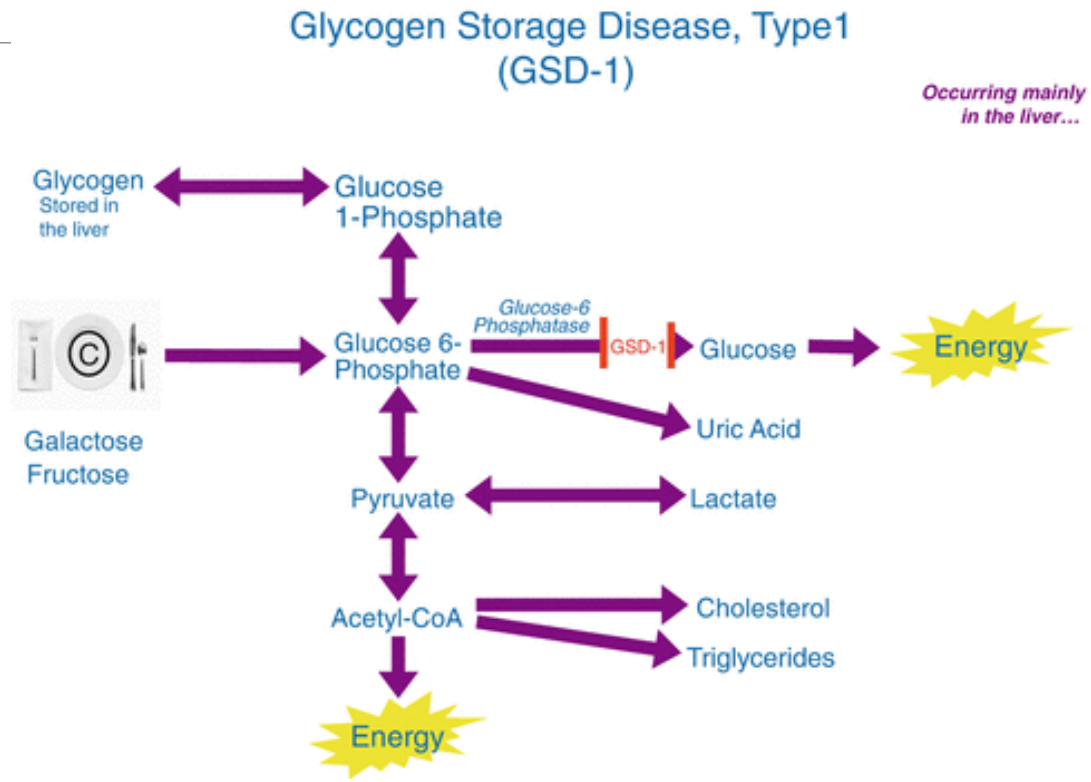
# Monitoring of patients with GSD

DR. HOSSEIN MORAVEJ

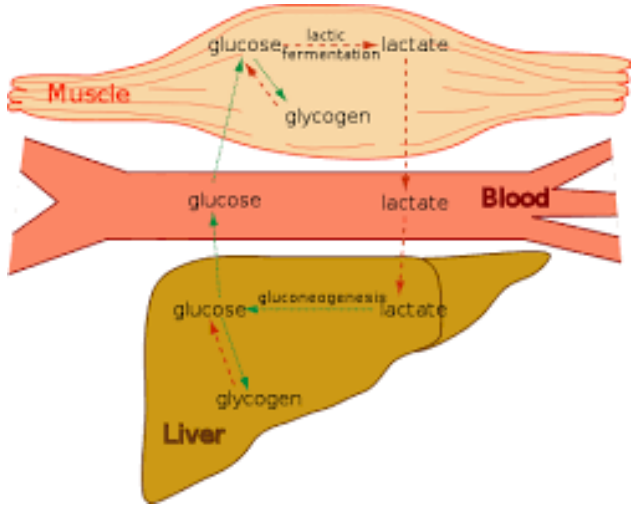
PEDIATRIC ENDOCRINOLOGY AND METABOLISM

SHIRAZ UNIVERSITY OF MEDICAL SCIENCES

# GSD type 1


Glycogen Storage Disease, Type1
(GSD-1)
Occurring mainly in the liver...
Glycogen
Stored in the liver
Glucose 1-Phosphate
Glucose-6 Phosphatase
GSD-1
Glucose
Energy
Glucose 6-Phosphate
Uric Acid
Galactose
Fructose
Pyruvate
Lactate
Acetyl-CoA
Cholesterol
Triglycerides
Energy

