Our aim is to review the imaging findings of glycogen storage disease (GSD), both pre and post liver transplantation.

From March 1996 - October 2006, 13 living donor liver transplantation and one split liver transplantation for GSD were performed. The transplant records were reviewed.

There were 9 female and 5 male patients. All were non-responsive to medical treatment. Ten patients had GSD type I and 4 had GSD type III. All type I patients were subtype Ia. Of the 4 children with type III, 2 were subtype IIIa based on debranching enzyme deficiency in the liver and muscle tissue biopsies. In 2 GSD type III patients, only liver biopsies were done. The mean age, weight, and height were 8.2 years, 23 kg and 114 cm respectively. The mean liver volume was 1366 cm$^3$.

The imaging findings in GSD type I were hepatomegaly (10/10), enlarged kidney (10/10), increased renal medullary echogenicity (10/10), hypervascularity of the hepatic tumor (2/10), nephrocalcinosis (1/10), and splenomegaly (1/10) before liver transplantation. Post liver transplantation, the increased renal medulla echogenicity and spleen size both return to normal.

In GSD type III, the imaging findings included hepatomegaly (4/4), enlarged liver with lobulated contour (1/4), and splenomegaly (1/4). The spleen size reverted to normal size post liver transplantation.

In summary, the common imaging findings in GSD type I include hepatomegaly without cirrhotic change and nephromegaly with increased echogenicity of the renal medulla. In contrast, in GSD type III, the findings revealed hepatomegaly without nephromegaly. Post liver transplantation, the increased renal medulla echogenicity and spleen size both return to normal.

Carbohydrate metabolism in the liver is responsible for plasma glucose homeostasis. Glycogen storage diseases (GSD) are metabolic disorders that result in abnormal storage amounts and/or forms of glycogen in tissues [1]. GSD type I (von Gierke disease) is caused by deficiency of glucose-6-phosphatase activity in the liver, kidney, and intestinal mucosa with glycogen overloading in these organs. Classically, patients with GSD type I either present in the neonatal period with hypoglycemia and lactic acidosis, or present at 3-4 months of age with hepatomegaly and/or hypoglycemic seizures [2]. The other manifestations include systemic acidosis, hyperlipidemia, hyperuricemia, and growth retardation. Without effective treatment, long-term complications occur including gout, osteoporosis, short stature, and hepatic adenomas with a possibility of malignant transformation [2, 3]. GSD type III (Cori disease) is caused by deficiency of glycogen debranching enzyme activity and is characterized with dextrin-like glycogen accumulation in both liver and muscle in most patients. Hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are the main manifestations in children [1] whereas liver cirrhosis and/or hepatocellular carcinoma may occur later [4, 5]. Owing to the lower incidence of GSD,
Radiological findings in glycogen storage disease

there are few manuscripts to describe the imaging characteristics in this disease especially in the setting of liver transplantation.

Our aim in this study is to review the imaging characteristics in GSD before and after liver transplantation.

PATIENTS AND METHODS

From March 1996-October 2006, 281 living donor liver transplantations (LDLT) were performed at Chang Gung Memorial Hospital-Kaohsiung Medical Center, Taiwan. Among them, 14 (5%) patients with GSD underwent liver transplantation (13 LDLT and 1 split liver transplantation). The transplant records were reviewed with special attention to the imaging manifestations of the disease.

Ultrasound protocol

Doppler ultrasound was performed using an Acuson 128 scanner (Acuson, Mountain View, CA) with a 3.5 or 7.0 MHz transducer available for imaging in the first 5 patients. An Acuson 512 scanner (Acuson, Mountain View, CA) with 7.0 or 4.0 scanner for imaging was used in the last 9 patients for initial evaluation of the liver and to measure the renal size and echogenicity.

Computed tomography and volumetric analysis

Computed tomography (CT) studies were conducted using a Multislice CT, Somatom Volume Zone scanner (Siemens AG, Germany). The CT examination was performed in all recipients before transplantation (mean period before transplant was 3 months). The CT number was obtained from GE Centricity Picture archiving and Communication System. The liver and spleen volumes were measured by hand tracing the organ outline on the axial portal venous phase images. The total volumes of the liver and spleen were then determined by adding the individual volumes through the organs.

Statistical Analysis

All values were expressed as mean ± SD and median as appropriate. Data were analyzed using statistics computer software STATA (STATA Corporation, College Station, TX).

