PEDIATRIC ENDOCRINOLOGY I.

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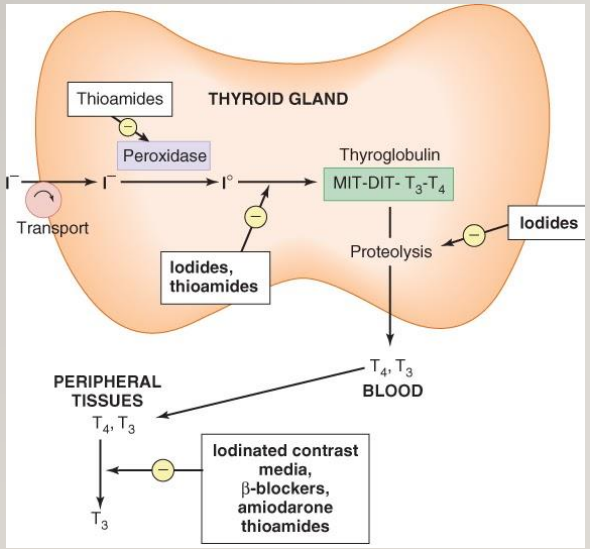
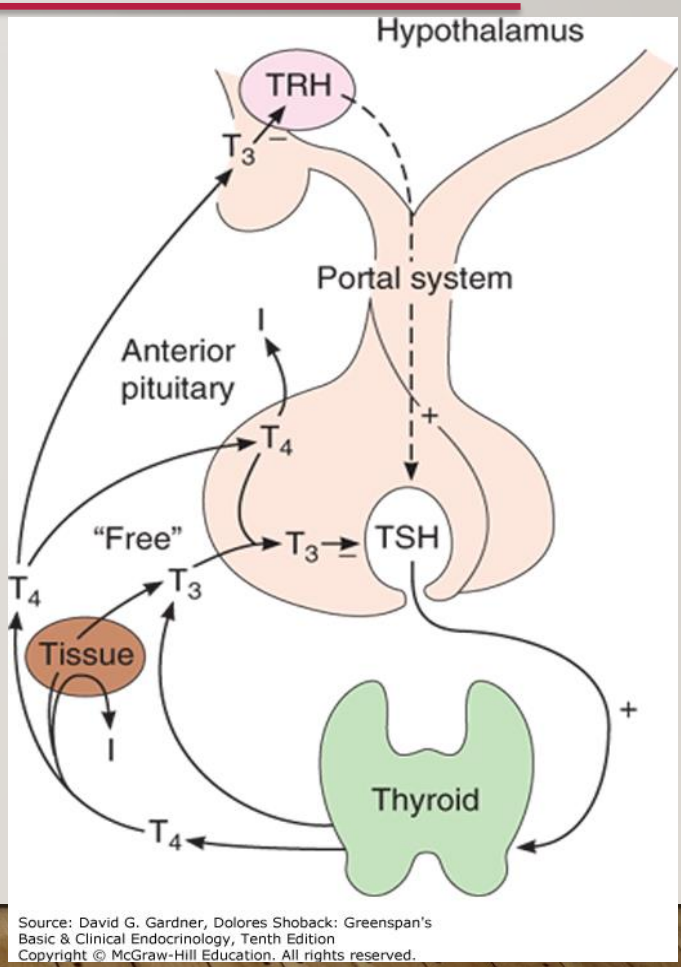
THYROID GLAND HORMONOGENESIS AND REGULATION



- **<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 (in cases of autoimmune thyreoditis)

- Coughing
- Discomfort on/in the neck

WHAT IS THE MAIN SYMPTOM…?