# Clinical manifestations



# GSD

Most commonly present between three to six months of age with:

- Hepatomegaly
- Hypoglycemia
- Poor growth, and
- Doll-like facies

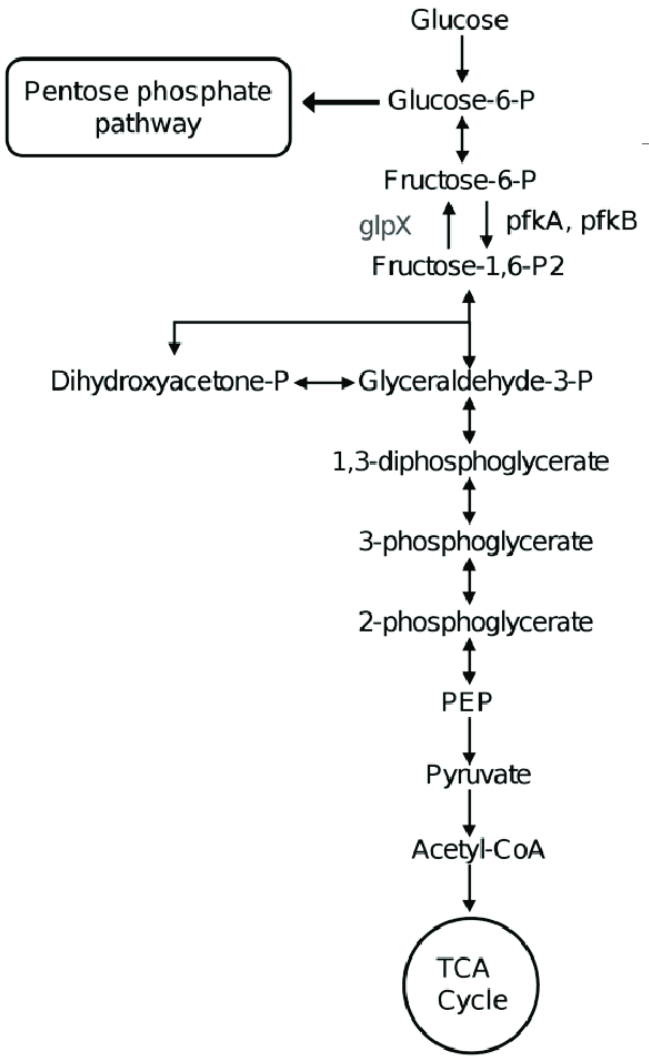
# Hypoglycemia

- Poor fasting tolerance, especially infants and young children,
- May develop hypoglycemia within an hour or two after a meal.
- Hypoglycemia is the hallmark finding in patients with GSD I.
- Unlike other GSDs, hypoglycemia in GSD I is characterized by hypoketosis due to inhibition of fatty acid oxidation by malonic acid .

- Symptoms of hypoglycemia include:
- fatigue,
- irritability,
- nighttime waking to feed
- Decreased level of consciousness
- seizures.
- Patients often adapt to hypoglycemia and may be asymptomatic despite low blood glucose values (<40 mg/dL).

# Lactic acidosis

- Inability to break down glycogen into glucose results in shunting of G6P down the glycolytic pathway with resultant lactic acid production.



# Hyperuricemia

- Secondary to decreased renal clearance and increased production via degradation of adenine nucleotides.
- Gout rarely develops before puberty.

# Hyperlipidemia

- Especially hypertriglyceridemia
- Xanthoma formation and pancreatitis.
- De novo triglyceride synthesis has been shown to increase over 10-fold in affected individuals, and the conversion of very-low-density lipoprotein (VLDL) to low-density lipoprotein (LDL) is delayed.

# Hematologic

- Anemia, uncommon in treated patients:
- Result from chronic kidney disease, nutritional deficiencies, hemorrhage of hepatic adenomas, enterocolitis in type Ib patients, and other factors.
- Platelet dysfunction, which is related to dyslipidemia, can result in easy bruising and epistaxis.

