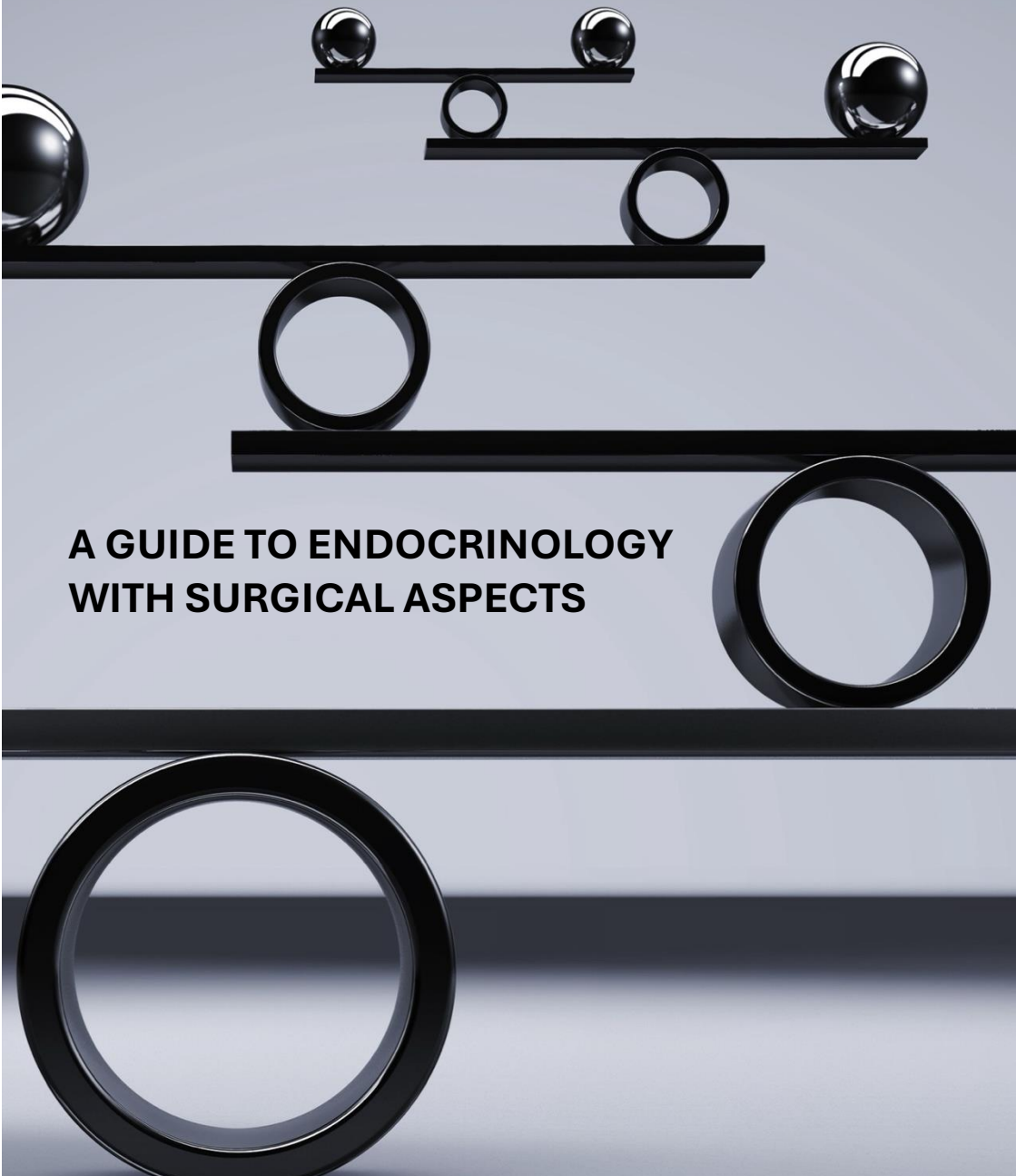
Edited by prof. Olesya P. Kikhtyak



A GUIDE TO ENDOCRINOLOGY WITH SURGICAL ASPECTS

Primedia eLaunch

A GUIDE TO ENDOCRINOLOGY WITH SURGICAL ASPECTS

Edited by prof. Olesya P.Kikhtyak

Third Edition Supplemented
Of Conceptual Endocrinology: Textbook for the stud. of higher med. educ. establishments

A textbook for students
of higher medical educational establishments of the 3rd and the 4th levels
of accreditation for English-speaking students

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The textbook “A guide to endocrinology with surgical aspects” has been written according to the educational qualification characteristics and educational programs of professional training, as well as the principles of the European Credit Transfer System. The textbook is designed for English-speaking students of Higher Medical Educational Establishments of the III and IV levels of accreditation. Though intended for medical students, this handbook will also be of use for general practitioners and medical specialists who speak English.

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Contents

Foreword

Although each organ system responds to hormones secreted (including the brain, lungs, heart, intestines, skin, and the kidneys), the clinical specialty of endocrinology deals primarily with the endocrine organs, the primary function of which is hormone secretion. These organs include the pituitary gland, the thyroid, the adrenals (or adrenal glands), the ovaries, the testes, and the pancreas.

The medical specialty of endocrinology focuses on the diagnostic estimation of a wide range of symptoms and variations and the long-term treatment of disorders in hormone secretion, including the deficiency or excess of one or more hormones.

The diagnosis and management of endocrine diseases are accomplished on the basis of laboratory tests to a greater extent than in other specialties. Many diseases are studied through stimulation or suppression tests. This may involve injection with a stimulating agent to check the function of an endocrine organ. Blood is then analyzed to assess the changes in the corresponding hormones or metabolites. An endocrinologist needs comprehensive knowledge of clinical chemistry and biochemistry to understand and explain the uses and restrictions of the investigations.

The second important aspect in endocrinology practice is distinguishing human individual variation from disease. Atypical models of physical development and abnormal test results should be assessed as indicative of disease or not. Incidental findings, called incidentalomas, may be revealed on diagnostic imaging of endocrine organs, which may or may not represent disease.

Endocrinology involves caring for the human biology as well as the nucleus, the enzymes as well as the disease. The majority of endocrine disorders are chronic diseases that need life-long management, monitoring and care. Examples of the most common endocrine diseases include diabetes mellitus, goiter, hypothyroidism, etc. Care for diabetic patients, management of obesity and other chronic diseases require understanding of the patient both at the personal and social levels as well as the molecular level, and the relationship physician–patient should be an important therapeutic process.

Emergency medicine (or emergentology) is a medical specialty in which physicians (DOs and MDs) care for patients with acute illnesses or injuries which call for immediate medical attention. Emergency medicine physicians usually do not provide long-term or permanent care, but they diagnose various illnesses and undertake urgent interventions to resuscitate and stabilize patients. Emergency medicine physicians work in hospital emergency departments, in pre-hospital settings through immediate medical services, other locations where they provide initial medical treatment of acute diseases, and lately in the intensive-care unit. While clinicians operate according to rules in large emergency systems, emergency

practitioners work to diagnose emergent conditions and stabilize the patient for definitive care.

Physicians, specializing in emergency medicine in certain countries, (for example the US and Canada) can join fellowships to get credentials in subspecialties. These include palliative medicine, critical care medicine, medical toxicology, wilderness medicine, pediatric emergency medicine, sport medicine, emergency medical services, undersea and hyperbaric medicine.

Endocrine emergencies constitute the group of potentially life-threatening conditions, which are often overlooked, resulting in late diagnosis and treatment, factors that can further contribute to already high mortality rates, associated with the diseases. The true incidence of primary endocrine emergencies is not completely defined, because the disease process is often not well recognized. Although endocrine emergencies are often revealed in patients with endocrinopathy, the emergency may be the initial manifestation in previously healthy individuals. If these endocrine disorders are not identified early or if proper treatment is delayed, serious complications and even death may occur.

English-speaking students of medical faculty will have the possibility to learn five topics. The fifth one is dedicated to common endocrine condition – metabolic syndrome which is of course not a part of endocrine emergencies but usually accompany them as some scientists suggest.

prof. Olesya P.Kikhtyak

Each practical lesson is structurally organized (table 1)

Table 1

Structure of the practical lesson

№	Masic stages of practical lesson and tasks	Estimation	Facilities for better study	Duration in %
I Preliminary stage				
1. 2. 3.	Previous learning Acquired knowledge Integration between disciplines	• Oral quiz • Multiple choice questions	Tables, schemes, graphs	10%
II Basic stage				
4. 5	Formation of professional skills in the clinical setting (Lviv Regional Endocrinological Hospital) Management of a patient	• Practical training	Case reports, prescriptions of medicine, medical equipment	60%
III Concluding stage				
6. 7. 8. 9. 10. 11. 12.	Differantial diagnosis Laboratory evaluation Imaging Discussion Sizing up Home work Bibliography	• Assessment of the certain case by students themselves	Phonendoscope, tonometer, tip-termer, tuning fork, monofilament, etc.	30%

Part 1
(for fourth year of study in "Endocrinology")

1.1 Classification of diabetes mellitus. Etiology, pathogenesis, clinical presentation, diagnostic tests of type 1 and type 2 diabetes mellitus.

Instructive module 1: "Fundamentals of diagnosis, management, and prophylaxis of common endocrine disorders" in the module 1: "The basis of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 5.

1. Professional motivation: Diabetes is characterized as a major worldwide health problem with numbers forecast to reach 380 million by 2025. It often leads to significant morbidity and mortality mainly due to cardiovascular, eye and renal diseases as well as limb amputations. Diabetes is known to be the fourth leading cause of death in most developed countries, besides, there is also evidence that it is quite common in many developing and newly industrialized nations. Diabetes will definitely be one of the most widespread and challenging health problems in the 21st century, since the economic and health influences and outcomes of diabetes are considerable. Developing countries might be experiencing an even greater burden, since many of these countries are confronted with the double problem of rapidly escalating rates of diabetes and complications in addition to widespread infectious diseases.

Diabetes has been recognized as being heterogeneous in the presentation of patients with the condition for more than 2000 years. In its classic form, two main forms of diabetes are recognized: type 1 diabetes (formerly termed insulin-dependent diabetes mellitus or juvenile-onset diabetes) and type 2 diabetes (formerly termed non-insulin-dependent diabetes mellitus or maturity-onset diabetes). Type 2 diabetes constitutes approximately 90 % of general disease incidence.

