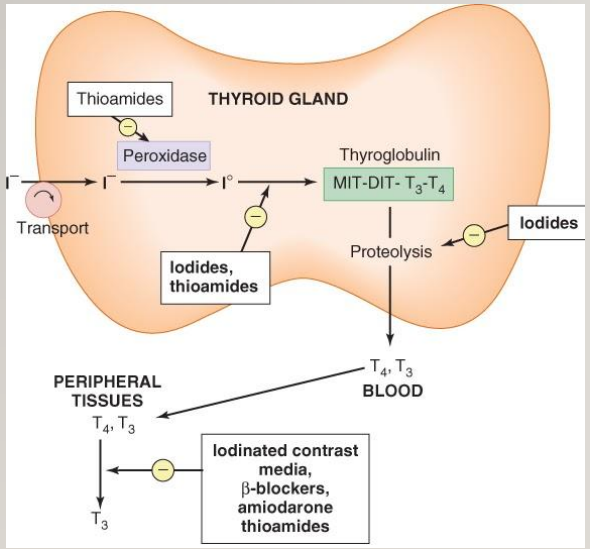
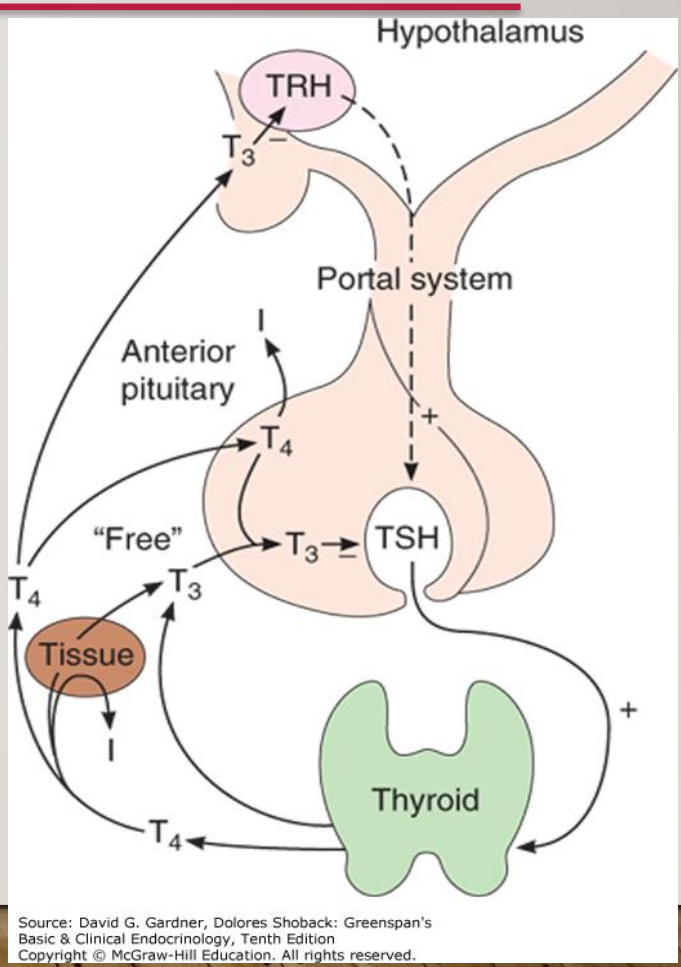
PEDIATRIC ENDOCRINOLOGY I.

J. KYTNAROVÁ , KPDPM 1. LF UK A VFN

THYROID GLAND HORMONOGENESIS AND REGULATION



- **<u>Substrates:</u> iodine and amino acids**
- **Iodine - 59-65%**
- **prohormone – thyreoglobulin**
- **thyroxine (T4)**
- **3,5,3´triiodothyronine (T3)**
- **T3 3-8x more efficient than T4**
- **Production T4/T3 3:1**



Source: http://doctorsgates.blogspot.com/2011/01/

WHAT IS THE MAIN SYMPTOM...?

