Hereditary disorders of sugar metabolism
Disorders of metabolism of monosaccharides („small molecules“)

   Fructose

   Galactose

Disorders of metabolism of polysaccharides („large molecules“)

   Glycogen storage disorders (also lack of product)

Disorders of glycosylation of proteins
   product deficiency
Inherited disorders of fructose metabolism
Fructose

Fructose (β-D-fructofuranose)

Honey, vegetables and fruits

Saccharose

Fructose is the main sugar of seminal fluid

raffinose, stachyose, inulin - no role in human nutrition

sorbitol – sugar alcohol, derived from glucose, abundant in fruits. Sorbitol dehydrogenase converts sorbitol to fructose - a source of fructose.

GLUT5 – glucose transporter isoform is probably responsible for fructose transport in the small intestine

Fructose is probably transported into the liver by the same system as glucose and galactose
Inherited disorders of fructose metabolism

Daily intake of fructose in Western diets: 100 g

Metabolised in liver, kidney, intestine

Intravenous fructose in high-doses is toxic: hyperuricemia, hyperlactacidemia, ultrastructural changes in the liver.

Essential fructosuria

Hereditary fructose intolerance (aldolase B deficiency)

Hereditary fructose 1,6-bisphosphatase deficiency

Autosomal recessive disorders
Toxicity of fructose

Rapid accumulation of fructose -1-phosphate

The utilization of F-1-P is limited by triokinase

Depletion of ATP

Hyperuricemia

Hyperuricemic effect of fructose results from the degradation of adenine nucleotides (ATP).

Adenine dinucleotides → → → uric acid

Increase in lactate
Hereditary fructose intolerance

Deficiency of fructoaldolase B of the liver, kidney cortex (isoenzymes A,B,C)

Severe hypoglycemia upon ingestion of fructose

Prolonged fructose intake: poor feeding, vomiting, hepatomegaly jaundice hemorrhage, proxima tubular renal syndrome, hepatic failure, death

Strong distaste for fructose containing foods

Fructose -1- phosphate inhibits gluconeogenesis: phosphorylase and aldolase

Patients are healthy on fructose-free food

Diagnostics: (i.v. fructose tolerance test), DNA analysis.
Hereditary fructose 1,6-bisphosphatase deficiency

Fructose 1,6-bisphosphatase catalyzes the irreversible splitting of fructose 1,6-bisphosphate into fructose 6-phosphate and inorganic phosphate (P)

Autosomal recessive disorder

Severe disorder of gluconeogenesis, gluconeogenetic precursors (amino-acids, lactate, ketones) accumulate after depletion glycogen in the patients

Episodes of hyperventilation, apnea, hypoglycemia, ketosis and lactic acidosis, potentially lethal course

Episodes often triggered by fasting and infection

Aversion to sweets does not develop, tolerance to fasting improves with age
Essential fructosuria

Deficiency of liver fructokinase

Asymptomatic metabolic anomaly - benign

Hyperfructosemia and hyperfructosuria
Hereditary disorders of galactose metabolism
Hereditary disorders of galactose metabolism

The main sources of galactose are milk and milk products.

Galactose is present as the disaccharide lactose (β-D-galactopyranosyl-(1→4)-D-glucose)

Genetic disorders:
Galactokinase

Galactose-1-phosphate uridyltransferase

Uridine diphosphate galactose 4-epimerase.
Classical galactosemia: galactose-1-phosphate uridyltransferase deficiency

In the first weeks of life: poor feeding and weight loss, vomiting, diarrhea, lethargy, and hypotonia.

Severe liver dysfunction, hepatomegaly, icterus, vomiting, lethargy bleeding tendencies, septicemia, renal tubular syndrome

Cataracts

Elevated galactose, galactitol, galactose-1-phosphate

Long-term complications
effects on cognitive development,
ovarian failure in females
An ataxic neurologic disease.