Type 1 diabetes is characterized by greater likelihood of ketoacidosis, and total dependence on insulin in order to survive.

Type 2 diabetes has a long asymptomatic pre-clinical course, that's why it often goes undetected. This type of diabetes is often diagnosed when half or more patients have already developed one or more diabetes complications.

Retinopathy is diagnosed in 20 % to 40 % of patients at the time of diabetes diagnosis. It has been estimated that type 2 diabetes may have its onset up to 12 years before its clinical diagnos, since the development of retinopathy is associated with duration of diabetes. It has been proven that the prevalence of undiagnosed diabetes is 50 % over that of diagnosed diabetes.

2. Study aim of this lesson.

To acquaint students with natural history of diabetes and its complications that face contemporary society, as well as with classification, etiology, pathogenesis and evaluation of metabolic control in diabetes (α=1)

In the study process students should know (α=2):

- the incidence of diabetes mellitus and associated risk factors,
- the definition of diabetes mellitus,
- the main etiological factors (genetic predisposition, viral infections, diet regimen, physical activity, etc.), and pathogenesis (role of human immunity, insulin resistance, hyperinsulinemia),
- how to interpret diagnostic tests,
- how to discern type 1 from type 2 diabetes,
- the concept of syndrome X.

In the study process student should be able to (α=3):

- prescribe oral glucose-tolerance test,
- make an analysis by express method (glucose in blood, glucose and acetone in urine),
- interpret oral glucose-tolerance test, glucose in urine, acetone in urine, level of fasting glucose, HbA1c (glycated hemoglobin), and C-peptide in blood,
- carry out physical examination,
- organise therapeutic approach.

3 Educational aim of this lesson

Is to pay attention to classification, treatment approach, and evaluation of metabolic control in diabetes mellitus.

4. Interdisciplinary integration (see Table 2).

Table 2

Interdisciplinary integration

Discipline	To know	How to do
I. Previous Normal anatomy Normal physiology Histology Pathological physiology	Endocrine gland (morphology of the pituitary, hypothalamus, and other glands of endocrine secretion, capillaries, veins, nerve endings)	

Pathological anatomy Biochemistry	Mechanism of interaction between hormones. Carbohydrate, lipid and protein metabolism in the human body	
Discipline	To know	How to do
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology Nephrology	Clinical symptoms of diabetes mellitus, distinguishing features of type 1 and type 2 diabetes, differential diagnostics	To examine a patient, to prescribe appropriate laboratory tests, to invite required specialists to diagnose a case.
III. Interdisciplinary integration	Current evaluation of metabolic control in diabetes	To institute adequate investigation

5. Contents of the lesson.

- Definition of diabetes mellitus.
- Natural history of diabetes mellitus (occurrence, distribution, environmental and genetic factors, distribution of late diabetic complications, prognosis).
- Evaluation of metabolic control in diabetes.
- Specific signs and symptoms of type 1 and type 2 diabetes.
- Type 1 diabetes mellitus (etiology, pathogenesis, clinical presentation).
- Type 2 diabetes mellitus (etiology, pathogenesis, clinical presentation).
- Syndrome X (on the whole).

6. Plan and organization structure of this lesson.

(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*

Choose the correct answer/statement. One answer/statement is correct.

#1

What is the major action of insulin?

A) Proteolysis

B) Conversion of glucose to glycogen

C) Conversion of fatty acids to glucose
D) Glycogenolysis
E) Gluconeogenesis

#2
Results of oral glucose-tolerance test are: 1st sample – 5.1 mmol/l, 2nd sample – 8.0 mmol/l. What does it mean?
A) Normal
B) Impaired glucose tolerance
C) Diabetes mellitus
D) Impaired fasting glucose
E) Potential abnormality of glucose tolerance

#3
What criterion does compensation stage in diabetes represent?
A) Glycosuria
B) Fasting glucose – 6.0 mmol/l, postprandial glucose – 7.8 mmol/l,
C) Fasting glucose – 6.3 mmol/l, postprandial glucose – 7.0 mmol/l
D) Ketoaciduria
E) HbA1c equal to 7.8 %

#4
Development of type 2 diabetes is characterized by:
A) Increased insulin sensitivity
B) Overwhelming secretion of α-cells in Langerhans islets
C) Overwhelming secretion of β-cells in Langerhans islets
D) Increased glucose level in plasma
E) Hypercortisolism

7.2. Recourses for the main stage of the lesson.

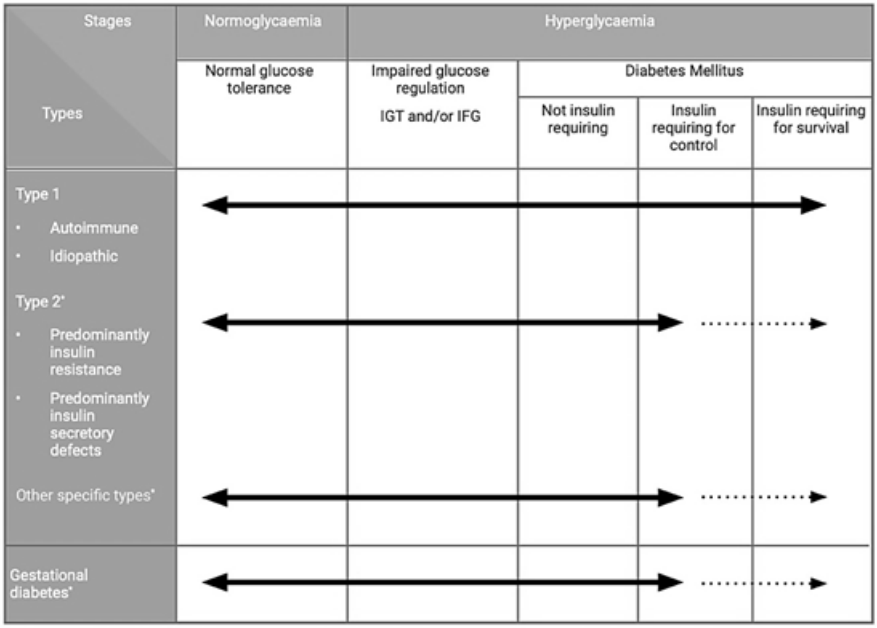
Diabetes Mellitus is a complex combination of syndromes, characterized metabolically by hyperglycemia as well as altered metabolism of glucose. It may be wrongly taken for certain microvascular complications, macrovascular disease due to accelerated atherosclerosis, and different additional complications, namely, neuropathy, complicated pregnancy and an increased vulnerability to infection.

A committee of the World Health Organization (WHO) has revised the classification, taking into account the pathogenesis of diabetes, to conclude the classification of diabetes mellitus in Geneva 2019 (see Table 3).

Classification of diabetes mellitus **Table 3**

Type of diabetes	Brief description	Change from previous classification
Type 1 diabetes	β-cell destruction (mostly immune-mediated) and absolute insulin deficiency; onset most common in childhood and early adulthood	Type 1 sub-classes removed
Type 2 diabetes	Most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity	Type 2 sub-classes removed
Hybrid forms of diabetes		New type of diabetes
Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving type 1 in adults but more often has features of the metabolic syndrome, a single GAD autoantibody and retains greater β-cell function	Nomenclature changed – previously referred to as latent autoimmune diabetes of adults (LADA)
Ketosis-prone type 2 diabetes	Presents with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune-mediated	No change
Other specific types		
Monogenic diabetes - Monogenic defects of β-cell function - Monogenic defects in insulin action	Caused by specific gene mutations, has several clinical manifestations requiring different treatment, some occurring in the neonatal period, others by early adulthood Caused by specific gene mutations; has features of severe insulin resistance without obesity; diabetes develops when β-cells do not compensate for insulin resistance	Updated nomenclature for specific genetic defects
Diseases of the exocrine pancreas	Various conditions that affect the pancreas can result in hyperglycaemia (trauma, tumor, inflammation, etc.)	No change
Endocrine disorders	Occurs in diseases with excess secretion of hormones that are insulin antagonists	No change
Drug- or chemical-induced	Some medicines and chemicals impair insulin secretion or action, some can destroy β-cells	No change
Infection-related diabetes	Some viruses have been associated with direct β-cell destruction	No change
Uncommon specific forms of immune-mediated diabetes	Associated with rare immune-mediated diseases	No change
Other genetic syndromes sometimes associated with diabetes	Many genetic disorders and chromosomal abnormalities increase the risk of diabetes	No change
Unclassified diabetes	Used to describe diabetes that does not clearly fit into other categories. This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis	New types of diabetes
Hyperglycaemia first detected during pregnancy		
Diabetes mellitus in pregnancy	Type 1 or type 2 diabetes first diagnosed during pregnancy	No change
Gestational diabetes mellitus	Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy	Defined by 2013 diagnostic criteria
Diagnostic criteria for diabetes: fasting plasma glucose ≥ 7.0 mmol/L or 2-hour post-load plasma glucose ≥ 11.1 mmol/L or Hba1c ≥ 48 mmol/mol **Diagnostic criteria for gestational diabetes**: fasting plasma glucose 5.1–6.9 mmol/L or 1-hour post-load plasma glucose ≥ 10.0 mmol/L or 2-hour post-load plasma glucose 8.5–11.0 mmol/L		

However, quite often you can come across the WHO classification of 1999, which is often used to understand the need for insulin therapy (Picture 1.)



*In rare instances patients in these categories (e.g. Vacor Toxicity, Type 1 presenting in pregnancy, etc.) may require insulin for survival.

Source: reproduced from the World Health Organization's 1999 classification (2).

Picture 1. Disorders of glycaemia: aetiological types and clinical stages (WHO, 1999)

Diabetes Mellitus, type 1

Aetiology. Genetic predisposition associates with diabetogenic gene(s): alleles of insulin gene on the 11th chromosome and short arm of 6th chromosome either within or very close to the major histocompatibility complex region – the HLA region. β cells may be infected and damaged by numerous human viruses: viruses of mumps, variants of Coxsackie B (often B_4), measles, rubella, varicella, and cytomegalovirus. Pathogenetic outcome in genetically predisposed individuals may also be caused by stress.

Pathogenesis. Pathogenetic mechanism implies selective destruction of β cells (other islet cells maintain secretion) by autoimmunity, genetic and environmental factors. If 80-90% of β cells are destroyed it leads to total insulin deficiency. Hyperglycaemia and ketoacidosis are the outcomes of isulin deficiency. Remission ("honeymoon" phase) may take place within 1-3 months after the diagnosis. Remission occurs as a result of temporary recovery of β cell function and can last

from weeks up to 2 years. The extent of insulin insufficiency is likely to increase with time.