1. Goiter

- Palpation

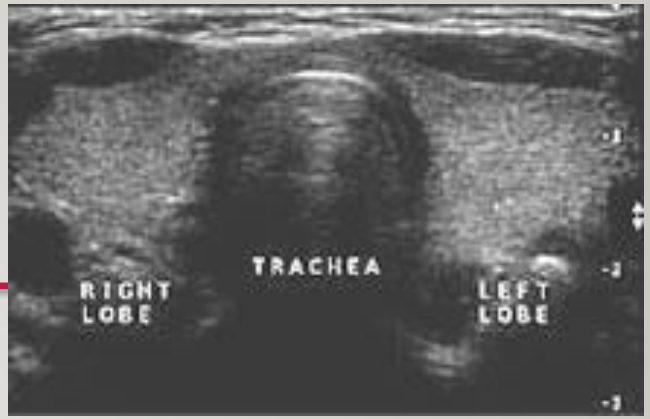
2. Symptoms of pressure (autoimmune thyreoditis)

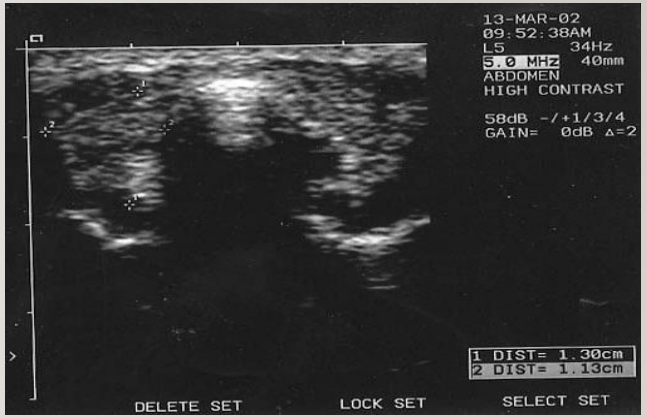
- Coughing
- Discomfort on/in the neck

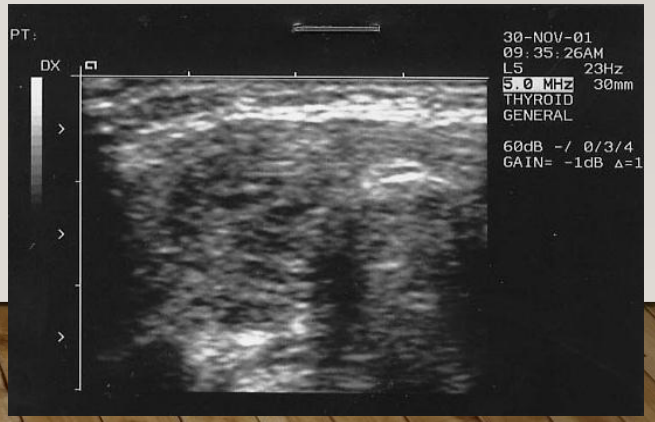
- **3. Signs of impaired function of thyroid gland**
- Hypofunction, hyperfunction
-

THYREOPATHIES DIAGNOSTICS

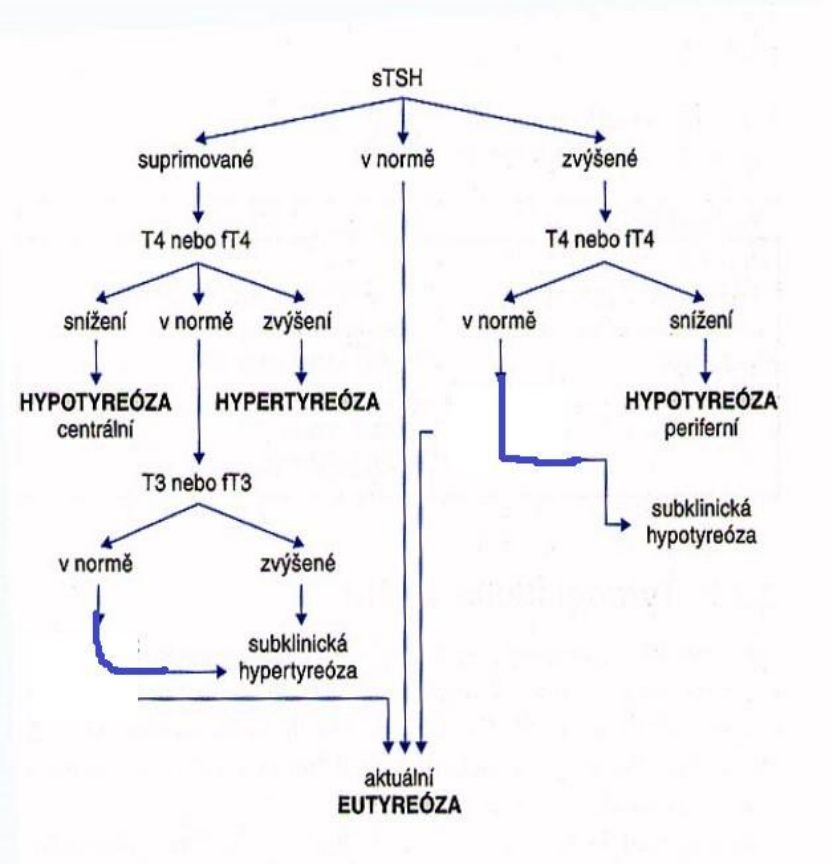
- **Physical examination**
- Clinical signs of impaired thyroid function
- Goiter –the presence of goiter should always be verified by sonography!!
- **Ultrasound**
- **size** – goiter
- **structure** - -signs of autoimmune disease
- - focal changes