RESULTS

The demographic, clinical, imaging, and pathologic characteristics of the patients were shown in Table 1. There were 5 male and 9 female recipients. Ten patients had GSD type I (4 males and 6 females) and 4 had GSD type III (1 male and 3 females). All GSD type I patients were subtype Ia. Of the 4 children with GSD type III, 2 were subtype IIIa based on debranching enzyme deficiency in the liver and muscle tissue biopsies. In 2 GSD type III patients, only liver biopsies were performed. The mean age was 8.2 ± 4.1 years (range, 0.5-19.2). The mean body weight was 12.5 ± 8.8 kg (range, 5.1-54). There was an early mortality in one patient with GSD type Ia due to acute pancreatitis and sepsis 2 months after transplantation. The minimum follow-up in the 13 surviving patients was 24 months.

GSD Type I

Liver: Hepatomegaly was noted in 10 out of 10. The mean liver size by CT volumetry was 1342 ±438 cm³ (range, 505-2124) (Fig. 1a). There was no significant cirrhotic change. The CT number was high (2/6), normal (2/6), and low (2/6). The pathologic examination showed that all patients had glycogen deposition in the liver. Two patients had 20% and 60% fatty liver change, respectively. Pretransplantation images revealed a 2 cm hypervascular tumor in liver segment S4 in one patient (Fig. 1b) and a 3 cm hypoechoic tumor in the left lateral segment of the liver in another patient. The pathology of these tumors was an nodular hyperplasia in the former and adenoma in the latter.

Spleen: Splenomegaly was not common. The mean spleen size by CT volumetry was 165.4 ± 185.6 cm³ (range, 65-670). Only one patient showed an enlarged spleen.

Kidney: The relative increment in kidney length in all patients is shown in (Fig. 2a). The mean right renal length was 10.1 ± 1.1 cm (range, 9-12), and left renal length was10.2 ± 1.1 cm (range, 8.6-12). All kidneys showed a relative increase in the echogenicity of the renal medulla (Fig. 2b). Posttransplantation, the sizes of kidneys did not show significant changes but the echogenicity of the renal medulla gradually reverted to normal(10/10).

One patient was noted to have nephrocalcinosis (Fig. 2c) pretransplant. All patients had normal serum creatinine both pre- and posttransplantation.

GSD Type III

Liver: All patients showed hepatomegaly (4/4). The mean liver size by CT volumetry was 1426 ± 151 cm³ (range, 1253-1609). A lobulated contour of the liver was found in one patient (1/4). Two patients
<table>
<thead>
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<th>Patient</th>
<th>GSD type</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Body weight (Kg)</th>
<th>Liver volumetry (cm³)</th>
<th>Spleen volumetry (cm³)</th>
<th>Liver CT number</th>
<th>Liver tumor</th>
<th>Right kidney size(cm)</th>
<th>Left kidney size(cm)</th>
<th>Increased renal medially echogenicity</th>
<th>Pathology finding</th>
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<td>88</td>
<td>-</td>
<td>N</td>
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<td>1149</td>
<td>108</td>
<td>-</td>
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<td>Np</td>
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<td>2124</td>
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<td>-</td>
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<td>-</td>
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<td>9</td>
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<td>Np</td>
</tr>
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<td>1476</td>
<td>65</td>
<td>-</td>
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<td>236</td>
<td>45</td>
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<tr>
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<td>23</td>
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<td>670</td>
<td>77</td>
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<td>9</td>
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<td>74</td>
<td>N</td>
<td>9.5</td>
<td>10</td>
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<td>Np</td>
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</table>

N=no; Y=yes; LLS=left lateral segment of liver; S4=segment 4 of liver; (-)=no data available; N*=not found in pre transplantation evaluation, but pathology showed 1.0 cm adenoma in the caudate lobe; Np=no special finding
Radiological findings in glycogen storage disease

showed cirrhotic change. The CT number was high in two patients. In two patients transplanted before the use of the Picture archiving and Communication System, the CT number could not be determined. Tumor was not found in all the livers by imaging and this was confirmed by pathologic examination.

Spleen: The mean spleen size by CT volumetry was 154.8 ± 139.8 cm$^3$ (range, 54-361). One patient showed mild splenomegaly.

Kidney: No enlarged kidneys were noted in any patient. The mean right renal length was 7.9 ± 0.9 cm (range, 7-9.2), and left renal length was 7.8 ± 0.9 cm (range, 7-9). All kidneys showed normal echogenicity. Nephrocalcinosis was also not seen in any patient.