The major vascular complications are premature atherosclerosis, intercapillary glomerulosclerosis, retinopathy, neuropathy, ulceration and gangrene of the extremities; they may result from capillary basement-membrane thickening. Accumulation of sorbitol and consequential osmotic swelling are significant in case of nerve disturbances and cataracts.

Diagnostics. Questioning of a patient (case history of disease and life), visual inspection, and laboratory tests (glucose in blood, HbA1c, glucose in urine, ketone bodies in urine).

Normal level of glucose in the blood is: 3.6-5.5 mmol/l (fasting) and less than 7.8 mmol/l (2 h after meal).

Level of glycosylated haemoglobin indicates an average blood concentration during the previous 2-3 months (red blood cells have life-span of 120 days). Normal value is <6.1 or <6.5 (%). American Diabetes Association in its recommendations states that an A1c level of about 5% indicates absence of diabetes, and in accordance with the revised evidence-based guidelines, an A1c of 5.7% to 6.4% indicates prediabetes, and an A1c level of 6.5% or higher shows presence of diabetes. Urine ketones should be measured in order to reveal the development of ketoacidosis.

Clinical picture. Type 1 diabetes usually starts in childhood or adolescence and the majority of patients are of normal or below normal weight. The level of serum insulin is zero or low. The patients may have tendency to ketosis as well as to hypoglycaemia. The level of glucose in the blood is increased and fluctuates strongly. The remission or "honeymoon" phase, may occur. Microangiopathy is usually observed in neuropathy, ophthalmopathy and nephropathy.

Diabetes Mellitus, type 2

Aetiology. There is inherited predisposition to develop type 2 diabetes mellitus. Not many patients experience disturbance in the conversion of proinsulin into insulin, abnormal insulin receptors and mutant insulin molecules. The development of evident clinical disease may be under the impact of such nongenetic environmental factors as obesity, diet, stress, physical activity, and aging influence.

Pathogenesis. Hyperinsulinemia and insulin resistance, glucose desensitisation of β cells precede disturbances in insulin secretion. Endogenous hyperinsulinemia (on the early stages of the disease) can maintain normal or mildly impaired glucose tolerance. Hyperinsulinemia and insulin resistance are related to hypertriglyceridemia, decreased high-density lipoprotein cholesterol, hypertension and increased risk of atherosclerosis. Macroangiopathy (atherosclerosis) often takes forms of myocardial infarction, angina pectoris, peripheral vascular disease with intermittent claudication, cerebral vascular disease, ulceration and gangrene in advanced stages.

Diagnostics. There is often an increased level of serum insulin. The high level of blood glucose is relatively constant (OGTT, and thus for type 1 diabetes mellitus). Oral glucose tolerance testing reveals impaired glucose tolerance if diabetes mellitus is suspected. The dose is 75 g glucose dissolved in 250-300 ml water; for children, it is 1.75 g glucose/kg body weight. The diagnosis of diabetes mellitus is shown in

Oral glucose tolerance testing

Diabetes mellitus (manifest)	Plasma (mmol/l)
fasting 2 hours after consuming of a standard amount of glucose (75g)	> 7.0 mmol/l > 11.0 mmol/l

Clinical picture. Patients with type 2 diabetes usually are middle-aged or elderly people, mostly after the age of 36 and overweight. This disease has also a strong hereditary incidence. Serum insulin level is often increased. Patients are not prone to ketosis and hypoglycaemia. The high level of glucose in the blood is relatively constant. Macroangiopathy is often forms of cerebral vascular disease, angina pectoris, peripheral vascular disease with intermittent claudication, myocardial infarction, ulceration,, myocardial infarction, ulceration and gangrene in advanced stages.

In recent years, significant progress has been made in the field of identifying the molecular genetics underlying various subtypes of diabetes since the last WHO classification. These advancements have shed light on the existence of genetically diverse clinical subgroups and have led to the discovery of new genetic syndromes associated with the disease. The most significant breakthrough has been the ability to use genetic diagnosis to enhance treatment outcomes for a small but significant segment of individuals with diabetes. Consequently, certain countries have begun to employ genetic testing as a means to aid in the clinical management of selected subgroups of patients. This highlights the growing importance of molecular genetics in the field of diabetes research and clinical practice.

Pathologies related to other specific types of diabetes are shown in Table 4.

Table 4

Other specific types of diabetes*

Monogenic diabetes Monogenic defects of β-cell function (mutated gene followed by clinical syndrome)	**Monogenic defects in insulin action (mutated gene followed by clinical syndrome)**
GCK MODY	INSR Type A insulin resistance
HNF1A MODY	INSR Leprechaunism
HNF4A MODY	INSR Rabson-Mendenhall syndrome
HNF1B RCAD	LMNA FPLD
mtDNA 3243 MIDD	PPARG FPLD
KCNJ11 PNDM	AGPAT2 CGL
KCNJ11 DEND	BSCL2 CGL
6q24 TNDM ABCC8 MODY INS PNDM WFS1 Wolfram syndrome FOXP3 IPEX syndrome EIF2AK3 Wolcott-Rallison syndrome	**Other generic syndromes sometimes associated with diabetes** (see Table 5)
Abbreviations: MODY = maturity-onset diabetes of the young; RCAD = renal cysts and diabetes; MIDD = maternally inherited diabetes and deafness; PNDM = permanent neonatal diabetes; TNDM = transient neonatal diabetes; DEND = developmental delay epilepsy and neonatal diabetes.	Abbreviations: FPLD = familial partial lipodystrophy; CGL = congenital generalized lipodystrophy
Diseases of the exocrine pancreas	**Endocrine disorders**
Fibrocalculous pancreatopathy	Cushing's syndrome
Pancreatitis	Acromegaly
Trauma/pancreatectomy	Phaeochromocytoma
Neoplasia	Glucagonoma
Cystic fibrosis	Hyperthyroidism
Haemochromatosis	Somatostatinoma
Others	Others
Drug- or chemical-induced diabetes (see Table 4)	**Uncommon forms of immune-mediated diabetes**
Infections	Insulin autoimmune syndrome (autoantibodies to insulin)
Congenital rubella	Anti-insulin receptor antibodies
Cytomegalovirus	«Stiff man» syndrome
Others	Others
Other clinically defined subgroups	
Diabetes associated with massive hypertriglyceridaemia	

*This is a list of the most common types in each category but is not exhaustive

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
27 years old patient M. has been admitted to a hospital. After recovering from flu, he complains of thirst, frequent urination, and weight loss. His blood glucose level is 12.3 mmol/l, glucose in urine – 3%, acetone in urine +.
1. What type and stage of compensation of Diabetes Mellitus should you suspect?
2. What additional laboratory tests and consultations should you order?

Case 2.
Child, 11 years old presents with recidivation of furunculosis. Fasting blood glucose is 5,5mmol/l, glucose and acetone are absent in urine.
1. What is the most likely diagnosis?
2. What additional examinations must be ordered?

Case 3.
After long-term use of thiazide diuretics, patient complains of itch on medial sides of the thighs. It is known that fetal weight of her two children was 4200 and 5000 g, respectively.
1. What is you diagnosis?
2. What additional laboratory tests should you order to confirm your diagnosis?

Case 4.
Patient G., is 19 years old and in her 32nd week of pregnancy. During her last planned consultation, glucose in urine was – 1%. Her glucose tolerant test was the following: 5.2 mmol/l, two hours later 7.9 mmol/l.
1. What is the most likely diagnosis?
2. How will you manage this patient?

Case 5.
Patient C. – 58 years old. Two years before the condition of acromegaly was established. He was treated in different clinics. One year ago thirst, frequent urination, weight loss, and reduction in eyesight started to manifest. Glucose in blood is10.2 mmol/l and glucose in urine – 2 % .
1. What is your diagnosis and stage of compensation?
2. Describe the proper plan of treatment.

1.2 Type 1 Diabetes Mellitus. Modern treatment approach.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of the common endocrine disorders" in module 1: "Fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 5.

1. Professional motivation: Insulin deficiency secondary to β-cell destruction is characteristic for type 1 diabetes mellitus. The typical pancreatic lesion of type 1A diabetes is a selective loss of almost all β-cells, while other islet cell types (A, D, and PP cells) are intact. In the absence of insulin therapy, the resulting metabolic disturbances finally lead to death. Before insulin was discovered, patients were treated with the Allen starvation diet and sometimes survived without insulin therapy for 5 or more years after diagnosis.
The onset of type 1 diabetes usually occurs under the age of 35.
Present-day treatment of type 1 Diabetes Mellitus includes prevention or elimination of ketoacids, glucose in the urea, hyperglycemia, obtaining and maintaining ideal weight, elimination of lipid and protein impairment and eventually preventing as much as possible the progression of atherosclerosis, diabetic microangiopathy, and neuropathy.
Insulin is the basic therapy for all patients with type 1 diabetes. Subcutaneous insulin therapy attempts to resemble normal physiologic secretion of insulin and metabolism regulation.

2. Study aim of this lesson.
To acquaint students with modern insulin therapy of type 1 diabetes mellitus, side effects of insulin treatment (α=1)

In the study process students should know (α=2):

- stages of diabetic compensation and diagnostic criteria of each stage, as well as setting goals of therapy,
- characteristics of the most widely available types of insulin regarding their action profile and constituents,
- principles of insulin therapy: initiation, daily requirements, combined use of insulin, calculation of a daily dose of insulin based on food-exchange concept,

- about regimens commonly used for insulin therapy (traditional split-mix regimen, three-shots-per-day regimen, intensive conventional therapy and continuous subcutaneous insulin infusion),
- side effects of insulin treatment.

In the study process student should be able to (α=3):
- establish the stage of compensation,
- calculate daily dose of insulin,
- use food-exchange concept in a clinical practice,
- prescribe type of insulin,
- discern hypoglycaemia from other side effects of insulin treatment,
- diagnose and prevent post-hypoglycaemic hyperglycaemia.

3 Educational aim of this lesson

Is to focus attention on modern insulin therapy of type 1 diabetes mellitus.