# Hematologic

- Patients with GSD Ib also have intermittent or chronic neutropenia and neutrophil dysfunction.
- neutropenia was documented before one year of age in 64 percent of patients but was first noted between six and nine years in 18 percent.
- Neutropenia was intermittent without a clear cyclical course in most patients and persistent in others

# Gastrointestinal

- Perioral and perianal infections and abscesses, and
- Inflammatory bowel disease (IBD) are common in GSD Ib.
- IBD can occur in GSD Ia and may be underrecognized

# Endocrine

- Short stature is common if patients are not appropriately managed.
- Puberty is often delayed, and menstrual cycles are frequently irregular.
- Polycystic ovaries and menorrhagia have been observed.
- Fertility does not seem to be reduced, and successful pregnancies without the use of assistive reproductive measures have been reported.
- An increased prevalence of thyroid autoimmunity and hypothyroidism has been reported in patients with GSD Ib.
- Vitamin D levels are often low.

# Renal

- Glycogen accumulation in the kidney
- Proteinuria, hematuria, nephrocalcinosis, and altered creatinine clearance typically follow a period of asymptomatic hyperfiltration.
- Stones result both from hypercalciuria and hyperuricosuria.
- The kidney appears enlarged.

# Hypertension

- Common
- Onset is typically in the second decade or later.
- A subset of patients develop progressive renal insufficiency and end-stage kidney disease

# Neurologic

- Hypoglycemic seizures
- IQ is normal.
- Brain function and structure may be altered as a result of recurrent, severe hypoglycemia.
- MRI abnormalities included dilation of the occipital horns and/or hyperintensity of subcortical white matter in the occipital or parietal lobes

# Hepatic adenomas

- Most adults develop liver adenomas in the second to third decade of life.
- The adenomas may lead to intrahepatic hemorrhage and undergo malignant transformation in approximately 10 percent of cases

# Bone density

Osteoporosis is seen in over half of adult patients with GSD I.

Due to a chronic lactic acidosis, the effect of cortisol release (in response to hypoglycemia) on osteoblasts, and treatment of GSD itself, which involves dietary restriction of lactose and galactose that leads to vitamin D deficiency

# Pulmonary hypertension

A small number of patients develop pulmonary hypertension, which can lead to progressive heart failure.

# DIAGNOSIS

# DIAGNOSIS

GSD I should be suspected in patients with:

- Hypoglycemia
- lactic acidemia
- Hypertriglyceridemia
- Hyperuricemia
- Hepatomegaly

DNA testing is necessary to confirm the diagnosis of GSD Ia or Ib.

Liver biopsies for histologic studies and enzyme analysis were performed historically but are rarely necessary nowadays.

# DIFFERENTIAL DIAGNOSIS

- Other hepatic forms of GSD that cause hypoglycemia:
- Types 0, III, VI, and IX.
- GSD type III may have extremely elevated AST and ALT and milder hypoglycemia. In addition, uric acid and lactic acid are normal.
- Ketosis is much more pronounced in GSD types 0, III, VI, and IX compared with type I.
- GSD type 0 does not cause hepatomegaly.

- Genetic testing is necessary to confirm the specific type of GSD.


TREATMENT
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# Goal

- The goal of treatment is maintenance of physiologic glucose levels.
- Other clinical and biochemical parameters, such as somatic growth, lactic acidosis, and hypertriglyceridemia, improve in parallel with improved glucose control.

# Monitoring

Preprandial blood glucose >63 to 72 mg/dL

- Urine lactate/creatinine ratio <0.06 mmol/mmol
- Serum uric acid concentration in high normal range for age
- Venous blood bicarbonate >20 mEq/L
- Serum triglyceride concentration < 530 mg/dL
- Normal fecal alpha-1 antitrypsin concentration for GSD Ib
- Body mass index between 0.0 and + 2.0 standard deviations

# Prevention of hypoglycemia

- Infants should be fed at regular, age-appropriate intervals.
  In rare instances, they may require more frequent feeding.
- Early infants should not be allowed to sleep through the night.
  Some may require continuous feeds through a nasogastric or gastrostomy tube. An optimal infusion should provide 8 to 10 mg/kg/minute of glucose for an infant and 4 to 8 mg/kg/minute of glucose in an older child.
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# Prevention of hypoglycemia

After one year of age, children should be given at least three daily meals with snacks in between.

Between meals: frequent oral administration of glucose, usually in the form of uncooked cornstarch

In many cases, a dose of cornstarch is needed during the night.

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# cornstarch

Long-term treatment with uncooked cornstarch improves growth in GSD I

Adverse effects of uncooked cornstarch include diarrhea, increased flatulence, and excess weight gain.