Post liver transplantation, the enlarged kidneys in GSD type I did not show any size changes but the increased echogenicity of the renal medulla gradually returned to normal (9/10). The spleen size returned to normal in the two cases with splenomegaly both in GSD I and GSD III.

**DISCUSSION**

The first description of GSD was reported by van Creveld in 1928 [6]. Since then, several hundred cases have been published in the literature. This autosomal recessive disorder is subdivided most frequently as: type I, deficiency in glucose 6 phosphatase; type II, deficiency in a-1-4 glucosidase; type III, deficiency in amylo-1-6 glucosidase; and type IV, deficiency in fl-phosphorylase or phosphorylase kinase. The other types are far rarer. The diagnosis of GSD type I depends largely on the awareness of the clinician but a number of clues can be obtained from the history, laboratory examination, and imaging studies. A definitive diagnosis requires DNA mutation analysis or a liver biopsy to demonstrate the enzyme deficiency[1].

There are two major GSD type III subtypes. GSD type IIIa is the most common subtype and accounts for 80% of the cases where patients have both liver and muscle involvement. GSD type IIIb accounts for approximately 15% of all GSD III where patients have enzyme activity lacking only in the liver. The symptoms common to both subtypes are hepatomegaly, hypoglycemia, short stature, and dyslipidemia [7]. Only patients with type IIIa have a myopathy and cardiomyopathy. A definitive diagnosis requires DNA mutation analysis or liver and muscle biopsy.

Liver transplantation is an excellent alternative treatment for GSD types I and III. There are few reports that focus on the imaging findings in patients with GSD types I and III during pre- and post liver transplantation periods.

**Figure 1.** Liver changes in GSD patients. a. Hepatomegaly in a 15-year-old boy with GSD type I. Coronal reconstruction CT scan shows a markedly enlarged liver with a volume of 1853 cm$^3$. b. Portal venous phase CT scan of the same patient shows a 2 cm hyperattenuating nodule in segment 4. Pathology revealed adenomatous hyperplasia.
GSD Type I

Hepatomegaly is a common finding in GSD type I owing to glycogen deposition with or without fatty infiltration. Glycogen deposition accounts for the increased density of the liver [8]. However, in our study, six patients with GSD type I had simultaneous hepatic infiltration with fat and glycogen that resulted in liver CT numbers ranging from 45-77 HU. The CT number depends on the ratio of glycogen deposition and fatty infiltration. Poor diet control may lead to fat deposition.

Although GSD I was first recognized by von Gierke in 1929 as a distinct entity, it was not until 1955 that the first description of liver tumors was reported in this condition [9]. Subsequently over 75 cases have been reported and was comprehensively reviewed by Bianchi [10]. A number of series of patients have been published which give a range of prevalence from 22%-75% depending on patient selection. Fatty infiltration may facilitate the demonstration of hepatic tumors in older patients [8]. The incidence of liver tumors in younger adults seems less than in older ones. Hepatic adenoma is the most common liver tumor seen in 2nd or 3rd decades of age.
life in GSD type I. Three patients (3/10) developed liver tumors with hypoechoic appearance on sonography and early hypervascular enhancement nodules on CT in our study. The typical imaging finding in hepatic adenoma in CT is the presence of a single or multiple masses that may contain areas of fat or hemorrhage and are otherwise isoattenuating relative to normal liver on unenhanced, portal venous phase, and delayed-phase images. The lesions are moderately hyperattenuating relative to the liver at hepatic arterial-phase imaging and enhance nearly homogeneously [11]. The ages of the three patients were 8.8, 14.5, and 15.5 years. In our study, there was also a higher incidence of liver tumors found in older children.

Hepatocellular carcinoma (HCC) is a rare complication in GSD type I. Franco LM, et al. [12] reported 8 patients (6 males, 2 females) with HCC and GSD type 1a. In contrast to hepatic adenoma, HCC may present as an ill-defined and rapidly growing lesion [11]. Magnetic resonance imaging with hepatocellular-specific contrast agents may help in the differential diagnosis but no single imaging modality can accurately differentiate between hepatic adenoma and HCC. Biopsy or even surgical resection to exclude a malignant neoplasm is recommended in ill-defined and rapidly growing lesions in the setting of GSD type I. Alpha feto-protein and carcinoembryonic antigen do not appear to be reliable indicators of the presence of hepatic malignancy in patients with GSD type I.