4. Interdisciplinary integration (see Table 5).

Table 5

Interdisciplinary integration

Discipline	To know	How to do
I. Previous Normal anatomy and physiology, histology, pathology anatomy and physiology, pharmacology	Pancreas (location, morphology, function); hormones, regulation	To estimate physiological reserve of the pancreas in order to prescribe proper treatment (doses and methods) To prescribe medications.
Discipline	To know	How to do
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology, Nephrology Ophthalmology.	Main clinical signs of Diabetes Mellitus, its types, differential diagnosis, treatment	To make clinical observation, prescribe proper diagnostic assays, consultation of associative specialists for verification diagnosis.

III. Interdisciplinary integration	Contemporary methods of treatment	To prescribe adequate treatment of diabetes mellitus.

5. Contents of the lesson.

- Stages of diabetic compensation and diagnostic criteria of each stage.
- Setting goals of therapy.
- Principles of diet therapy.
- Exercise and diabetes control.
- Characteristics of insulin preparations.
- Types of insulin based on their origin.
- Generations of insulin preparations.
- Principles of insulin therapy (regimens).
- Initiation of treatment and daily requirements.
- Food-exchange concept.
- Side effects of insulin treatment (hypoglycemia, post-hypoglycaemic hyperglycaemia, lipoatrophy, orthostatic hypotension, insulin allergy, insulin edema).

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
18 years old patient N. has been admitted to a hospital. After recovering from flu, doctor discovered high glucose level, and the diagnosis of type 1 diabetes was made. His fasting glucose is 15.3 mmol/l, glucose in urine – 3%, acetone in urine ++. What is your treatment approach?

A) Meal planning and diet prescription
B) Sulfonylureas
C) Biguanides
D) Insulin preparations
E) Meglitinides

#2
Insulin treatment is obligatory in the following cases except:

A) Moderate course of type 2 diabetes mellitus

B) Surgery in type 2 diabetes patient
C) Pregnancy in type 2 diabetes patient
D) Lactation in type 2 diabetes patient
E) Ketoacidosis in type 2 diabetes patient

#3
Initiation of insulin treatment may be calculated taking into account the following:
A) Glycated hemoglobin
B) 1 IU of insulin per 0.5 g of urine glucose
C) 0.3 IU/1 kg of body weight per day
D) Glucose tolerance test
E) 4 IU per 1 mmol of glucose in blood

#4
Which insulin is allowed for once-daily dosing?
A) Novorapid
B) Actrapid
C) Glargine
D) Protaphane
E) Insulin NPH

7.2. Recourses for the main stage of the lesson.
Replacement treatment with insulin medications is the main principle in type 1 diabetes mellitus management. Insulin is available to the patients in cartridges (pen device) as well as in vials, usually coloured. Red colour stands for 40 IUs of insulin in each 1 ml, orange colour – 100 IUs of insulin in 1 ml, however, there are also other options of concentration available. For example, insulin is available in a U500 dose for patients' use who have high requirements (>200 U per day). Various pumps may be used for constant subcutaneous insulin infusion. Insulin should be injected 30 minutes before meals, usually subcutaneously. In emergency cases insulin can be injected intramuscularly or IV with glucose or saline solution. Areas of insulin injection may be different and constant change of them is needed to avoid lipoatrophy. Common sites of insulin injection are the following: buttock, anterior thigh, abdomen and dorsal part of arm. Abdominal subcutaneous absorption happens faster in comparison with the limbs.
Based on their origin there are three types of insulin: porcine, beef and human. Beef is considered the most immunogenic; thus its production has been almost discontinued. Insulins are divided into four generations. The first generation includes a half from beef and pork pancreas with various amounts of contaminants, for example, proinsulin, somatostatin, glucagon, pancreatic polypeptide etc. To the second generation belongs mono-peak (MP) insulin, which is usually contaminated within 0.5%. The third generation includes monocomponent (MC) highly purified

insulin, the fourth generation – biosynthetic human insulin obtained from Saccharomyces cerevisiae or Escherichia coli with the lowest level of contamination. Initial dose of insulin for children under 1 year is 0.1 IUs/kg/day. Average daily dose is 0.15 IUs/kg at the age from 1 to 3 years, and 0.2-0.5 IUs/kg at the age over 3 years. Most often the daily need of insulin for young diabetics is within 0.6-0.8 IUs/kg. Need in 1.0 IU/kg/day may be advantageous at the beginning of treatment. Teenagers may also need 1.5 IUs/kg/day during the period of quick growth and development. During remission the dose may usually be less than 0.3 IUs/kg/day. Depending on the nutrient intake dose ratio of short-acting insulin may constitute 2:2:1 or 2:3:1. Insulin amount ratio of short-acting and moderate-acting is 25% and 75% respectively. Two thirds of the total dose of moderate-acting insulin should be given before breakfast and one third – before supper. In some cases treatment of type 1 diabetes should begin by administering moderate-acting insulin twice a day before breakfast as well as at bedtime or before supper at the dosage of 0,2 to 0.3 U/kg daily. The dose should be increased gradually with or without the use of short-acting insulin administered before breakfast and supper. During this treatment the blood glucose level should constantly be observed.

There are also different types of insulin according to its time properties. There are several groups of insulin regarding their duration (see Table 6).

Table 6

Classification of insulins according to time of their action

Group of insulin	Example	Average clinically evident		
		onset*	peak*	duration*
I. Rapid-acting**	Lispro(Humalog)	0.2 h	0.5-1.5 h	3-4 h
II. Short-acting**	Actrapid, Regular	0.3 h	1-3 h	6-8 h
III. Moderate-acting	Protaphane, NPH, Lente, Monotard.	1.5 h	5-8 h	8-12 h
IV. Long-acting	Ultralente, Ultratard, Glargine (Lantus)***	3-4 h	8-15 h without	20-30 h
V. Mixtures	Insuman-Comb 30/70 Mixtard	0.5-1 (biphasic action)	3-8 h (biphasic action)	18-24 h (biphasic action)

*Each produced insulin has its own specific action profile: the site and route of injection, outer and body temperature, concurrent diseases, complications, as well as many other circumstances which may influence pharmacokinetic properties of any insulin.

**Insulin with short or ultra-short duration (if given in large doses) may resemble the moderate-acting insulin.

***Only one insulin with sustained release without any peak.

Insulin therapy is used for treatment in the following cases: patients with type 1 diabetes, patients with gestational diabetes, patients having a fasting glucose level

of > 120 mg/l (6.6 mmol/l regarding conversion factor 0.055), patients with type 2 diabetes who don't respond to an adequate diet and oral hypoglycaemic medications. Insulin therapy is recommended before and after surgeries as well as during acute illnesses.

In the first trimester of pregnancy the need for insulin may drop slightly, and then increase gradually in the second trimester, and finally reach peak in the third trimester. The need drops and returns to its prepregnancy levels immediately after delivery.

During remission the use of insulin retards autoimmune process, discontinuation will potentiate insulin allergy. Insulin therapy unloads β cells from the hard work aimed at maintaining euglycemia and prevents prompt depletion of insulin. Use of insulin prevents complications of diabetes and facilitates the flow of diabetes mellitus.

Among the side effects of insulin therapy are: hypoglycaemia, post-hypoglycaemic hyperglycaemia (Somogyi phenomenon), lipohypertrophy, insulin edema, lipoatrophy, insulin allergy and postural hypotension.

Hypoglycaemia may be caused by: malnutrition, violation of insulin absorption (changes in blood flow at the site of injection as a result of massage or heat), concurrent diseases (renal failure, hypothyroidism, Addison's disease, hypopituitarism), excessive physical activity, overdose of insulin, altered metabolism of glucose (excessive alcohol consumption, salicylates, tetracyclines, β-adrenergic blockers), behaviour mistakes (mistakes in doses, carelessness, forgetfulness).

"Post-hypoglycaemic hyperglycaemia" or "Somogyi phenomenon" means chronic overinsulinisation. Frank diabetic ketoacidosis may be precipitated by "rebound" hyperglycaemia which may last two days. Hypoglycaemia at night (3 a.m.) is an evidence of possible subsequent hyperglycaemia and for diagnosis of Somogyi and dawn phenomenon. Reduction in insulin dose (as a rule in the second half of the day) can correct fasting hyperglycaemia.

Uncontrolled diabetes is accompanied by natriuresis and loss of fluid, while insulin treatment facilitates retention of fluid and sodium. It may be the cause of insulin edema. Glucagon has natriuretic effect, and on the contrary insulin retains sodium. Fluid retention is associated with weight gain, and may be frustrating for patients. In such cases diuretics may be recommended.

Lipoatrophy has evident relation to unpurified insulins. Presence of immunoglobulins, which can release cytokines, produces loss of fat in the site of injection. Vice versa the use of highly purified insulins can precipitate local hypertrophy of subcutaneous fat. Lipoatrophic areas must be treated with purified insulins. Change of injection site is required for prevention of insulin lipoatrophy or lipohypertrophy.

Autonomic neuropathy may cause the adverse effect of insulin: vasodilatation instead of vasoconstriction. Vasodilation causes hypotension. Orthostatic hypotension is sometimes mistaken for hypoglycaemia because of perspiration and tremor.

Nowadays high purification of insulin reduces problems with insulin allergy. Allergic reactions may be systemic or local. Desensitisation should be performed according to special schedule. Treatment approach may also involve oxygen, antihistamines, epinephrine and corticosteroids.

Several commonly used insulin regimens are: traditional split-mix regimen, three-shots-per-day regimen, intensive conventional therapy and continuous subcutaneous insulin infusion. The last two are the basis of intensive insulin therapy. This approach requires strict control of glucose in the blood, careful following of the diet, insulin regimen that resembles the normal diurnal and postprandial insulin excursions, and frequent adjustment of the insulin dosage to correspond to changing circumstances.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Patient N. 40 years old, complains of frequent urination, severe thirst and weakness. These symptoms were evidenced over several days. Fasting blood glucose is 18.0 mmol/l, glucose in urine – 2.5 %, acetone ++.

1. What is the most likely diagnosis?
2. What treatment should you administer?

Case N 2.

Patient A., 36 years old. Type 1 diabetes has been lasting for 26 years. Patient regularly receives insulin (daily dose – 60 IU). In the last three years patient was not examined by endocrinologist. Feet are cold, and pulse on *a. dorsalis pedis* and on *a. tibialis posterior* is faint. Fasting blood glucose is 8.0 mmol/l, glucose in urine – 0,5 %

1. Substantiate diabetic complication.
2. Choose the proper therapeutic approach.

Case 3.