AR, incidence 1:40 000-60 000,
Neonatal screening for galactose in some countries

Variants (Duarte)
Fig. 72-3 The conversion of galactose to galactitol by a nonspecific aldose reductase and to galactonic acid by aldehyde dehydrogenase.
Cataracts in classical galactosemia

Galactitol – osmotic swelling of lens fibres

**Figure.**—Ophthalmoscopic appearance of the lenses at 6 weeks.
Galactokinase deficiency

Cataracts - usually bilateral and detectable in the early weeks of life

Pseudotumor cerebri

Galactitol – osmotic oedema of lens

Treatable by galactose-restricted diet, cataract can resolve

Autosomal recessive, rare condition (cca 1:200 000)
Uridine diphosphate galactose 4-epimerase deficiency

**Severe form:**

Severe deficiency of epimerase activity

Newborns with vomiting, hepatopathy resembling classical galactosemia. Mental retardation

**Mild form:**

Partial deficiency of epimerase deficiency
In most patients apparently benign condition

Autosomal recessive
Hereditary disorders of glycogen metabolism
Glycogenoses
Glycogen storage disorders

Glucose: primary source of energy for eukaryotic cells

Glycogen: macromolecular storage form of glucose
– branched chain polysaccharide composed of glucose units.

straight chains \( \alpha-1,4 \text{ linkages} \)
branching points \( \alpha-1,6 \text{ linkages} \) at intervals of 4-10 glucose residues

Serves as an important source of energy between meals. Especially abundant in the liver and in the muscle

In the muscle: glycogen \( \beta \) particles- up to 60 000 glucose residues
In the liver: \( \alpha \) particles „aggregates“ \( \beta \) particles, glycosomes

Synthesis of glycogen: protein „primer“ - glycogenin

Glycogenoses: hereditary enzymopathies that result in storage of abnormal amounts and/or forms of glycogen
Glycogen storage diseases - overview

**Hepatic glycogenoses** – present principally either with hypoglycemia (GSD I, GSD III, GSD 0) or isolated hepatomegaly (GSD VI, GSD IV, GSD IX)

**Muscle glycogenoses** – present with exercise intolerance (GSD V, GSD VII and some very rare deficiencies)

**Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy**
GSD II - deficiency of lysosomal alpha glucosidase, presents with myopathy and cardiomyopathy (deficiency of LAMP 2 – disorder of autophagy – see lecture on lysosomal diseases)
AMP-activated protein kinase deficiency – presents with adult cardiomyopathy and Wolf-Parkinson-White syndrome

**Brain glycogenoses** – present with adult neurodegeneration, epilepsy and accumulation of polyglucosan bodies.
Glycogen metabolism and glycogen storage disorders

Roman numerals indicate GSD type
Red: liver glycogenoses
Violet: muscle glycogenoses
Green: generalized glycogenosis
* associated with hypoglycemia

Modified from Santer et al. in Saudubray et al. (eds) Inborn metabolic Diseases
Liver glycogenoses

*Fasting hypoglycemia, hepatomegaly, growth retardation*
5 types - most common is type I (von Gierke disease- glucose-6-phosphatase deficiency)
or hepatomegaly without tendency to hypoglycemia

Muscle glycogenoses

*Intolerance of exercise, cramps induced by exercise, rhabromyolysis, the heart is not affected*
6 types

Generalized glycogenosis and GSDs presenting with myopathy and cardiomyopathy

Type II (Pompe disease) – deficiency of lysosomal α-1,4-glucosidase
- lysosomal storage of normal glycogen
- activated AMP protein kinase deficiency: W-P-W syndrome

Brain glycogenoses

Adult polyglucosan body disease, Lafora disease and other disorders associated with accumulation of polyglucosan bodies in the brain neurodegenerative disease with adult onset, epilepsy,
- accumulation of polyglucosan bodies
Liver glycogenoses

Fasting hypoglycemia, hepatomegaly, growth retardation or hepatomegaly without tendency to hypoglycemia

prototypical GSD: GSD I (von Gierke disease- glucose-6-phosphatase deficiency), incidence approx. 1:100 000
common: GSD IX: phosphorylase kinase deficiency : incidence approx. 1:100 000
Type I Glycogen Storage Disease (Glucose 6-Phosphatase Deficiency, von Gierke Disease)

Excessive accumulation of glycogen in liver, kidney and intestinal mucosa

Patients usually present in infancy with hepatomegaly and/or hypoglycaemic seizures, hyperlactacidemia after a short fast