# cornstarch

The dose of uncooked cornstarch is 1.6 g/kg every three to four hours for young children and

1.7 to 2.5 g/kg every four to six hours for older children, adolescents, and adults. (1 tablespoon equals approximately 8.6 gram)

Dosing is adjusted for the individual patient.

# cornstarch

Since infants do not digest cornstarch well due to lack of salivary amylase expression, it is recommended to begin cornstarch therapy after 6 to 12 months of age, when amylase activity increases.

# Treatment of lactic acidosis

- Oral citrate or bicarbonate
- Potassium citrate is preferred over bicarbonate because hypocitraturia appears to worsen with age in GSD Ia.
- They also alkalinizes the urine and decreases the risk of urolithiasis and nephrocalcinosis

# Treatment of hyperuricemia

- No consensus
- Allopurinol can be used in patients with persistently elevated uric acid or with recurrent attacks of gout.
- Colchicine may be used during acute attacks.
- Use of medium-chain triglyceride oil was shown in a small study to improve uric acid levels and reduce carbohydrate requirements.

# Treatment of hyperlipidemia

- Lipid-lowering agents such as HMG-CoA reductase inhibitors and fibrate may be used.
- MCT may be effective at reducing triglyceride and lactic acid levels by improving fatty acid oxidation and reducing glycolysis but require additional evaluation.
- However, hyperlipidemia in patients with GSD I only responds partially to drug therapy and/or dietary measures. It resolves completely after liver transplantation.

Fish oil does not persistently lower serum triglyceride and cholesterol concentration and may increase atherogenesis by increasing lipoprotein oxidation.

# Neutropenia

- Patients with GSD Ib and neutropenia should be treated with G-CSF.
- G-CSF increases neutrophil count, decreases the frequency and severity of infections, and improves inflammatory bowel symptoms.
- Splenomegaly is the most serious complication of G-CSF.

- Reactive oxygen species are thought to play a role in activating apoptosis in neutrophils of patients with GSD Ib, antioxidant therapy may be beneficial.
  Supplementation with vitamin E has been shown to increase mean neutrophil count, decrease the frequency and severity of infections, and, in some cases, allow for dose reduction of G-CSF.

# Anemia

- May need iron supplementation and erythropoietin, depending upon the severity.

# Short stature

Growth hormone does not affect the final height and should not be used, because it can lead to the development of or an increase in the size or number of liver adenomas.

Good metabolic control leads to improved height and weight.

# Osteoporosis

Dual-energy x-ray absorptiometry (DXA) scans and vitamin D 25-OH levels should be checked regularly to monitor bone density and need for vitamin D supplementation.

# Renal disease

- A renal ultrasound should be obtained annually to assess for renal enlargement and nephrolithiasis.
- BUN, creatinine, urinalysis, quantitation of microalbumin, and other renal function studies should be checked at routine intervals, typically annually in children and every six months in adults.
- Alkalinization of the urine with oral citrate decreases the risk of stone formation.

ACE inhibitor or angiotensin receptor blocker (ARB) should be started in patients with persistent microalbuminuria to decrease deterioration of renal function.

Hypertension that persists despite ACE inhibition should also be treated.

Kidney transplant can be performed in patients with end-stage kidney disease.

# Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is a known late complication GSD I.
- Adenoma to HCC transformation may occur despite good metabolic control.
- A liver ultrasound should be performed every 12 to 24 months in children <18 years of age to screen for HCC.
- CT or MRI with contrast is recommended every 6 to 12 months in older patients.
- Oral contraceptive pills are contraindicated in women with GSD I since estrogen increases the risk for hepatic adenomas. However, progestin-only contraceptives are an option.

# Pulmonary hypertension

- An echocardiogram should be performed starting at 10 years of age to screen for pulmonary hypertension.
- Every three years or sooner if clinically indicated.

# Liver transplantation

**Indications:**

poor metabolic control,

worsening adenomas,

HCC, and/or

liver failure

# Liver transplantation

The 1-, 5-, and 10-year survival rates are 82, 76, and 64 percent, respectively.

Transplantation results in resolution of hypoglycemia and secondary metabolic disturbances including lactic acidosis, hypertriglyceridemia, and hyperuricemia.

Patients can eat a normal diet after liver transplantation.
Growth deficiency and neutropenia often persist in GSD Ib after transplantation.


Best
wishes!
WE WILL MISS YOU