Patient C., 27 years old. Patient has been sufferening from type 2 diabetes for 9 years. Anthropometric data: weight 120 kg, height 160 cm. Patient takes insulin preparations in daily dose 105 IU. Patient's fasting blood glucose is 17 mmol/l, glucose in blood at 3 o'clock in the morning 2.7 mmol/l.

1. What complication will this patient have?
2. What approach do you need in order to eliminate these complications?

1.3 Type 2 Diabetes Mellitus. Modern treatment approach.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of common endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 5.

1. Professional motivation: Type 2 diabetes mellitus is the most common endocrine disease. It affects approximately 300 million people in the world. Development of type 2 diabetes is strongly influenced by genetic and environmental factors, including obesity, low physical activity and overeating. The degree of obesity is the major risk factor influencing type 2 diabetes incidence. Studies show that the risk of the disease rises substantially with increasing body mass index. Besides, a pattern of body fat distributed around the central abdomen (also called visceral adiposity) increases the risk of type 2 diabetes more than a similar degree of excessive fat does that is more uniformly distributed.
Type 2 diabetes usually occurs after the age of 35.
β-cell mass is relatively well preserved in type 2 diabetes, but insulin secretion is reduced in response to specific secretagogues such as glucose, and strong evidence exists for resistance to the action of insulin in the peripheral tissues.
Type 2 diabetes is a chronic disease, resulting in the complications of the kidney, eyes, and heart which develop over many years, sometimes decades after the appearance of hyperglycemia. Besides, the diagnosis of type 2 diabetes is usually made in 10-12 years after the onset of the disease, because patients do not have any complaints until serious complications develop.
At first, sulfonylureas were the only class of oral agents available in the world. With time, biguanides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, meglitinides, and GLP-1 agonists became available. The choice of medications from these groups for treatment of patients is based on international recomendations.

2. Study aim of this lesson.
To acquaint students with modern therapy of type 2 diabetes mellitus, side effects of insulin treatment (α=1)

In the study process students should know (α=2):

- stages of diabetic compensation and diagnostic criteria of each stage, as well as setting goals of therapy,

- principles of diet in type 2 diabetes mellitus and physical activity,
- characteristics of the most widely available pharmacological groups regarding their action profile (sulfonylureas, biguanides, α-glucosidase inhibitors, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists),
- side effects of oral hypoglycemic drugs,
- principles of oral agents treatment: initiation, combined use of drugs and combination with insulin preparations,
- AACE/ACE (2006) and ADA/EASD (2006, 2009) consensuses regarding treatment of type 2 diabetes mellitus.

In the study process student should be able to (α=3):

- establish the stage of compensation,
- order diet and exercise,
- prescribe oral agents used to treat type 2 diabetes, taking into account dose, frequency of administration, contraindications, side effects,
- discern hypoglycaemia from other acute complications,
- diagnose secondary failure to sulfonylureas.

3. Educational aim of this lesson

Is to focus attention on modern treatment of type 2 diabetes mellitus.

4. Interdisciplinary integration (see Table 7).

Table 7

Interdisciplinary integration

Discipline	To know	How to do
I. Previous Normal anatomy and physiology, histology, pathology, anatomy and physiology, pharmacology	Pancreas (location, morphology, function); hormones, regulation	To estimate physiological reserve of pancreas in order to prescribe proper treatment (doses and methods) To prescribe medications.
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology	Main clinical signs of Diabetes Mellitus, its types, differential diagnosis, treatment	To make clinical observation, prescribe proper diagnostic assays, consultation of associative

Ophthalmology, Nephrology Ophthalmology.		specialists for verification of diagnosis.
III. Interdisciplinary integration	Contemporary methods of treatment	To prescribe adequate treatment of diabetes mellitus.

5. Contents of the lesson.

- Stages of diabetic compensation and diagnostic criteria of each stage.
- Setting goals of therapy.
- Principles of diet therapy.
- Exercise and diabetes control.
- Groups of oral glucose-lowering agents and their main differences (sulfonylureas, biguanides, α-glucosidase inhibitors, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists).
- Characteristics of oral hypoglycemic agents (indications, contraindications, doses, frequency of administration, side effects).
- Insulin therapy in type 2 diabetes mellitus.
- AACE/ACE (2006) and ADA/EASD (2006, 2009) consensuses.

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Mechanism of sulphonylureas' action includes:
A) Inhibiting insulin resistance
B) Stimulating beta cells to synthesize insulin
C) Inhibiting beta cells to secrete insulin
D) Beyond pancreatic activity
E) Stimulation of beta cells to secrete insulin

#2

Which drug is considered to be first-generation sulfonylureas?

A) Glimepiride
B) Glyburide
C) Glipizide
D) Chlorpropamide
E) Gliquidone

#3

Development of type 2 DM is characterised by:

A) Overwhelming secretion of β-cells in Langerhans islets
B) Overwhelming secretion of α-cells in Langerhans islets
C) Increased insulin sensitivity
D) Decreased glucose level in plasma
E) Hypercortisolism

#4

Which of the following statements is not correct for oral hypoglycemic drugs?

A) Stimulation of insulin release
B) Anorexigenic effect
C) Reduction in carbohydrate absorption
D) Inhibition of gluconeogenesis
E) Stimulation of insulin synthesis

7.2. Recourses for the main stage of the lesson.

Type 2 diabetes mellitus treatment includes phytotherapy, physical exercises, diet and oral hypoglycaemic agents. Dieting means limiting and eliminating simple carbohydrates, which are contained in products such as sugar, certain drinks (e.g. Coca-Cola, lemonade etc.), sweets, jam, honey, cakes, chocolate etc. This food should be restricted because it instantly raises blood glucose level. However, unrefined carbohydrates are recommended. They are contained in food like bread, potatoes, cereals, rice, and pasta. These products are digested much slower and thus prevent glucose elevation. Diet should be formed based on the balance with oral hypoglycaemic agents.

Blood glucose level may also be lowered, mostly in extrapancreatic way, by using certain herbs. These are: Galega officinalis, Phaseolus vulgaris, Vaccinium myrtillus, Cichorium intybus, Taraxacum officinale, Artemisia vulgaris, Aralia mandshurica etc. Phytotherapy alone may be effective only at the early stages of type 2 diabetes mellitus, while in later stages of type 2 diabetes it can only serve as supportive and accessory means.

Oral hypoglycemic drugs include such groups: carbohydrate inhibitors, thiazolidinediones (or PPAR-γ agonists), biguanides, meglitinides (phenylalanine derivates, benzoic acid derivates), sulfonylureas, DPP-4 inhibitors, GLP-1 analogues and combined agents. Biguanides, thiazolidinediones, and α-glucosidase inhibitors are regarded as euglycemic or antihyperglycemic agents, as they posess no obvious hypoglycaemic effect in non-diabetic individuals except for certain conditions (simultaneous alcohol consumption etc.)

Oral agents are mainly prescribed depending on pathogenetic stage of the illness. Sulfonylureas and meglitinides as being secretagogues can be useful when the level of insulin is normal or decreased to some extent, while PPAR-γ agonists are used in case of hyperinsulinemia. When relative insulin deficiency changes to absolute one, replacement treatment with insulin is obligatory.

Strong contraindications for oral hypoglycaemic agents are: pregnancy, lactation, surgery, heart attack, stroke, X-rays or other procedures with contrast agents injected, metabolic acidosis, including diabetic ketoacidosis, serious infection, illness, or injury.

Acarbose and miglitol belong to carbohydrase inhibitors. They inhibit the α-glucosidases in the intestinal brush border, which causes a delay in absorption of the carbohydrate. For both agents, the therapeutic dose is 50-100 mg; higher doses lead to abdominal distention, flatulence, malabsorption, and diarrhoea. The use of these drugs causes only average improvements in measurements of glycated haemoglobin. Contraindications for the use of carbohydrate inhibitors are: diseases of gastrointestinal tract with impaired digestion and absorption (ulcerative colitis, peptic ulcer, Crohn's disease) and obstruction or blockage in the intestines.

At present biguanides include only metformin. Metformin reduces absorption of glucose from the gastrointestinal tract, probably due to glucose uptake inhibition on the mucosal surface, and inhibits production of hepatic glucose as well as increases insulin-stimulated glucose uptake at the periphery, stimulating the GLUT 4 glucose transporter. Unlike the therapy with insulin or sulfonylureas, therapy with metformin does not cause weight gain and may even lead to insignificant weight loss resulting from slight anorectic effect of the drug. During its proper use the occurrence of lactic acidosis is rare. Thus, metformin is contraindicated in patients with impaired function of the kidneys. Starting dosages of metformin range from 1.0 to 2.0 per day in single doses of 500 mg or 850 mg. The maximum dosage is 3 g, usually administered in three single doses. Treatment of type 2 diabetes in overweight patients usually begins with biguanides. Impaired creatinine clearance, heart failure, liver disease, chronic obstructive lung disease, and alcohol abuse are contraindications to metformin therapy. Side effects are usually gastrointestinal, including abdominal discomfort, diarrhoea, nausea and vomiting.

Thiazolidinediones enhance insulin sensitivity. Two medications in this category are presently marketed in the United States: rosiglitazone and pioglitazone. In 2011

Rosiglitazone was recalled from most European markets because of its hepatic toxicity and side effects causing heart problems.

All thiazolidinediones associate with a reportedly increased incidence of edema and increased weight in comparison with placebo. Edema may be mild or moderate. The thiazolidinediones should not be used for treatment of patients with congestive heart failure. These drugs cause the increase in volume of plasma fluid and may be the reason of mild, dilutional-related decreases in haemoglobin, hematocrit, and amount of white blood cells. Many patients with type 2 diabetes may also gain weight. It is necessary to closely monitor liver enzymes prior to and during treatment (every 2 months). Rosiglitazone should not be administered simultaneously with insulin, but pioglitazone is approved in combination with insulin preparations.

Meglitinides are the postprandial hypoglycaemic agents. Meglitinides are divided into two groups with one drug in each group. Phenylalanine derivates represent nateglinide, and benzoic acid derivates – repaglinide. Recommended dosage for repaglinide is 0.5-4 mg at mealtime 2-4 times daily with a maximum dosage of 16 mg per day. Nateglinide is produced in tablets of 60 and 120 mg. Each dose should be taken 1-30 min. prior to food intake 2-4 times a day. Tablets should be taken with plenty of water. If a meal is skipped by the patient, so should be the dose for this meal. An additional meal requires taking one more tablet. The main contraindications to meglitinides are liver diseases.