Gout, hyperlipidemia (hypertriglyceridemia), skin xanthomas

Doll-like face, thin extremities, short stature, protuberant abdomen (hepatomegaly), inflammatory bowel disease

Fibrosis, liver adenomas -cave: malignant transformation, Atherosclerosis

Fasting tolerance improves with age, long-term complications

Treatment: frequent feeding, nocturnal nasogastric drips in infancy, uncooked cornstarch, liver transplantation

Autosomal recessive, overall incidence is 1:10000, frequent in Ashkenazi

The diagnosis is based on clinical presentation, abnormal blood/plasma concentrations of glucose, lactate, uric acid, triglycerides, and lipids, and molecular genetic testing.
Glucose -6-phosphatase system

Localized to luminal face of ER

Type Ia GSD: deficient activity of phosphatase
Type Ib GSD: a defect in the microsomal membrane transport system of G-6-P
Type Ic GSD: a defect in microsomal phosphate or pyrophosphate transport,

Non-a types associated with neutropenia and inflammatory bowel disease with recurrent bacterial infections and oral ulcers
The metabolic consequences of GSD I

- ATP
- ADP
- IMP
- Glucose-6-P
- PP-ribose-P
- Uric Acid
- Hypouricemia
- Lactic Acid
- Lactic acidemia
- Lactate
- Hyperalaninemia
- Pyruvate
- α-Ketoglutarate
- TCA cycle
- Glycogen
- Glucose
- Glycerol-P
- Acetyl-CoA
- Fatty Acids
- Triglycerides
- Hyperlipidemia
- Cholesterol
- Adipose Tissue
Type III Glycogen Storage Disease (Debrancher Deficiency; Limit Dextrinosi
s; Cori or Forbes Disease)

Both liver and muscle are affected: frequent cirrhosis, myopathy, often cardiomyopathy, with fasting ketotic hypoglycemia about 15% percent of patients have only hepatic presentation myopathic presentation - also in adulthood Abnormal glycogen: limit dextrin

Type IV (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

Abnormal glycogen resembling amylopectin – fewer branching points presents in infancy with liver failure leading to cirrhosis, rare hypoglycemic, cardiomyopathy death at 4-5 years without liver transplantation

Neuromuscular presentation - accumulation of polyglucosan bodies in tissues - myopathy, adult polyglucosan body disease
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Type IX Glycogen Storage Disease (deficiency of phosphorylase kinase (PhK) and subunits)

Degradation of glycogen is regulated by a metabolic cascade resulting in activation of glycogen phosphorylase by phosphorylase kinase.

Phosphorylase kinase enzyme has four copies of 4 subunits each - α, β, γ, δ. Subunit γ is catalytic, subunits α and β are regulatory, δ is calmodulin.

The most common form (90% of cases), liver PhK deficiency (X-linked liver glycogenosis) is due to the deficiency of liver form of α subunit.

deficiency of muscle form of α subunit: X - linked muscle glycogenosis
deficiency of subunit β: autosomal recessive PhK deficiency in liver and muscle;
deficiency of subunit γ, autosomal recessive liver PhK deficiency.
AMP-activated Protein Kinase (AMPK) Deficiency

AMPK activates phosphorylase kinase

AMPK is a cellular energy sensor. It is activated by exercise in muscle and an increase in the AMP/ATP ratio. Heterotrimeric complex: a catalytic subunit (α) and two regulatory γ.

Mutations in the gene encoding γ subunit (PRKAG2) cause ventricular pre-excitation (Wolf-Parkinson-White syndrome) predisposing to supraventricular arrhythmias. Fully penetrant autosomal dominant trait.

Arrow: typical delta wave of W-P-W syndrome
Brain glycogenoses

Adult polyglucosan body disease

Deficiency of the branching enzyme (GSD IV) in astrocytes leads to accumulation of polyglucosan bodies in the brain and slowly progressive neurodegenerative disorder.

Slowly progressive gait disturbance, urinary incontinence, loss of sensitivity in lower extremities, later cognitive decline.
In peripheral nerves and in the brain storage of amylopectin-like glycogen in polyglucosan bodies.
Rare, found almost exclusively in Ashkenazi Jewish patients, AR.

Lafora disease

Progressive severe myoclonic epilepsy with onset usually in adolescence, progressive dementia, aphasia, apraxia.
Leads to vegetative state and death in 10 years from onset.