3. Signs of impaired function of thyroid gland

Hypofunction

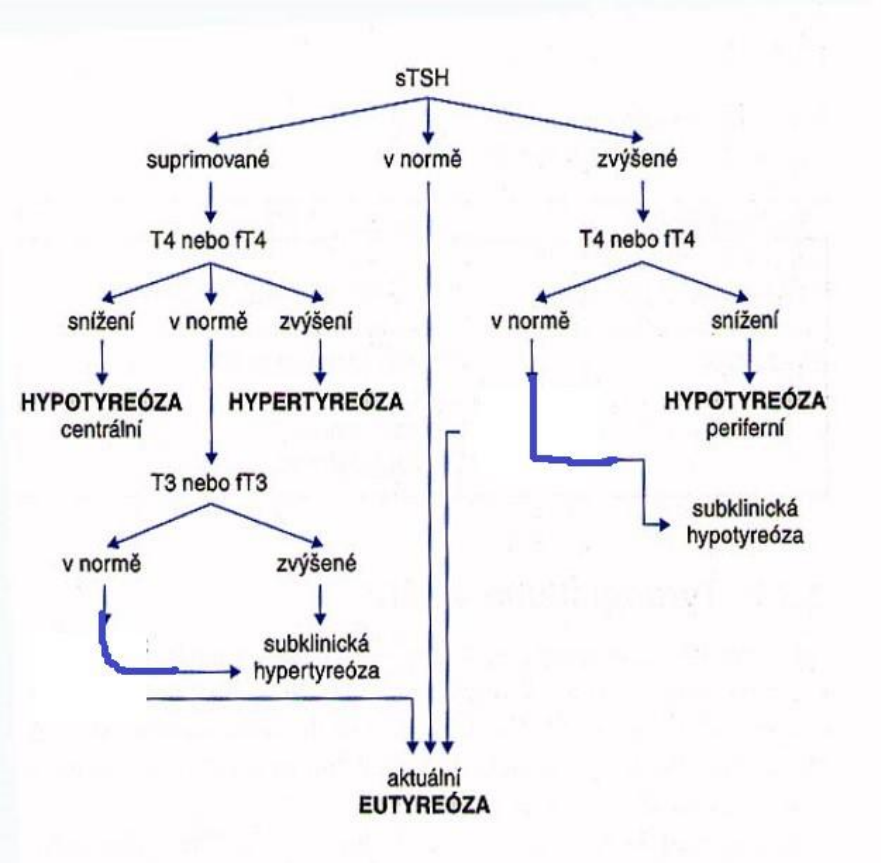
- Decreased growth velocity
- Weight gain
- Obstipation
- Cold intolerance
- ***Hyperfunction***
- Tachykardia, palpitations
- Weight loss
- More frequent stools
- Insomnia
- Mood changes……., enuresis nocturna…. (rare)

….And other signs and symptoms…..

THYREOPATHIES DIAGNOSTICS

- **Physical examination**
- Clinical signs of impaired thyroid function
- Goiter –the presence of goiter should always be verified by sonography!!
- **Ultrasound**
- **size** – goiter (discrepancy between palpation and US 25-29,7%)
- **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 to repeat! (1x in 1-2 years)

TRAK - TSH-R-Ab (stim)

CAVE! Only Graves disease, monitoring the dynamics is necessary

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

SCINTIGRAPHY - INDICATIONS

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

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

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

FNAB (FINE NEEDLE BIOPSY)

- **Advantages**
- simple, rapid, cheap
- relatively non-invasive substantial informations
- **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“

- **<u>Fetus</u>**
- Abortions, stillbirths, congenital anomalies, ↑ perinatal mortality
- **<u>Neonates, infants</u>**
- Endemic cretenism, psychomotor retardation, goiter, hypothyroidism
- **<u>Children and adolescents</u>**
- **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)*

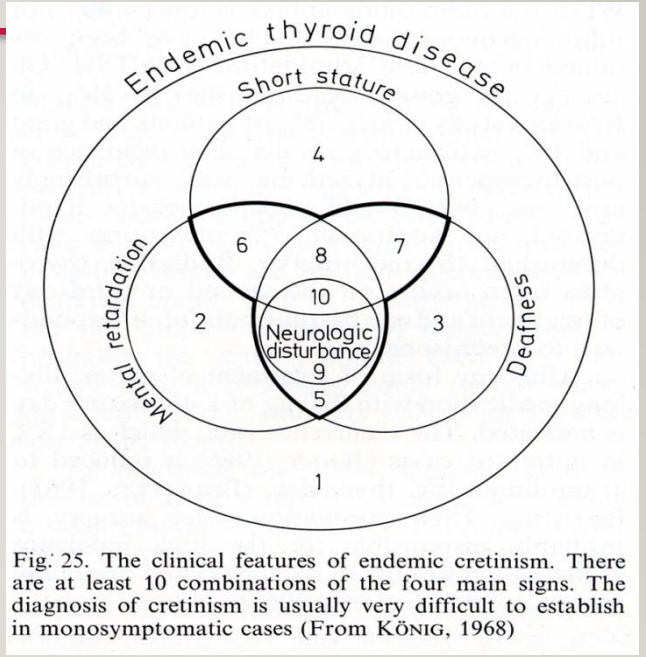


Fig. 25. The clinical features of endemic cretinism. There are at least 10 combinations of the four main signs. The diagnosis of cretinism is usually very difficult to establish in monosymptomatic cases (From KÖNIG, 1968)