It is possible to use nateglinide or repaglinide in combination with metformin. Meglitinides should not be administered with sulfonylureas. Alcohol increases the risk of hypoglycaemia. Therapeutic effect of nonsteroidal anti-inflammatory drugs, salicylates, diuretics, and beta-blockers may be changed under the influence of meglitinides following concurrent use.

Three generations of sulfonylureas are available on the pharmaceutical market. Second generation of sulfonylureas possesses 100 times higher intrinsic activity than the first generation. They may have higher effect by applying lower dosages. The first generation is presented with chlorpropamide (100 or 200 mg in each tablet). Second generation includes Glipizide (5 mg or 10 mg in each tablet), glyburide (3.5 or 5 mg in each tablet is available), gliclazide (80 mg in each tablet), prolonged form of gliclazide – gliclazide MR (30 mg in each tablet), gliquidone (30 mg in each tablet). The third generation includes only one drug – glimepiride with available doses 1 or 2 or 3 or 4 mg in each tablet.

Sulfonylureas have primary and secondary failures. The primary failure results from inadequate diet. The secondary failure is related to inability of β cells to secrete insulin.

Sulfonylureas close K^+ channel, inducing changes in membrane charge. This process leads to opening of Ca^+ channels. Calcium enters the cell and forces insulin out of the cell into the blood stream.

The priority is given to once daily sulfonilureas. Once daily regimen allows to increase patients' compliance and improve glycemic control, for this reason gliclazide MR and glimepiride may be prescribed. Other SU are usually taken two or three times every day, and each dose is to be taken with a full glass of water. Contraindications for prescription are the following: hepatic insufficiency and renal insufficiency (except gliclazide MR, gliquidone, glipizide).

Alcohol and decreased sugar in the blood may also interfere with sulfonylureas. Therapeutic effect of nonsteroidal anti-inflammatory drugs, diuretics, salicylates, beta-blockers, over-the-counter cough or cold drugs may be altered with sulfonylureas following concurrent use.

Combined hypoglycaemic drugs are often associated with the composition of two pharmacological agents (different sulfonylureas and biguanides, i.e. metformin). For example: (glyburide 2.5 mg + metformin 400 mg), (gliclazide 80 mg + metformin 500 mg) etc.

Glucagon-like peptide analogs and agonists (GLP-1 analogs and agonists) are sometimes called incretins. These drugs decrease the level of glucose physiologically following two different mechanisms. GLP-1 analogs and agonists, as the group for the replacement treatment approach, increase the level of glucagon-like peptide, helping to prepare β-cells for insulin production after glucose stimulation. But dipeptidyl peptidase-4 inhibitors (DPP-4) decrease the intrinsic amount of dipeptidyl peptidase that destroys GLP-1. To DPP-4 inhibitors belong saxagliptin and sitagliptin which are available in form of tablets. Saxagliptin can be prescribed once a day (5 mg in each tablet). Sitagliptin is available in 25 or 50 or 100 mg in each tablet on the pharmaceutical market.

Exenatide is the first GLP-1 agonist recommended to be administered in case of type 2 diabetes. Exenatide is not interchangeable for GLP, rather it is a GLP agonist. Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and enlarges its half-life. Typical reductions in A1C values constitute 0.5–1.0%. Liraglutide is a once daily human analogue (97% homology). Both drugs should be used in treatment subcutaneously. Exenatide is produced in ampoules (5 or 10 μg in 1 ml), as well as liraglutide (0.6 or 1.2 or 1.8 mg in 1 ml). Exenatide should be administered twice a day before meal, while liraglutide – once a day regardless of meals.

Sodium/glucose cotransporter type 2 (SGLT2) inhibitors, also known as gliflozins or flozins, belong to a class of medications that exhibit the ability to inhibit sodium-glucose transport proteins located in the nephron, which is the functional unit of the kidney. In contrast, SGLT1 inhibitors perform a similar function, but in the intestinal mucosa. The primary metabolic impact of SGLT2 inhibitors is the inhibition of glucose reabsorption in the kidney, resulting in a decrease in blood sugar levels. These inhibitors work by targeting the sodium/glucose cotransporter 2 (SGLT2). They are commonly prescribed once or twice per day for the management of type 2

diabetes. In addition to their glucose-regulating properties, gliflozins have been found to confer substantial cardiovascular advantages for individuals with type 2 diabetes. The most common drugs from this group are Canagliflozin (approved in March 2013 – 100 mg; 300 mg), Dapagliflozin (approved in 2012 – 5 mg, 10 mg), and Empagliflozin (approved in August 2014 – 10 mg, 25mg).

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
Patient N. 46 years old, complains of itch in the region of the genitals, frequent urination, tiresome thirst, weight gain. These symptoms were evidenced over several months. Fasting blood glucose is 12.0 mmol/l, glucose in urine – 1.5 %.
1. What is the most likely diagnosis?
2. What treatment should you order?

Case 2.
Patient A., 56 years old. Type 2 diabetes lasts for 10 years. Patient regularly receives gliburide (5 mg in each tablet) one tablet 3 times per day. In the last three years patient was not examined by endocrinologist. Feet are cold, and pulse on *a. dorsalis pedis* and on *a. tibialis posterior* is faint. Fasting blood glucose is 15.0 mmol/l, glucose in urine – 2.0 %
1. Substantiate diabetic complications.
2. Choose the proper therapeutic approach.

Case 3.
Patient C., 67 years old. Patient has been suffering from type 2 diabetes for 9 years. Patient follows diet, takes oral agents for the treatment of type 2 diabetes, namely sulfonylureas with maximal therapeutic doses. Patient's fasting blood glucose is 17 mmol/l, glucose in urine – 3%.
1. What complications of sulfonylureas treatment should you consider?
2. What approach do you need to take in order to eliminate these complications?

1.4 Diabetic acidosis, hyperosmolar coma and lactic acidosis. Cardiovascular complications of diabetes mellitus. Diabetic neuropathy. Diabetic nephropathy. Diabetes and the eye. The diabetic foot. Diabetes mellitus and pregnancy. Gestational diabetes. Surgery in diabetic individuals. Gut microbiota in diabetes mellitus.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of common endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 4.

1. **Professional motivation**: The diabetic acidoses and comas remain a significant cause of mortality and morbidity, most of which can be avoided. Infection is the most common causative factors for diabetic acidosis, since it causes a marked increase in secretion of hormones cortisol and glucagon. Other precipitating factors are omission of insulin intake, acute myocardial infarction, cerebrovascular accidents, and also trauma.
Hyperosmolar hyperglycemic non-ketonic coma appears to be approximately the tenth in the incidence of classic diabetic ketoacidosis; however, it causes a much higher mortality. It usually occurs in patients with type 2 diabetes mellitus and is often the first sign that the patient has diabetes. The causative factors for hyperosmolar hyperglycemic nonketotic coma are: infection, cardiovascular emergencies (cerebrovascular accident and myocardial infarction), and cerebrovascular accident. These clinical cases may be associated with the inability to drink, and hyperosmolality can follow.
Hypersecretion of counterregulatory hormones may also occur, causing metabolic disturbances.
The risks for late complications vary substantially in individuals but usually increase with increasing duration of diabetes mellitus. Hyperglycemia causes the primary metabolic changes in the kidneys, peripheral nervous system and retina in diabetics, but evidence suggests that when these structural changes reach a certain stage, factors other than hyperglycemia determine the subsequent cause. The signs and symptoms of late complications of diabetes mellitus resemble those of pathologically similar or indistinguishable disease in the same organ or system in

nondiabetics. For instance, coronary artery disease (manifested by angina pectoris and / or myocardial infarction) and peripheral vascular disease (manifested by intermittent claudication and gangrene) are more common in diabetics than in nondiabetics. The signs may be present at diagnosis in the patients with type 2 diabetes mellitus, but not in those with type 1 diabetes.

Approximately 15% of individuals with diabetes mellitus develop a foot ulcer, and a significant number of them will finally undergo amputation (14 to 24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include: male sex, diabetes >10 years duration, peripheral neuropathy, abnormal structure of foot (bone abnormalities, callus, and thickened nails), peripheral arterial disease, smoking, poor glycemic control, and history of previous ulcer or amputation.

Before the appearance of insulin, few young diabetic women survived to childbearing age. Before 1922, less than 100 pregnancies in diabetic women were reported, with a >90% infant mortality rate and a 30% maternal mortality rate. In the mid-1970s, physicians were still advising diabetic women to avoid pregnancy. Perinatal mortality rates have decreased to levels observed in the general population, since the pathophysiology of pregnancy, complicated by diabetes, has been elucidated and treatment programs have achieved and maintained normoglycemia during pregnancy.

The other meaning of gestational diabetes mellitus is pregnancy-related diabetes that usually refers to diabetes occurring during pregnancy and disappears after the delivery. Gestational diabetes usually occurs during the second half of pregnancy in those who are overweight, or aging, and who have a family history of diabetes. Most women recover to normal glucose tolerance after delivery, but a significant risk (30 to 60%) of developing diabetes mellitus later in life remains.

Increased requirement for surgical procedures and postoperative morbidity and mortality are associated with diabetes mellitus. Diabetic patients undergo surgical procedures more often than nondiabetic people do. The stress and excitement before major surgery can greatly affect glucose homeostasis in the diabetic patients. Major surgical operations require a period of fasting during which oral antidiabetic drugs cannot be taken. Patients can develop severe hyperglycemia and ketosis during and after surgery regardless of whether they are receiving prior medication therapy. The stress reaction itself may precipitate diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome during or after surgery, with possible negative consequences. Hyperglycemic hyperosmolar syndrome is a well-known postoperative complication following certain procedures, including cardiac bypass surgery, where it is associated with 42% mortality. In addition, gastrointestinal violation caused by anesthesia, medications, and stress-related vagal overlay can lead to nausea, vomiting, and dehydration. This compounds the volume contraction that may already be present from the osmotic diuresis induced by hyperglycemia,

thus increasing the risk for ischemia and acute renal failure. Insignificant to gross deficiency in basic electrolytes (mainly potassium, but also magnesium) may pose an arrhythmogenic risk, which is often superimposed on a milieu of endemic coronary artery disease in middle-aged or older diabetic people. Thus, any diabetic patient undergoing surgery should be provided the best nutritional, metabolic, and general conditions as much as possible.