Lafora bodies in neurons - abnormal glycogen storage.

Mutations in laforin carbohydrate-binding phosphatase and the malin E3 ubiquitin ligase.
Enzyme deficiency is not known.
Muscle glycogenoses (without cardiac involvement)

Excercise intolerance, often followed by rhabdomyolysis

prototypical: GSD V, McArdrie disease, deficiency of myophosphorylase
myalgia and stiffness of exercising muscles relieved by rest, often rhabdomyolysis, later in life
may be present muscle wasting

AR inheritance

no pharmacological treatment
Generalized glycogenosis: Morbus Pompe
M. Pompe

Deficiency of lysosomal acid alpha-glucosidase (acid maltase)
Lysosomal storage of glycogen with normal structure

**Infantile type:**
First symptoms in the first months of life: cardiomegaly, muscle weakness, macroglossia
Progressive course, death due to cardiopulmonary failure in the first two years of life

**Adult type**
Slowly progressive proximal myopathy and/or slowly progressive respiratory failure
Heart is not affected

**Intermediate types**

**Diagnostics:**
proof of glycogen storage in tissues
measurement of enzyme activity

**Treatment**
Enzyme supplementation therapy (Myozyme)
Congenital disorders of glycosylation (CDG)
Glycoproteins

N-glycosylation

O-glycosylation

**Disorders of glycosylation:**
CDGs (previously known as carbohydrate-deficient glycoprotein syndromes)
Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common N-linked Oligosaccharide

Precursor oligosaccharide is held in the ER membrane by dolichol,
Processing of oligosaccharide chains of glycoproteins in ER and Golgi
Congenital disorders of N-glycosylation

**CGD I:** >16 disorders of N-glycan assembly (CDG Ia-m) including dolichol-phosphate synthesis defects

(CDG Ia: phosphomannomutase 2 deficiency)

**CDG II:** >8 disorders of processing of N-glycans

**Congenital disorders of O-glycosylation**

> 6 disorders

**Disorders of glycolipid glycosylation**

3 disorders: GM3 synthase deficiency, ...

Highly variable phenotype

Autosomal recessive disorders

Autosomal dominant: 1 disorder (hereditary multiple exostoses sy.)
Congenital disorders of glycosylation

Aberrant protein glycosylation

Diagnostic paradigm:
analysis of glycans → molecular defect

Screening:
Isoelectric focusing of sialyltransferin in defects of N-linked glycans
Isoelectric focusing of apo CIII in defects of N-linked glycans

Structural analysis of glycans

Measurement of enzyme activities

Mutation analysis

CDG-x: abnormal glycosylation detected by screening techniques, but with unknown molecular defect
Isoelectrofocusing of serum sialotransferins

A, G controls,
B to F: type-I pattern
B phosphomannomutase def., C phosphomannose isomerase (PMI) deficiency D, hypoglucosylation defect; E, F unidentified
H to J: type-II pattern
H, N-acetylglucosaminyltransferase (GnT II) def; I, Junidenti®ed
Glycoproteins Reported to Be Abnormal in Phosphomannomutase Deficiency and Showing an Abnormal Pattern on Isoelectrofocusing, Two-dimensional Electrophoresis, Western Blotting, and/or Decreased or Increased Concentration or Enzymatic Activity

**Serum**
- Transport Proteins
  - Apoprotein B, apoprotein CII, apoprotein E, ceruloplasmin-haptoglobin, α2-macroglobulin, retinol-binding protein, sehormone-binding globulin, thyroxine-binding globulin, transcobalamin II, transcortin, transferrin, vitamin D-binding globulin
- **Coagulation and Anticoagulation Factors**
  - Antithrombin, α2-antiplasmin, coagulation factors II, V, VI, VIIIIX, X, XI, and XII, heparin cofactor II, plasminogen, protein C, protein S
- **Hormones**
  - Follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone
- **Lysosomal Enzymes**
  - Arylsulphatase A, α-fucosidase
- **Other Enzymes**
  - N-Acetylglucosaminidase, carboxypeptidase, cholinesterase
- **Other Glycoproteins**
  - Amyloid P, α1-acid glycoprotein, a1-antichymotrypsin, α1-antitrypsin, α1-B glycoprotein, clusterin, complement C3a, complement C4a, complement C1 esterase inhibitor, α2-HSglycoprotein, immunoglobulin G, orosomucoid, peptide PLS:29, peptide PLS:34, Zn-a2-glycoprotein