LABORATORY TESTS



Antibodies

Anti TPO – against peroxidase (CLT 90%, GBT 86%)

Anti Tg - against thyreoglobulin (CLT 70%, GBT 30%)

CAVE! Only when anti TPO are negative

Long-term follow-up of antibodies has no prognostic significance! It is not necessary repeat them! (1x in 1-2 years)

TRAK - TSH-R-Ab (stim)

CAVE! Only Graves disease, dynamics monitoring is useful

Source: doporučený postup „Diagnostika a léčba tyreopatií". Novelizace 2015. Límanová Z. a kol. Společnost všeobecného lékařství.

SCINTIGRAPHY - INDICATIONS

- **1. congenital hypothyreoidism**
- Ectopic thyroid tissue
- Dyshormonogenesis

- **2. Autonomous production of thyroid hormones (independent adenoma)**

- **3. Metastases of thyroid gland carcinoma after elimination of thyroid gland**

FNAB (FINE NEEDLE BIOPSY)

- **Advantages**
- simple, rapid, cheap
- relatively non-invasive
- substantial informations
- Genetics – somatic mutation
- **Disadvantages**
- it may not be consistent with histology

GOITER

The most common causes of thyroid enlargement ??

CAUSES OF THYROID ENLARGEMENT

- **1. – 2. Iodine deficiency X AITD (autoimmune thyroid disease)**
- Improved iodine supplementation
- ↓ difuse goiter with normal function
- ↑ AITD
- (*Němeček a kol., 2005)*
- **x**
- 3. Congenital defects of hormonogenesis
- 4. Graves disease
- 5. Tumors…..

Hill a Adamson, 1847, first photograph of goiter. www.ganfyg.org

IODINE

- **Recommended daily intake of iodine (**UNICEF, ICCIDD, WHO, 2007)
- *(Assessment of iodine deficiency disorders and monitoring their elimination.http://apps.who.int/iris/bitstream/10665/43781/1/9789241595827_eng.pdf)*

Age	Recommended daily intake of iodine (ug/den)
Preschool children (0-59 months)	90
School children (6-12 years)	120
Adolescents and adults (above 12 years)	150
Pregnant and lactating women	250

„IODINE DEFICIENCY DISEASE“

- **Fetus**
- Abortions, stillbirths, congenital anomalies, ↑ perinatal mortality
- **Neonates, infants**
- Endemic cretenism, psychomotor retardation, goiter, hypothyroidism
- **Children and adolescents**
- **Goiter with normal function,** hypothyroidism, impaired mental function
- (prolongated reaction time), delayed physical development, short stature,
- Spastic diplegia (source: *Assessment of iodine deficiency disorders and monitoring their elimination.http://apps.who.int/iris/bitstream/10665/43781/1/9789241595827_eng.pdf)*

(Source: Labhart A. Clinical Endocrinology, 1974)

„IODINE DEFICIENCY DISEASE“

- ↓ number of countries with iodine deficiency
- in 2007 and 2011 there was no country with proved severe iodine deficiency
- 37/128 countries with sufficient iodization in at least 90% of households
  39/128 countries, where iodization covers less than 50% of the population
  70% of households worldwide have access to iodized salt
- *(Zimmermann M.B., Andersson M. Update on iodine status worldwide, Current Opinion in Endocrinology, 2012,*
- *Andersson M, Zimmermann M.B. ICCIDD, Global iodine nutrition: a remarkable leap forward in the past decade, 2012)*
-

SALT IODIZATION

- **Czech Republic – iodization since 1950s, changes in 1994**
- Iodide (KI) → iodate
- 25 mg/kg → 35 mg/kg (20 – 34 mg/kg)
- Iodization of food salt and some food products
- **Excessive iodine intake**
- 350 - 500 ug
- „trigger“ of autoimmune disease, Iodine ↑antigenicity TG