Traditionally, insulin resistance (IR), defects in the immune response, and chronic inflammation processes were believed to be the common pathogenetic mechanisms of diabetes and thyroid dysfunction. However, recent research has revealed that many endocrinopathies are associated with changes in the gut microbiota (GM), both in terms of its function and structure. Additionally, the GM has been found to have remote effects on the functioning of various organs. For instance, there is evidence linking the GM to the development of diseases such as T1DM, T2DM, diffuse toxic goiter, hypothyroidism, autoimmune thyroiditis, atherosclerosis, cardiovascular diseases, oncopathology, chronic kidney disease, non-alcoholic fatty liver disease, bone damage, and depression.

2. Study aim of this lesson

is to acquaint students with therapy of emergency conditions in diabetes, management of diabetic complications, treatment of the pregnant diabetic women and management strategies of diabetic individuals during perioperative period (α=1).

In the study process students should know (α=2):

- pathophysiology of diabetic ketoacidosis, hyperosmolar coma and lactic acidosis,
- clinical presentation of emergency conditions and their differences,
- diagnosis and classification of cardiovascular complications of diabetes mellitus,
- diagnosis and classification of diabetic retinopathy,
- diagnosis and classification of diabetic nephropathy,
- diagnosis and classification of diabetic neuropathy,
- diagnosis and classification of the diabetic foot,
- diagnosis of gestational diabetes,
- treatment of the pregnant diabetic women,
- general treatment strategy of diabetic patients undergoing surgery.

In the study process student should be able to (α=3):

- differentiate hypoglycaemia from other acute complications,
- differentiate macrovascular and microvascular events,

- treat patients with chronic diabetic complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic foot, macrovascular complications),
- manage patients with emergency conditions,
- be familiar with diagnostic criteria for gestational diabetes,
- treatment approach of labor and delivery in diabetic women,
- prescribe insulin to patients before undergoing surgery.

3. Educational aim of this lesson

Is to focus attention on treatment of emergency conditions, late diabetic complications, labor and delivery as well as patients before undergoing surgery

4. Interdisciplinary integration (see Table 8).

Table 8

Interdisciplinary integration

Discipline	To know	How to do
I. Previous		
General anatomy and physiology, histology, pathological anatomy and physiology, pharmacology	Pancreas (location, morphology, function); hormones, regulation	To estimate physiological reserve of pancreas in order to prescribe proper treatment (doses and methods) To prescribe medications.
II. Future		
Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology, Nephrology Ophthalmology.	Main clinical signs of Diabetes Mellitus, its types, differential diagnosis, treatment Emergency states and late diabetic complications	To make clinical observation, prescribe proper diagnostic assays, consultation of associative specialists for verification of diagnosis.
III. Interdisciplinary integration	Contemporary methods of diagnostics and treatment	To prescribe adequate treatment of diabetes mellitus.

5. Contents of the lesson.

- Diabetic acidosis: pathophysiology, precipitating factors, signs and symptoms, diagnosis, initial laboratory investigations, treatment, prevention.
- Hyperosmolar coma: pathophysiology, precipitating factors, presentation, diagnosis, treatment.
- Lactic acidosis: pathophysiology, presentation, diagnosis, treatment.

- Cardiovascular diseases in diabetes and their classification.
- Management of diabetic ischemic heart disease (diet plan, exercise, drug therapy, surgical approaches such as balloon angioplasty and coronary artery bypass surgery).
- Diabetic neuropathy: classification, clinical picture, pathogenesis and therapeutic implications.
- Diabetic nephropathy: classification, clinical course, laboratory abnormalities and treatment.
- Diabetic retinopathy: classification and characteristics of each stage, management. Other eye disorders in diabetes (diabetic cataract, diabetic ophthalmoplegia, glaucoma) and their management.
- The diabetic foot: pathophysiology (neuropathy, ischemia, infection), management and threatening factors (foot ulcer, limb-threatening infections, osteomyelitis).
- Diabetes mellitus and pregnancy: diagnostic strategies, treatment.
- Differential diagnostics of emergency conditions.
- Treatment strategies of diabetic patients that undergo surgery.
- The GM and diabetes mellitus: laboratory abnormalities and treatment

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
One of the main causes of hypoglycaemia is:
A) Unaccustomed exercise
B) Stress
C) Weight loss
D) Weight gain
E) Diarrhoea

#2
Patient K., suffering from diabetes mellitus during the past 8 years, is in coma. The skin is dry, Kussmaul's respiration, acetone breath is evidenced. What type of coma is it?

A) Hypoglycemic coma
B) Lactic acidosis
C) Hyperosmolar state
D) Ketoacidosis
E) Brain coma

#3
Macroangiopathy in diabetes mellitus, most often destroys vessels of:
A) Lung
B) Brain
C) Retina
D) Kidneys
E) Liver

#4
Which assertion is not correct as regards to angiopathy of lower extremities?
A) Trophic disturbance step by step beginning with toes
B) Pain in legs when walking
C) Decrease of foot temperature
D) Development of foot gangrene
E) Paresthesia

7.2. Recourses for the main stage of the lesson.

Diabetic ketoacidosis is the result of complete or relative insulin deficiency which causes dehydration, hyperglycemia and a resulting osmotic dieresis, and electrolyte depletion. The deficiency of insulin activates glycogenolysis (breakdown of glycogen to glucose) and gluconeogenesis (breakdown of proteins that leads to nitrogen loss and amino acids production, which are precursors in new glucose formation). In addition to this, lipolysis causes the production of free fatty acids and glycerol, which then facilitates fuel production of new glucose. The low utilization of peripheral glucose (secondary to both insufficiency of insulin and resistance) and the volume depletion (secondary to osmotic diuresis), that decrease renal blood flow and thus the amount of glucose filtered and excreted by the kidney, cause later hyperglycemia. Free fatty acids are transported to the liver where ketone bodies are produced (ketogenesis) with subsequent ketonemia, which is enhanced by decreased peripheral utilization. This causes ketonuria, which further depletes electrolytes through an associated obligatory loss of cations. Acidosis occurs as body bases are exhausted during buffering the ketone bodies that are formed in an uncontrollable mode (Fig. 1).

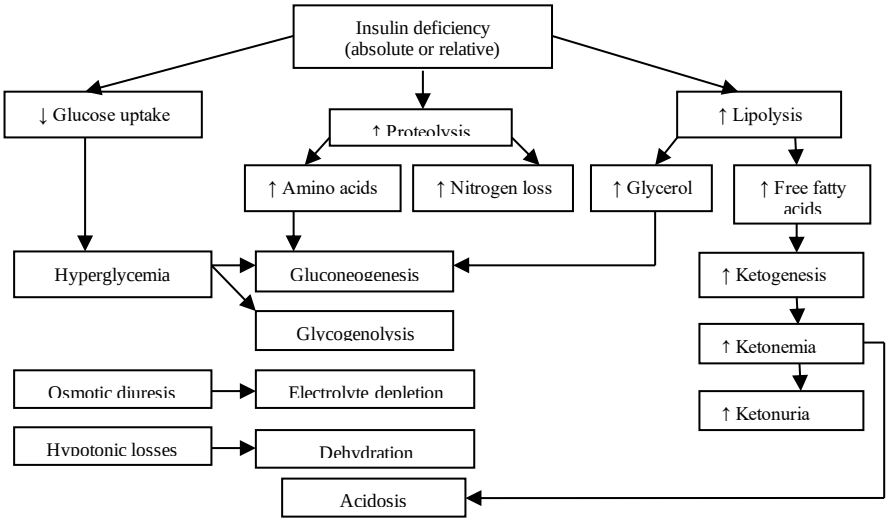


Figure 1. Pathophysiology of diabetic ketoacidosis.

Table 9 shows the symptoms and physical manifestations of diabetic ketoacidosis, which as a rule develop within 24 hours. Diabetic ketoacidosis may be the first symptom that could help to diagnose type 1 diabetes mellitus, however it more often occurs in patients who already were diagnosed with diabetes. During physical examination the doctor should look for signs of infection, which may precipitate diabetic ketoacidosis, even if there is no fever. Ischemia of the tissue (heart, brain) can also be one of precipitating factors.

Table 9

Symptoms and physical findings of diabetic ketoacidosis

Symptoms	Physical findings
Nausea/vomiting	Tachycardia
Thirst/polyuria	Dry mucous membranes/reduced skin turgor
Abdominal pain	Dehydration/hypotension
Shortness of breath	Tachypnea/Kussmaul respiration/respiratory distress
	Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
	Lethargy /obtundation/cerebral edema/possibly coma

Diabetic ketoacidosis is a condition of uncontrolled diabetes mellitus in which hyperglycemia is observed (usually >16.7 mmol/l) with a significant decrease of arterial blood pH (<7.3) and an increase in total blood ketone body concentration (β-

hydroxybutyrate plus acetoacetate >5 mmol/l). The cutoff between diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma is rather arbitrary, although hyperglycemia is often much more severe in the latter, with ketone body levels lower.

Types of treatment of diabetic ketoacidosis are given in Table 10.

Table 10

Management of diabetic ketoacidosis

1.	Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2.	Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH < 7.00 or unconscious.
3.	Assess: Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate) Acid-base status—pH, HCO_3^-, P_{CO2}, β-hydroxybutyrate Renal function (creatinine, urine output)
4.	Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (5–10 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 250 mg/dL (14 mmol/L).
5.	Administer regular insulin: IV (0.1 units/kg) or IM (0.4 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 h. If initial serum potassium is < 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected to > 3.3 mmol/L (3.3.meq/L).
6.	Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).
7.	Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8.	Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9.	Replace K^+: 10 meq/h when plasma K^+ < 5.5 meq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ <3.5 meq/L or if bicarbonate is given.
10.	Continue above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11.	Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection

Note: CXR, chest x-ray; ECG, electrocardiogram.