**Cerebrospinal Fluid**
- β-Trace protein, transferrin

**Leukocytes**
- **Lysosomal Enzymes**
  - α-Fucosidase, β-glucuronidase, α-iduronidase, α-mannosidase, β-mannosidase

**Sialoglycoproteins on B lymphocytes**

**Fibroblasts**
- Biglycan, decorin

**Liver**
- α1-Acid glycoprotein, α1-antitrypsin, haptoglobin, transferrin

Glycosylation defects lead to abnormal glycoproteins, which normally have diverse functions.
Today, more than 70 disorders of glycosylation are known...

and we still do not know all of them

recent review:

http://www.jbc.org/content/288/10/6936.full
Patients with CDGs can be referred to specialists in different fields of medicine

<table>
<thead>
<tr>
<th>Field</th>
<th>Symptoms / Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurology</td>
<td>axial hypotonia; hyporeflexia; developmental delay, seizures, stroke-like events, micro- and macrocephaly, myopathy</td>
</tr>
<tr>
<td>Gastroenterology/Hepatology</td>
<td>failure to thrive, vomiting, protein-losing enteropathy, liver dysfunction; hepatomegaly, cholangitis, chronic diarrhoea</td>
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<tr>
<td>Neonatology</td>
<td>hydrops, ascites, multiorgan failure; failure to thrive; floppy baby</td>
</tr>
<tr>
<td>Haematology</td>
<td>thrombocytosis, thrombocytopenia, coagulopathy, thrombosis, anaemia, leukocytosis, thrombocytopenia</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>hyperinsulinemic hypoglycemia; hypothyroidism; hypergonadotropic hypogonadism; growth retardation</td>
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<tr>
<td>Clinical genetics</td>
<td>dysmorphic features</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>osteopenia; joint contractures; kyphosis/scoliosis; short limbs; arthrogryposis</td>
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<tr>
<td>Ophthalmology</td>
<td>abnormal eye movements; squint, cataract; retinitis pigmentosa; nystagmus, iris coloboma; cortical blindness</td>
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<tr>
<td>Radiology</td>
<td>cerebellar hypoplasia, calcification of white matter; delayed myelinisation, micropolygyria, renal hyperechogenicity</td>
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<tr>
<td>Histology</td>
<td>liver fibrosis, liver cirrhosis, lamellar inclusions in hepatocytes; intestinal villus atrophy</td>
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<tr>
<td>Dermatology</td>
<td>ichthyosis; abnormal fat distribution</td>
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<tr>
<td>Nephrology</td>
<td>nephrotic syndrome; tubulopathy; cystic kidneys</td>
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<tr>
<td>Immunology</td>
<td>recurrent infections; hypogammaglobulinaemia</td>
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<tr>
<td>Cardiology</td>
<td>cardiomyopathy, pericardial effusions</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>hypocalbuminaemia, elevated transaminases, low cholesterol, triglycerides, decreased antithrombin III, decreased factor VIII and XI, decreased protein C and S, elevated FSH, LH and prolactin; elevated TSH, low free T4</td>
</tr>
</tbody>
</table>
Phosphomannomutase 2 deficiency
Treatment of phosphomannose isomerase deficiency by mannose supplementation
Disorders \(o\)-linked glycosylation

A number of rare disorders with highly variable clinical presentation

Examples:

**\(\alpha\)-Dystroglycanopathies** – a group of disorders that adds O-mannose-linked glycans to \(\alpha\)-dystroglycan. Congenital muscular dystrophies

**X-linked paroxysmal nocturnal hemoglobinuria**
Defect in synthesis of GPI-anchor (gene PIG-A)

**Walker-Warburg syndrome**
brain and eye malformations, muscular dystrophy
defect in synthesis of mannosylated \(O\)-linked oligosaccharides

**Hereditary multiple exostoses**
Dominant disorder
deficiency of two glucosyltransferases that function in synthesis of heparan sulfate