HYPOTHYROIDISM

- **<u>Congenital</u>**
- **1. Thyroid gland dysgenesis - 80-85%** ***(agenesis, ectopic thyroid gl., hypoplasia)***
- **2. Dyshormonogenesis**
- **3. Central hypothyroidism (hypothalamus – pituitary)**
- 4. Transplacental transmission of goitrogenic agents
- 5.Target tissue resistence against thyroid hormones
-

CONGENITAL HYPOTHYROIDISM CLINICAL SIGNS AND SYMPTOMS

5-10% newborns after delivery

Development during weeks up to 2-3 months

↑ BW and BL

Large anterior fontanelle, small f. opened

Prolongated jaundice

↓ Physical activity

Hypotonia

Hypothermia

Source: Labhart A. Clinical Endocrinology, 1974

CONGENITAL HYPOTHYROIDISM CLINICAL SIGNS AND SYMPTOMS

- Poor feeding
- Decreased stooling or constipation, vomiting
- **myxedema**
- **-** skin, face, periorbital edema
- - Respiratory tract → respiratory distress, perioral cyanosis
- **- macroglossia**
- **Wide and flat nasal root**
- **Teeth eruption delay**
- **Psychomotor retardation**
- **Growth retardation**
- **Hearing loss**

Source: Labhart A. Clinical Endocrinology, 1974

NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM

- The most common ***treatable*** cause of mental retardation
- Czech Republic - screening since 1985
- **Incidence**
- Czech Republic - year 2016 1 : 3 521 newborns
- Word 1 : 3000-4000 newborns
- **TSH** 48.-72. hour after delivery dried blood spot

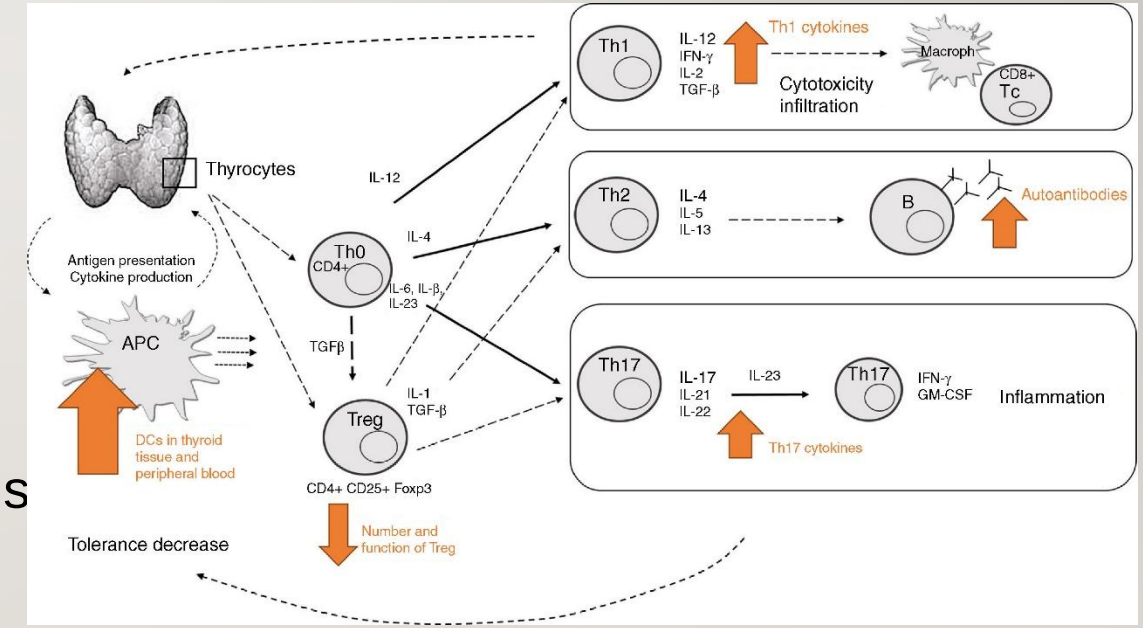
- *Cave! does not detect central hypothyroidism!*

ACQUIRED HYPOTHYROIDISM CAUSES

- **Chronic autoimmune thyroid disease (CAITD)**
- Central hypothyroidism (TRH/TSH)
- Thyroidectomy
- ^{131}I therapy
- Strumigens (↑ iodine intake, cobalt)
- Thyroid gland infiltration (cystinosis, histiocytosis X)
- Craniospinal radiotherapy ……..

