorders (Table 2), and that the significant discriminants of fatty liver were obesity, plasma triglyceride, total protein, glucose and glutamic pyruvic transaminase (GPT) (Table 3). These factors elucidated by multivariate analyses were coincident with our clinical experiences with fatty liver (8).

Table 1. Background of subjects who visited Keio Health Counseling Center.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Fatty liver (−)</th>
<th>Fatty liver (+)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>1792</td>
<td>566</td>
<td>2029</td>
<td>329</td>
<td>2358</td>
</tr>
<tr>
<td>Age</td>
<td>48±9</td>
<td>48±10</td>
<td>48±10</td>
<td>49±9</td>
<td>48±10</td>
</tr>
<tr>
<td>Alcohol (Gou/day)</td>
<td>1.3±1.1</td>
<td>0.2±0.5***</td>
<td>1.0±1.1</td>
<td>1.2±1.2</td>
<td>1.0±1.1</td>
</tr>
<tr>
<td>Broca’s index (%)</td>
<td>7±13</td>
<td>6±15</td>
<td>5±12</td>
<td>20±12***</td>
<td>7±13</td>
</tr>
<tr>
<td>systolic BP (mmHg)</td>
<td>125±14</td>
<td>121±16***</td>
<td>123±14</td>
<td>130±15***</td>
<td>124±15</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
<td>82±9</td>
<td>79±9***</td>
<td>81±9</td>
<td>85±9***</td>
<td>81±9</td>
</tr>
<tr>
<td>T-G (mg/dl)</td>
<td>163±105</td>
<td>109±56***</td>
<td>138±86</td>
<td>223±130***</td>
<td>150±98</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>53±14</td>
<td>62±15***</td>
<td>56±15</td>
<td>48±12***</td>
<td>55±15</td>
</tr>
<tr>
<td>GPT (IU/l)</td>
<td>18±19</td>
<td>11±8***</td>
<td>14±15</td>
<td>30±24***</td>
<td>17±17</td>
</tr>
<tr>
<td>ChE (mEq/l)</td>
<td>2833±563</td>
<td>2628±912</td>
<td>2918±502</td>
<td>3019±432</td>
<td>2710±569</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>106±18</td>
<td>99±14***</td>
<td>103±17</td>
<td>113±22***</td>
<td>105±18</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>4.8±0.3</td>
<td>4.7±0.3***</td>
<td>4.7±0.2</td>
<td>4.6±0.2</td>
<td>4.7±0.2</td>
</tr>
</tbody>
</table>

Significance of differences between men and women (*: P<0.05; **: P<0.01; ***: P<0.001).
Significance of differences between those with fatty liver and without fatty liver (#: P<0.05; ##: P<0.01; ###: P<0.001).

Table 2. Principal component analysis and fatty liver.

<table>
<thead>
<tr>
<th>Component loading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>1st comp.</td>
</tr>
<tr>
<td>Prop.</td>
</tr>
<tr>
<td>Sex (Man+, Woman−)</td>
</tr>
<tr>
<td>Alcohol intake</td>
</tr>
<tr>
<td>Broca’s index</td>
</tr>
<tr>
<td>T-G</td>
</tr>
<tr>
<td>GPT</td>
</tr>
<tr>
<td>FBS</td>
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<tr>
<td>T-P</td>
</tr>
</tbody>
</table>

(T-G: Triglyceride, GPT: Glutamic pyruvic transaminase, FBS: Fasting blood sugar, T-P: Total protein, comp.: Component)
III. Lipoprotein Profiles in Hypertriglyceridemic Patients with Fatty Liver

Methods

As the next step, we analyzed the plasma lipoprotein and apolipoprotein profiles in 168 outpatients with hypertriglyceridemia (128 males and 40 females) at Keio University Hospital, among whom 73 (60 males and 13 females) had fatty liver diagnosed by US and CT (Table 4). At the same time, we measured the area of visceral fat and subcutaneous fat on the umbilical slice of CT. Blood sample was drawn after overnight fasting, and plasma lipids were determined by enzymatic methods. Very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) were collected by ultracentrifugation. Apolipoproteins were measured by immunoturbidity method. We also checked post heparin plasma lipase activity by using the enzymatic method (9).

Results and Discussion

Plasma triglyceride levels were 404±387 mg/dl for those with fatty liver, while 338±298 mg/dl for those without fatty liver. We could not find any particular differences, in lipoprotein profiles (Fig. 4).

In apolipoproteins, the severity of fatty liver correlated significantly with apo-AI, apo-All, apo-CII, apo-CIII, and apo-E. Among all, apo-All correlated best (Fig. 5).

Interestingly, according to the severity of fatty liver, apo-All and apo-Al moved reciprocally. Discriminant analysis with stepwised method on the same data also revealed that apo-All and apo-Al were contributed to fatty liver independently, and reciprocally.

At the same time, it became clear that those who had fatty liver had more visceral fat, i.e. 237±70 vs. 162±70 (cm²).

Furthermore, we compared the activity of hepatic triglyceride lipase (HTGL), and we found that those with fatty liver had significantly higher HTGL activities i.e. 25.2±8.0 vs. 10.4±4.4 (µmol/ml/hr).

IV. Hypertriglyceridemic Patients with Fatty Liver and Insulin Resistance Methods

These data so far suggested that hypertriglyceridemic patients with fatty liver were related to insulin resistance syndrome (10). First, we examined 75 g-oral glucose tolerance test to the same patients who were enrolled in the foregoing experiment.
Hypertiglyceridemia and Fatty Liver

**Cholesterol**

![Bar chart showing VLDL, LDL, and HDL levels in fatty liver and non-fatty liver samples.](image)

**Triglyceride**

![Bar chart showing VLDL, LDL, and HDL levels in fatty liver and non-fatty liver samples.](image)

*Fig. 4.* Fatty liver and lipoprotein profiles.

*Fig. 5.* The severity of fatty liver and apolipoproteins.
We measured plasma glucose (PG) and insulin (PI) concentration at 0 min, 30 min, 60 min, 90 min, 120 min and 180 min after giving soda pop contained 75 g sugar. To evaluate the insulin secretion and sensitivity, we calculated 4 formulas, i.e. (PG at 30 min-PG at 0 min)/(PI at 30 min-PI at 0 min), and PI area/PG area, as the indexes of insulin secretion; the area of delta PG between 60 min and 120 min/the area of delta PI between 0 min and 60 min, and the area of PG between 60 min and 120 min/the area of PI between 0 min and 60 min, as the indexes of insulin sensitivity.

This preliminary study showed that the insulin secretion correlated well with the existence of fatty liver. Then, we performed the same test to 33 non-diabetic outpatients with fatty liver, whose modified Broca's index numbers were below 120% and plasma triglyceride levels were higher than 150 mg/dl, and the same numbers of matching controls without fatty liver.

Results and Discussion

Among hypertriglyceridemic patients without obesity, the existence of fatty liver was accompanied by the insulin resistance, but had no influence of the indexes of insulin secretion.

In short, as the insulin sensitivity went down, the rate of fatty liver increased in these patients. In case that the degree of insulin resistance were the same, those who had the fatty liver had higher insulin secretion values than those without fatty liver.

References

(6) Okudaira M: Fatty liver—From the view point of pathology—. Liver 21: 914-918, 1980 (in Japanese)