Renal enlargement was described by Von Gierke [13] in the first pathologic description of hepatorenal glycogenesis and is regarded as a common feature of GSD type I. It is ascribed to glycogen deposition in the kidney (similar to that seen in the liver) and glomerular enlargement [14]. Several reports revealed nephromegaly and increased renal echogenicity on ultrasonography [15]. All of our patients with GSD type I had renal enlargement. One 15.8-year-old had nephrocalcinosis. Renal stones or nephrocalcinosis are also common findings in patients with GSD type I; although, these findings have mostly been primarily reported in adults [16]. Fick and Beek [17] reported a child who had bilateral enlarged echogenic kidneys and medullary calcium deposition at the age of 6 months. Several factors might contribute to stone formation. These are hypercalciuria, hyperuricosuria, distal renal tubular acidosis, and hypocitraturia. Nephrocalcinosis or renal stones are rarely reported in young children with GSD type I.

### GSD Type III

Hepatomegaly is noted in childhood due to accumulation of abnormally short-branched glycogen [18]. Combined with abnormally short-branched glycogen deposition and liver fibrosis, the CT number in GSD type III is usually high. Liver cirrhosis is thought to be due to progressive accumulation of glycogen that is abnormal in structure leading to damage to the hepatocytes, and gradual development of cirrhosis. But hepatic involvement in GSD type III is considered mild and almost always self-limiting. The mechanism for tumorigenesis in GSD type III is unknown but appears different from GSD type I which is believed to be an adenoma-carcinoma sequence. In GSD type III, it may be that cirrhosis is facilitating this carcinoma transformation which is a well-recognized association. There are few reports on HCC developing in GSD type III patients [19]. Approximately, there are only six patients reported in the English literature on GSD type III patients who developed HCC. In contrast to GSD type I, adenomas are not as common in patients with GSD type III. Demo E, et al. [19] reported that only 2 out of a cohort of 45 patients (4.4%) that were followed-up for more than 30 years have developed adenomas; and in both patients the tumor was small and stable. In our study, one patient (1/4) demonstrated a lobulated appearance of the liver in CT study but no liver tumor was seen.

### CONCLUSION

The common abdominal imaging findings in GSD type I include hepatomegaly without cirrhotic change and nephromegaly with increased echogenicity of the renal medulla. In GSD type III, a common finding is hepatomegaly without nephromegaly. Increased renal medulla echogenicity gradually returned to normal after liver transplantation. Although nephromegaly is not always present in GSD type I, this characteristic finding may help in the differential diagnosis between GSD types I and III in the pediatric age group.

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小兒糖原貯存疾病在肝臟移植前後腹部影像學表徵

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回顧探討糖原貯存疾病（GSD）在肝臟移植前後具有特殊性的腹部影像學表徵。
從 1996 年 3 月到 2006 年 10 月 總共十四位糖原貯存疾病病患接受十三例活體肝移植和一例劈離式，肝移植，回顧探討肝臟移植前後腹部影像學表徵。
總共有 9 位女性和 5 位男病患對於藥物治療無效。其中 10 位病患為 GSD Ila 子類型，
4 位為 GSD III 型，在有 III 類型的 4 個孩子中，有 2 個是經由肝臟和肌肉組織切片證實為肝
酵去分支酶基因缺乏的 IIIa 子類型。在另外 2 位 GSD III 類型病患，只有做肝臟組織切片。平
均的年齡，身高和體重是 8.2 歲，114 公分和 23 公斤。平均的肝體積是 1366 立方公分。在
GSD I 型腹部影像學表徵為肝臟腫大（10/10），腎臟腫大（10/10），增加腎髓質的回響反射
性（10/10），肝臟富含血管的腫瘤（2/10），腎鈣質沉積症（1/10），以及脾臟腫大（1/10）。在
GSD III 型腹部影像學表徵為肝臟腫大（4/4），腫大的肝臟合併 lobulated 輪廓（1/4），以及脾
臟腫大 (1/4)。在肝臟移植後追蹤發現，腎臟腫大在大小尺寸上並未改變，但是腎的骨髓回響反射
性逐漸恢復正常（9/10）。並且脾臟腫大的病患也恢復到正常的尺寸大小的脾臟。
GSD I 型糖原貯存疾病病患特殊性的腹部影像學表徵包括肝臟腫大沒有合併肝硬化的變
化，腎臟腫大合併增加腎髓質的回響反射性。在 GSD III 型為肝臟腫大沒有合併腎臟腫大。在
肝臟移植後，被增加的腎髓質的回響反射性和腎臟尺寸都恢復正常。