AUTOIMMUNE THYROID DISESAE (AITD) ETIOLOGY AND PATHOGENESIS

- **Genetic factors (predisposition) (HLA system)**
- **Environmental factors („triggers“)**
- **1. *Infections (biological factors)***
- Viral **-** enterovirus – coxsackie B, retroviruses – GBT
- Bacterial – Yersinia, borrelia, …..
- **2. *Physical and chemical factors***
- **Drugs** -Amiodaron, drugs with iodine content, cytokins
- X – ray contrasts, psychofarmacs (lithium)
- **Radiation, smoking… free radicals, chemical toxins**
- **3. *stress including mental stress***



Source: Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms | Endocrinología y Nutrición (English Edition)

AITD – CLASSIFICATION

- ***Chronic autoimmune thyroid disease (CAITD) – Th1 cellular immune response***
- Hashimoto thyreoiditis (goiter, nodular changes)
- Chronic lymphocytic thyreoiditis without goiter and/or with atrophy
- Chronic lymphocytic thyreoiditis of children and adolescents
- Chronic fibrotic thyreoiditis
- Postpartum thyreoiditis
- ***Graves-Basedow hyperthyroidism – Th2 antibody response***

HYPOTHYROIDISM
CLINICAL SIGNS AND SYMPTOMS

Skin	**dry rough skin, myxedema, macroglossia, swelling, hair dry, coarse, hair thinning soft swelling of the face, yellowed skin rigid soaked forearm**
Labor	**muscle weakness, fatigue, change of voice**
Metabolism	**weight gain (accumulation of fluid in myxedema, decreased metabolism) decreased appetite constipation, winter intolerance….**
Nervous system	**slowness, sleepiness**
Circulation	**Bradycardia**

(Source: Šilink K, 1962)

HYPOTHYROIDISM
CLINICAL SIGNS AND SYMPTOMS

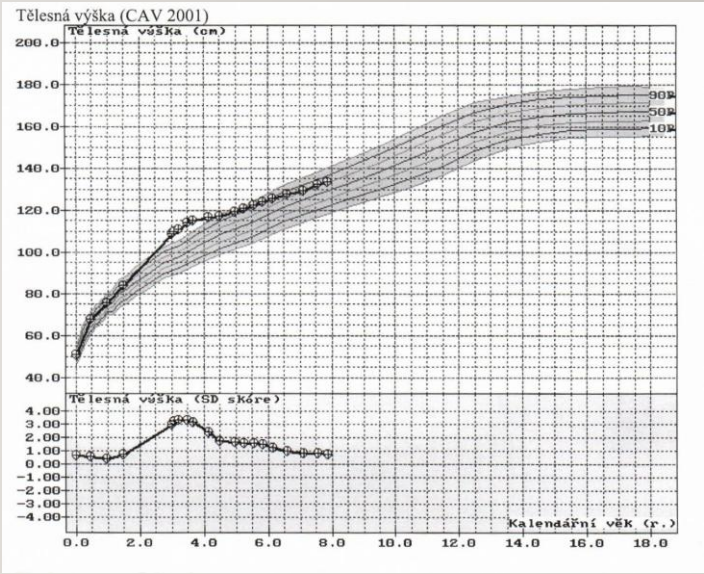
- **<u>Differences in childhood</u>**
- **Decreased growth velocity**
- **Delay of puberty, bone maturation**
- **Irreversible CNS damage up to 3 years of age**

HYPERTHYROIDISM - CAUSES

Immune	**Graves disease** Transient hyperfunctional phase of CAITD
Autonomous production	**Nodular goiter** **Adenoma with autonomous production**
Iatrogenic	Medication ↑ iodine intake
Central hyperthyreodism	Pituitary adenoma with ↑ TSH secretion
Ostatní - vzácně	Differenciated thyroid Ca metastasis Neonatal hyperthyroidism (transplacental TRAK transfer) McCune-Albright syndrom

HYPERTHYROIDISM - SIGNS AND SYMPTOMS

Skin	sweaty wet skin, tremor, thinning of hair
Labor	muscle weakness, myopathy
Metabolism	Weight loss with increased appetite more frequent stools heat intolerance osteoporosis ***Cave! Acceleration of growth velocity!***
Nervous system	nervousness, irritability, ↓ attention, tremor, insomnia
Circulation	tachycardia, palpitations
Eyes	protrusion, orbitopathy