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 myxedema $\rightarrow$ respiratory distress, perioral cyanosis
- **makroglossy**
- **Wide and flat nasal root**
- **Teeth eruption delay**
- **Psychomotor retardation**
- **Growth retardation**

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 2015 1 : 2 669 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***

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

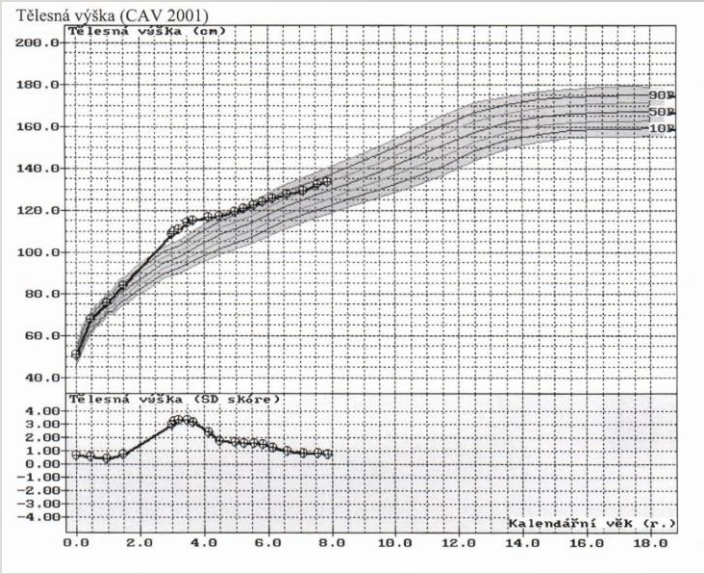
- **Differences in childhood**
- **Decreased growth velocity**
- **Delay of puberty, bone maturation**
- **Irreversible CNS damage up to 3 years of age**

HYPERTHYROIDISM - CAUSES

Immune	**Graves disease** Transient hyperfunctional phase of CAITD
Autonomous production	**Nodular goiter** **Adenoma with autonomous production**
Iatrogenic	Medication ↑ iodine intake
Central hyperthyreodism	Hypophyseal 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**) 0.5 mg / kg / day, **propylthiouracil** (Propycil)
- Duration of treatment ??? long enought - 6- 12-18 months
- block-replace x titration therapy
- **recurrence 50-86%**
- 2**. Surgical treatment - total thyroidectomy**
- indications: disease recurrence, insufficient treatment effect, intolerance of therapy, non-compliance ..
- 3. **Radioactive iodine 131I?**
- Czech Republic - ablative doses of radioiodine, contraindicated in childhood
- USA, western Europe, CR - adults - fractionated low doses

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**

DIABETES MELLITUS – CLASSIFICATION SPECIFIC TYPES

- **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 dekarboxylase)
- 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, clinical manifestation - Kussmaul breathing**

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 or hyperosmolar hyperglycemia)**
- 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

- **The biochemical criteria for diabetic ketoacidosis (DKA)**
- 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

- **<u>Volume expansion (resuscitation)</u>**
- 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**
- **<u>Subsequent fluid management (deficit replacement)</u>**
- **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
- **Fasting BG 4.4 – 8 mmol/l**
- **Postprandial rise of 1-2 mmol/l, max. 3 mmol/l**
- **Glycated haemoglobin (HBA1C)**
- Optimal compensation of <5.8 mmol/mol, satisfactory 5.9 – 7.6 mmol/mol, unsatisfactory over 7.6 mmol/mol
- *For children, adolescents, and young adults ≤25 years who have access to comprehensive care a target of HbA1c of <53 mmol/ mol is recommended*
- *Source: ISPAD Clinical Practice Consensus Guidelines 2018 . https://www.ispad.org/page/ISPADGuidelines2018*

Goals of therapy of DM 1

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

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, koef. Variab. ≤ 36%)

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

DM I – INSULIN THERAPY

- **Basal and prandial insulins schedule (subcutaneous) -** as close to physiological insulin replacement as possible (optimal glycemic control must be the aim)
- Long - acting analog (or human NPH) - 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)**
- *„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 „*
- **fingerstick BGs testing - 6 to 10 times per day**
- *Source: ISPAD Clinical Practice Consensus Guidelines 2022 . https://www.ispad.org/page/ISPADGuidelines2022*

FINALLY FROM HISTORY OF PUMPING….