Glycogen storage disease (GSD) is an inherited metabolic defect of glycogenolysis and gluconeogenesis. Fifteen types of GSD have been identified. They are categorized into hepatic and muscle/cardiac types according to the involving organ. Patients with hepatic type of GSDs are associated with endocrine abnormalities such as short stature, delayed puberty, fasting hypoglycemia, and dyslipidemia. In addition, patients with GSD Ib are also at risk of autoimmune hypothyroidism.

**Objectives**
- This study was performed to investigate endocrine complications in patients with hepatic type of GSD.

**Subjects and Methods**
- This study included 56 patients with hepatic type GSD who were diagnosed between January 1995 and December 2018; GSD type Ia, Ib, III, IV, and IXa.
- All patients were genetically confirmed by Sanger sequencing of the causative genes. Patients with muscle glycogenosis were excluded in the study.
- Clinical and endocrine characteristics were retrospectively analyzed such as height, weight, hypoglycemia, lipid profiles, and bone mineral density.

**Etiologic spectrum of patients**
- A total of 56 patients from 46 families with hepatic type GSD were included: GSD type Ia (38 patients from 34 families), Ib (N = 3), III (6 patients from 4 families), IV (N = 1), and IXa (8 patients from 4 families)

**Figure 1.** Proportion of patients with hepatic GSD according to type

**Growth**
- Mean height- and weight-SDS at diagnosis were -1.84 ± 1.9 and -1.45 ± 1.6 respectively.
- Of these, short stature (-SDS < -2) was apparent in 23 patients (41%).
- Twenty out of 38 (52.6%) GSD type Ia, two of 6 (33.3%) GSD type III, and one of 8 (12.5%) GSD type IXa patients were diagnosed with short stature.
- Serum IGF-1 and IGFBP-3 levels were measured in five patients with GSD-type Ia. Three of them (60%) had significantly lower levels of IGF-1 levels. The mean serum IGF-1 of these three patients was 5.1 ± 4.4 ng/mL. They showed profound short stature with the mean current height-SDS of -5.84 ± 1.4.
- A total of 24 patients (M = 14, F = 10) reached adulthood (age > 18 yrs) at the last visit. Their mean age was 27.3 for male patients and 27.0 for female patients, respectively. The average of final adult heights were 158.8 cm (SDS -2.98) in males and 158.4 cm (-0.54 SDS) in females.

**Introduction**

**Objectives**

**Subjects and Methods**

**Etiologic spectrum of patients**

**Growth**

**Table 1.** Clinical characteristics and growth profile

<table>
<thead>
<tr>
<th>GSD type</th>
<th>Ia</th>
<th>Ib</th>
<th>III</th>
<th>IV</th>
<th>IXa</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>56</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Mean age at diagnosis (yr)</td>
<td>9.1</td>
<td>4.3</td>
<td>1.4</td>
<td>1.8</td>
<td>2.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Short stature (cm / Total) (%)</td>
<td>20 / 38</td>
<td>0 / 6</td>
<td>1 / 6</td>
<td>0</td>
<td>1 / 8</td>
<td>23 / 56 (12.5%)</td>
</tr>
<tr>
<td>Mean height-SDS at diagnosis</td>
<td>-2.31 ± 2.1</td>
<td>-1.14 ± 0.7</td>
<td>-1.24 ± 1.2</td>
<td>-0.29</td>
<td>-0.8 ± 1.03</td>
<td>-1.84 ± 1.9</td>
</tr>
<tr>
<td>Mean weight at diagnosis</td>
<td>1.26 ± 1.8</td>
<td>0.09 ± 1.2</td>
<td>-0.17 ± 0.7</td>
<td>-0.04</td>
<td>0.18 ± 1.1</td>
<td>-0.81 ± 1.7</td>
</tr>
<tr>
<td>Mean current age (yr)</td>
<td>19.8</td>
<td>16.8</td>
<td>11.8</td>
<td>13.2</td>
<td>6.7</td>
<td>16.8</td>
</tr>
<tr>
<td>Mean current height-SDS</td>
<td>-1.76 ± 1.7</td>
<td>-1.78 ± 1.8</td>
<td>-1.06 ± 1.0</td>
<td>0.71</td>
<td>-0.46 ± 0.6</td>
<td>-1.45 ± 1.6</td>
</tr>
<tr>
<td>Mean current weight-SDS</td>
<td>-0.88 ± 1.5</td>
<td>-0.1 ± 3.7</td>
<td>0.19 ± 0.8</td>
<td>0.21</td>
<td>-0.17 ± 0.6</td>
<td>-0.61 ± 1.5</td>
</tr>
</tbody>
</table>

**Hypertriglyceridemia**
- Hypertriglyceridemia was found in all patients with hepatic GSD at the initial presentation.
- The mean serum triglyceride (TG) level in patients with GSD type Ia was the highest (659.7 ± 490 mg/dL), and GSD type IXa patients showed the mildest abnormalities (186 ± 99.9 mg/dL).
- Fenofibrate was administrated to the adolescent and adult patients with persistent hypertriglyceridemia.
- The mean serum TG level was 520 ± 448.3 mg/dL at diagnosis and decreased to 346.3 ± 390.5 mg/dL at last follow-up ($p = 0.04$).

**Table 2.** Lipid profiles of hepatic GSD patients

<table>
<thead>
<tr>
<th>GSD type</th>
<th>Ia</th>
<th>Ib</th>
<th>III</th>
<th>IV</th>
<th>IXa</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TG at Diagnosis (mg/dL)</td>
<td>659.7 ± 490</td>
<td>275 ± 103.8</td>
<td>259.5 ± 71.9</td>
<td>112</td>
<td>186 ± 99.9</td>
<td>520 ± 448.3</td>
</tr>
<tr>
<td>Mean TG at last follow-up (mg/dL)</td>
<td>441.8 ± 429.4</td>
<td>302.5 ± 228.4</td>
<td>141.8 ± 79.8</td>
<td>No data</td>
<td>93.7 ± 47.6</td>
<td>346.3 ± 390.5</td>
</tr>
</tbody>
</table>

**Thyroid function**

**Vitamin D deficiency and osteoporosis**
- Serum vitamin D concentration was analyzed in 37 patients. Vitamin D deficiency (25-hydroxyvitamin D3 <20 ng/mL) was found in 19 of 37 patients (51.3%). The mean 25-hydroxyvitamin D3 of these patients were 11.8 ± 4.3 ng/mL.
- Dual-energy X-ray absorptiometry analysis was performed in 16 patients. As a result, osteoporosis (bone mineral density Z score <2 SDS) was documented in 11 patients. The mean Z-score of L-spine was −3.24 ± 0.7 (range −4.0 to −2.1).

**Conclusions**
- This study described that patients with GSD type Ia developed significant growth retardation.
- In addition, other endocrine abnormalities such as dyslipidemia, osteoporosis, vitamin D deficiency can be associated with hepatic GSD.
- Dietary treatment with uncooked cornstarch improves growth and partially corrects the biochemical findings.
- Future longitudinal studies with a large number of patients may allow a better understanding of factors that impact endocrine complications.

**Disclosure statement**
The authors have nothing to disclose.