GBT - THERAPY

- **1.Conservative - drugs**
- **Thyreostatics** - the first drug of choice
- **Methymazole (thyrozole**) 0,15 - 0,5 mg/kg/day, after 4-6 weeks ↓ 25-50% dose reduction
- Duration of treatment - long lasting enough > 3 years
- block-replace therapy
- **Overall remission rate afte 2 years therapy** 20- 30%
- **2. Definitive treatment**
- indications: disease recurrence, insufficient treatment effect, intolerance of therapy, non-compliance ..
- **ČR - Surgical treatment - total thyroidectomy (TTE)**
- **Europe** – **Radioiodine 131I (RAI) (ČR -** radioiodine contraindicated in childhood)
- ***(2022 European Thyroid Association Guideline for the management of pediatric Graves' disease – PubMed)***

NEONATAL HYPERTHYROIDISM

- 1. **Transplacental transfer TSH-R (stim) antibodies**
- (active mother´s GBT), could be present after TTE, ablation by radioiodine… !!!
- 2. **Activation mutation of G protein** (McCune-Albright syndrome)
- 3. **Activation mutation of TSH receptor**

Signs and symptoms

IUGR, hydrops faetalis

craniostenosis

Poor weight gain, diarrhea, vomiting

tachykardia, heart failure, arrhytmia

neonatal GBT – self limiting – up to 48 weeks

DIABETES MELLITUS

- **Definition**
- a group of metabolic diseases characterized by **chronic hyperglycemia**
- **Causes**
- insufficient insulin **secretion**
- Insufficient insulin **action (insulin resistance)**
- a combination of both of the above
- **Consequences**
- Insufficient effect of insulin in target tissues → abnormalities of carbohydrate, fat and protein metabolism

DIABETES MELLITUS

- One of the most serious and most common metabolic diseases in childhood
- USA - incidence is higher than all malignancies
- ČENDA (Czech national register of childhood DM, ČDS JEP)
- **420 newly diagnosed children/year 2019**
- **508 newly diagnosed children/year 2022**
- **475 newly diagnosed children/year 2023**
- **diabetic ketoacidosis (DKA) - first manifestation of DM in 15% -70% of children**

DIABETES MELLITUS CLASSIFICATION
(ADA 1997, WHO 1998)

- **Typ I** (IDDM…)
- β cells destruction
- **Typ II** (NIIDM, maturity onset)
- mainly insulinoresistance with relative lack of insuline
- **Gestational diabetes mellitus**
- **Other specific types**

SPECIFIC TYPES OF DM

- **Genetic defects of β cells**
  - MODY (at least 14 different known MODY mutations), monogenic diabetes, mitochondrial DM
- **Pancreatic diseases**
  - cystic fibrosis, pankreatitis, hemochromatosis, Tumors..
- **Infections c**ong. rubella, CMV...
- **Drugs -** glucocorticoids, thyroid hormones, diazoxide, phenytoin….
- **Endocrinopathies** acromegaly, Cushing, pheochromocytoma…..
- **Genetic syndromes –** Turner, Prader-Willi sy, Klinefelter, Down…..

CHARACTERISTICS OF DM I. AND II.

	DM I	DMII
Age of onset	Usually <30 let	Usually >40 let
Weight (BMI)	Obesity uncommon	80% are obese
Genetics	Polygenic (HLA associated)	Polygenic (non HLA associated)
Antibodies against β cells	++	-
Insuline therapy	The only choice, permanent	Usually not necessary
Complications	Frequent	Frequent
Frequency (%)	90-95%	2% (Caucasian population)

ETIOLOGY OF DM I

- chronic immune-mediated destruction of pancreatic β-cells

- **Antibodies**
- ICA (against β cells)
- IA2 (against tyrosin fosfatase)
- GAD65 (against glutamic acid decarboxylase)
- IAA (against insuline)
- ZnT8 (againts zinc transporter 8)

GENETIC AND ENVIRONMENTAL FACTORS

- **Genetic factors**
- Interaction of many genes, the strongest association with HLA (Human Leucocyte Antigen)
- ↑risk HLA DR3 - DQA1*0501-DQB1*0201 , HLA DR4 - DQA1*0301 -DQB1*0302
- ↓risk HLA DR2 - DQA1*0102 -DQB1*0302
- risk in first-degree relatives - ↑ 15x
- **Nongenetic factors – environmental „triggers“**
- Seasons – ↑ winter, autumn
- **Infections – enteroviruses (Coxsackie virus B)**
- Nutrition – duration of breast feeding, cow milk, nitrates and nitrites…
- Perinatal and early childhood period – ↑ mother´s age, ↓ contacts with peers ….
- Hygiene theory…..

PATHOPHYSIOLOGY OF DM I

- ↓ insuline secretion → catabolism
- → utilisation of energy from fat and muscle tissue (↑ lipolysis and ↑ proteolysis)
- → ↑ gluconeogenesis in liver (↑ AMK a FFA in hepatocytes)
- ↑ ketogenesis
- 2. ↓ insuline/glucagon ratio →↑ ketone levels by direct effect on hepatocytes
- ↓ peripheral utilization of glucose and ketones
- ↑ ketones (β hydroxybutyrate, acetoacetat) → **metabolic acidosis**

COURSE OF DM I
SIGNS AND SYMPTOMS DEVELOPMENT

- **postprandial hyperglycaemia**
- fasting **hyperglycaemia** - late sign, ↑ gluconeogenesis
- **glycosuria** - renal threshold for glucose (10 mmol/l)
- osmotic diuresis → **polyuria**, loss of electrolytes to the urine,
- **dehydration**
- compensatory **polydipsia**

CLINICAL CHARACTERISTICS AT PRESENTATION OF DM 1

- **<u>Non-emergency presentations</u>**
- Recent onset of **enuresis** in a previously toilet-trained child (may be misdiagnosed as a urinary tract infection)
- Chronic **weight loss** or failure to gain weight in a growing child
- Irritability and decreasing school performance
- Perineal **candidiasis,** especially in prepubertal girls. Recurrent **skin infections**
- *Source: ISPAD Clinical Practice Consensus Guidelines 2022. https://www.ispad.org/page/ISPADGuidelines2022*

CLINICAL CHARACTERISTICS AT PRESENTATION OF DM 1

- **Emergency presentations (diabetic ketoacidosis)**
- Moderate to severe **dehydration**
- Frequent vomiting, abdominal pain (may be misdiagnosed as gastroenteritis)
- Continuing **polyuria** despite the presence of dehydration
- **Weight loss** due to fluid loss and loss of muscle and fat
- Acetone detected on the breath
- **Kussmaul respiration** (Hyperventilation of diabetic ketoacidosis,
- **Alteration of consciousness** (disoriented, semicomatose, or rarely comatose)
- **Shock** (rapid pulse rate, poor peripheral circulation with peripheral cyanosis)
- Hypotension (a very late sign and rare in children with diabetic ketoacidosis)
- *Source: ISPAD Clinical Practice Consensus Guidelines 2022 . https://www.ispad.org/page/ISPADGuidelines2022*

DKA – BIOCHEMICAL CRITERIA

- Hyperglycemia (blood glucose >11 mmol/l
- Venous pH <7.3 or serum bicarbonate <15 mmol/l
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) or moderate or large ketonuria

- *Source: ISPAD Clinical Practice Consensus Guidelines 2022*
- *https://www.ispad.org/page/ISPADGuidelines2022*

CRITERIA FOR THE DIAGNOSIS OF DM

- **1. Hyperglycaemia (≥11.1 mmol/L) and symptoms of diabetes or hyperglycemic crisis**
- **or 2. Fasting plasma glucose ≥7.0 mmol/L.**
- **or 3. OGTT - two-hour postload glucose ≥11.1 mmol/L**
- **or 4. HbA1c ≥6.5%b**
- unclear cases – **repeated glucose measurements!!!** Fasting/postprandial (2 hours) or glycemic profile
- *OGTT should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria, as excessive hyperglycemia can result from the test!!!!.*
- *OGTT may be useful in diagnosing other forms such as type 2 diabetes, monogenic diabetes*
- **Antibodies GAD, IA2, IAA, ZnT8, HbA1C**
- OGTT (fasting gly >7 mmol/l, 2 hours > 11,1 mmol/l)
- *Source: ISPAD Clinical Practice Consensus Guidelines 2022 . https://www.ispad.org/page/ISPADGuidelines2022*

DKA – GOALS OF THERAPY

- correct dehydration (ECF loss – moderate DKA 5-7%, severe DKA 7-10%)
- correct acidosis and reverse ketosis (bicarbonate therapy when pH < 6,9)
- gradually restore blood glucose concentration to near normal
- To correct salt depletion (Na, K)
- monitor for complications of DKA and its treatment
- identify and treat any precipitating event.

- *ISource: ISPAD Clinical Practice Consensus Guidelines 20122. https://www.ispad.org/page/ISPADGuidelines2022*

DKA - REHYDRATATION

- **Volume expansion (resuscitation)**
- 0,9% saline **10 ml/kg** infused over **30 – 60 min (10-20 ml/kg 0,9% saline over 1-2 hours)**
- **shock - bolus 20 ml/kg**
- **Subsequent fluid management (deficit replacement)**
- **0,45 – 0,9 % saline or a balanced salt solution (Plasmalyte)**
- with added **potassium** chloride, potassium phosphate or potassium acetate
- replace the estimated fluid deficit over 24 to 48 hours (50% first 8 hours, 50% 16 hours
- **5% glucose** should be added to the IV fluid when the plasma glucose falls to approximately 14 to 17 mmol/L
- *Source: ISPAD Clinical Practice Consensus Guidelines 2022 https://www.ispad.org/page/ISPADGuidelines2022*

DKA- INSULIN THERAPY

- Start insulin infusion at least 1 hour after starting fluid replacement therapy
- **Dose: 0.05 to 0.1 unit/kg/h** (dilute 50 units regular insulin in 50 mL normal saline, 1 unit = 1 mL)
- Route of administration IV
- An IV bolus should not be used at the start of therapy; may increase the risk of cerebral edema,
- **glucose typically decreases at a rate of 2 to 5 mmol/L/h**
- **Cave!!** *If BG falls very rapidly (>5 mmol/L/h) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 17 mmol/L.*
- *If glycemia falls rapidly or is low before resolving DKA, ↑ the amount of glucose administered, do not reduce the dose of insulin!*
- **Keep glycemia around 11 mmol/l**
- *ISource: ISPAD Clinical Practice Consensus Guidelines 2022. https://www.ispad.org/page/ISPADGuidelines2022*

Goals of therapy of DM 1

- **Optimal metabolic compensation –** prevention of long-term chronic complications of DM
- **Low variability** of BGs over 24 hours, without hypoglycaemic episodes
- **BG 4.4 – 10 mmol/l**

HBA1C < 53 mmol/mol kompenzace
< 48 mmol/mol (remission, availability of technologies)

https://www.ispad.org/page/ISPADGuidelines2022

CGM – 14 days
>70% expected range (3,9 – 10 mmol/l)
< 4% pod 3,9 mmol/l
< 1% pod 3 mmol/l
< 25% nad 10 mmol/l
< 5% nad 13,9 mmol/l
➢ Variabilty coeficient (CV)≤ 36%

DM I – INSULIN THERAPY

- **Basal and prandial insulins schedule (subcutaneous) -** as close to physiological insulin replacement as possible
- Long - acting analog 1-2 x daily
- At least 3 rapid – acting insulin (analog) injections
- **Fixed of flexible** insuline dosing ????
- **Dose:** prepubertal children 0,7 – 1,4 IU/kg /day (partial remission < 0,5 IU/kg)
- puberty 1,2 -2 IU/kg/day
- 30 – 50% of daily dose – long – acting analog
- **insulin pump treatment (Continuous subcutaneous insulin infusion [CSII])**

NUTRITIONAL MANAGEMENT

- Dietary recommendations are based on healthy eating principles suitable for all children and families
- *Remember! Only 10% of patients with DM I always follow the nutritional plan (at least at 90% of meals) !*
- *Three meals a day incorporating a wide variety of nutritious foods from all food groups, with appropriate healthy snacks (if necessary), will supply all essential nutrients, maintain a healthy weight, prevent binge-eating and provides a framework for regular monitoring of blood glucose levels and supervision of insulin doses (as required).*

BGS SELF- MONITORING

- **Continuous glucose monitoring (CGM)**
- **Flash glucose monitoring (FGM) (freestyle libre)**
- **fingerstick BGs testing - 6 to 10 times per day**

- *„Regular self-monitoring of glucose (using accurate fingerstick blood glucose [BG] measurements, with or without continuous glucose monitoring [CGM] or intermittently scanned CGM [isCGM]), is essential for diabetes management for all children and adolescents with diabetes „*

Source: ISPAD Clinical Practice Consensus Guidelines 2022 . https://www.ispad.org/page/ISPADGuidelines2022

FINALLY FROM HISTORY OF PUMPING….