Precipitating factors causing diabetic ketoacidosis are: infection (pneumonia / urinary tract infection / gastroenteritis / sepsis), errors in use of insulin, infarction (cerebral, coronary, mesenteric, and peripheral), drugs (cocaine), and pregnancy. The typical patient suffering hyperosmolar hyperglycemic nonketotic coma is an elderly person with type 2 diabetes mellitus, who has a several week history of polyuria, with weight loss and reduced oral intake causing mental confusion, lethargy, and coma. Physical examination of such patient may show severe dehydration, hyperosmolality and hypotension, tachycardia, and altered mental condition, while there is no vomiting, nausea, pain in the abdomen and the Kussmaul respiration characteristic of diabetic ketoacidosis. A serious, concurrent disease such

as myocardial infarction or stroke may often precipitate hyperosmolar hyperglycemic nonketotic coma. It should be also born in mind that pneumonia, sepsis, and other serious infections are common precipitants too. Moreover, a serious condition (prior stroke or dementia) or social situation that compromises water intake may be contributing factors to the development of the illness.
Relative lack of insulin and inadequate fluid intake are the causes of hyperosmolar hyperglycemic nonketotic coma. Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle (see above description of diabetic ketoacidosis). Hyperglycemia is accompanied by osmotic diuresis that causes intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in hyperosmolar hyperglycemic nonketotic coma has not been fully explained yet. Presumably, the lack of insulin is only relative and less acute than in diabetic ketoacidosis. Some studies have revealed lower levels of counterregulatory hormones and free fatty acids in hyperosmolar hyperglycemic nonketotic coma than in diabetic ketoacidosis. Another cause may be that the liver is less capable of ketone body synthesis or that the insulin/glucagon ratio does not favor ketogenesis.
The laboratory features are summarized in Table 11.

Table 11

Laboratory values in diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic coma (HHNC)

Laboratory values	DKA	HHNC
Glucose,[a] µmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium,[a] meq/L	Normal to ↑[b]	Normal
Magnesium[a]	Normal[b]	Normal
Chloride[a]	Normal	Normal
Phosphate[a]	↓	Normal
Creatinine, µmol/L (mg/dL)	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/-
Serum bicarbonate,[a] meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial P_{CO2},[a] mmHg	20–30	Normal
Anion gap[a] [Na - (Cl + HCO_3)], meq/L	↑	Normal to slightly ↑

Notes: [a] - Large changes occur during treatment of DKA. [b] - Although plasma levels may be normal or high at presentation, total-body deposites are usually depleted.

Diabetic ketoacidosis and hyperosmolar hyperglycemic nonketotic coma are usually accompanied by depletion of volume and hyperglycemia. As a result, their treatment

includes several elements. In both disorders it is vital to monitor the patient's fluid condition, laboratory data, and the rate of insulin infusion. Underlying or precipitating conditions should be revealed and treated. During hyperosmolar hyperglycemic nonketotic coma, loss of fluid and dehydration are usually more evident than in diabetic ketoacidosis because of the longer course of the illness. Patients with hyperosmolar hyperglycemic nonketotic coma are older, more likely to have changes in mental condition, and a life-threatening precipitating event with accompanying diseases. Hyperosmolar hyperglycemic nonketotic coma causes much higher mortality, even under appropriate treatment, than diabetic ketoacidosis (up to 15% in some clinical cases).

Lactic acidosis happens when the pyruvate and lactate metabolism is blocked. In this case blood lactate levels are >5 mmol/l, and there is a significant decrease in arterial blood pH (<7.2).

Different causes of lactic acidosis are summarized in Table 12.

Table 12

Classification of lactic acidosis

Type	Description
Type A	Hypoxic, poor tissue perfusion, shock
Type B1	Associated with common disorders: diabetes mellitus, renal failure, liver failure, infection, leukemia
Type B2	Due to drugs or toxins: phenformin, metformin, buformin, ethanol, salicylates, fructose, methanol
Type B3	Hereditary forms: glucose 6-phosphatase deficiency, infantile lactic acidosis
Type B4	Miscellaneous

The incidence of lactic acidosis has decreased significantly since its connection with phenformin (and buformin) use was revealed. Metformin is now the only biguanides that is widely available; the incidence of lactic acidosis caused by its use is five to ten per 100,000 patients, which is only insignificantly above the incidence in non-metformin users.

Hypotension more often occurs in patients suffering from lactic acidosis; as well as obvious illness and hyperventilation. Such patients are likely to be oliguric or anuric, have a history of metformin use or cardiovascular disease, and probably recent cerebrovascular accident or myocardial infarction. The scheme given in Table 14 helps in diagnosis.

Treatment of lactic acidosis has not proven to be effective, with mortality rate being 50% in biguanides-associated cases and 60% to 80% - in other cases. The first priority is vascular support and reversal of hypotension. Any cause should undergo

treatment (e.g., cessation of biguanides administration). Reversal of the academia is as well important. When pH is below 7.0, the liver produces, rather than clears, lactate and is not able to generate hydroxyl ions through lactate oxidation. That is when a vicious cycle develops. In such cases sodium bicarbonate should be used in large doses, 250 mmol/1 hour initially, with repeated similar doses until the pH is >7.1. In some patients, amount of 2500 mmol has been effective. Almost inevitably, hemodialysis or peritoneal dialysis is required as it may also be helpful in removing the hydrogen ion load and any related drugs. However, it should be kept in mind that the most effective treatment is prevention.
Bedside differential diagnosis of coma is summarized in Table 13.

Table 13

Bedside differential diagnosis of coma

Diagnosis	Blood glucose (mg/dl)	Plasma ketones*	Hyperventilation	Dehydration	Blood pressure	Skin
Diabetic ketoacidosis	>300	+ to +++	++	++	Low to normal	Warm
Hyperosmolar, hyperglycemic, nonketotic coma	>500	0 to +	0	+++	Low to normal	Normal
Hypoglycemic coma	<50	0	0	0	Normal	Cold, clammy
Lactic acidosis	20-200	Trace to +	+++	0	Low	Warm
Nonmetabolic comas	Normal or raised	0 to trace	0 to +	0 to +	Variable	Normal

Notes: + - mild, ++ - moderate, +++ - severe, * - using test strips.

Diabetes mellitus chronic complications influence many organ systems and may cause the majority of morbidity and mortality cases connected with the disease. Such chronic complications can be vascular and nonvascular (see Table 14).

Table 14
Chronic complications of diabetes mellitus

Microvascular
Eye disease
Retinopathy (nonproliferative/proliferative)
Macular edema

Neuropathy
Sensory and motor (mono- and polyneuropathy)
Autonomic
Nephropathy
Macrovascular
Coronary artery disease
Peripheral vascular disease
Cerebrovascular disease
Other
Gastrointestinal (gastroparesis, diarrhea)
Genitourinary (uropathy/sexual dysfunction)
Dermatologic
Infectious
Cataracts
Glaucoma

Cardiovascular diseases are common in patients with type 1 or type 2 diabetes mellitus. Patients with type 2 diabetes without a prior myocardial infarction have a similar risk for coronary artery related cases as nondiabetic individuals who have suffered a prior myocardial infarction. Patients with diabetes mellitus usually have no chest pain ("silent ischemia"), and a thorough cardiac examination is indicated in individuals undergoing major surgical procedures. Coronary artery disease is more likely to influence multiple vessels in patients suffering from diabetes.

Risk factors for macrovascular disease in patients with diabetes include dyslipidemia, hypertension, insufficient physical activity, excessive weight, and smoking. Additional risk factors in diabetes also include microalbuminuria, severe proteinuria, an increase of serum creatinine, and abnormal function of platelets. Insulin resistance, with high serum insulin levels, causes increased risk of cardiovascular complications in individuals both with and without diabetes mellitus. It has not been proven that improved control of glycemia reduces cardiovascular complications in diabetes mellitus; in fact, such therapy may be ineffective or macrovascular complications may be even worsened. Concerns about the atherogenic potential of insulin remain, since in nondiabetic patients, higher serum insulin levels (signs of insulin resistance) mean a greater risk of cardiovascular morbidity and mortality cases.

The order of priorities in hyperlipidemia treatment is: (1) lower the LDL cholesterol, (2) raise the HDL cholesterol, and (3) decrease triglycerides. Improvement in glycemic control lowers triglycerides and has a moderate positive effect on raising HDL. HMG CoA reductase inhibitors are the agents of choice for lowering the LDL.

Hypertension can facilitate development of diabetes mellitus complications, in particular, cardiovascular diseases and nephropathy. Treatment of hypertension should primarily be aimed at changing the life-style such as weight loss, exercise, stress management, and limiting the amount of sodium. Antihypertensive agents

should be selected considering the advantages and disadvantages of the therapeutic agents, bearing in mind risk factor profile of an individual patient. Diabetes mellitus-related conditions include the following:

- ACE inhibitors being glucose- and lipid-neutral or glucose- and lipid-beneficial and have a positive influence on the cardiovascular risk profile. For example, α-adrenergic blockers slightly improve insulin resistance and so there is positive impact on the lipid profile, while beta blockers and thiazide diuretics may increase insulin resistance and have negative influence on the lipid profile. Calcium channel blockers, vasodilators and central adrenergic antagonists are lipid- and glucose-neutral.
- The risk of developing type 2 diabetes mellitus may be slightly increased by betablockers. Hypoglycemic symptoms might be masked but beta blockers are safe in most diabetic patients and reduce the risk of cardiovascular disorders.
- Sympathetic inhibitors and α-adrenergic blockers could increase orthostatic hypotension in patients with diabetes mellitus who have autonomic neuropathy.
- Reducing equivalent blood pressure with the help of various classes of agents may not involve equivalent protection from cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs have a positive impact on cardiovascular endpoints (MI or stroke). The cardiovascular protective property of central adrenergic antagonists, calcium channel blockers, and α-adrenergic blockers is either ambiguous or not completely studied. ACE inhibitors and ARBs delay the progress of diabetic renal disease; the effect of other classes of agents on diabetic nephropathy has not been revealed yet.
- It is preferable to use non-dihydropyridine calcium channel blockers (verapamil and diltiazem) rather than dihydropyridine agents (amlodipine and nifedipine) in diabetics.

Patients aged over 20 may develop blindness as a result of diabetes mellitus. This is usually caused by progressive diabetic retinopathy and clinically evident macular edema. Diabetic retinopathy can be nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually occurs late in the first decade or early in the second decade of the disease and is accompanied by blot hemorrhages, retinal vascular microaneurysms, and cotton wool spots. Mild nonproliferative retinopathy develops to more serious condition, characterized by changes in caliber of venous vessels, intraretinal microvascular abnormalities, and more numerous hemorrhages and microaneurysms.

In case of diabetic retinopathy prevention is the most effective therapy. Thorough monitoring of glycemia and blood pressure will delay or slow the development of retinopathy. Paradoxically, established diabetic retinopathy may transiently worsen during the first 6 to 12 months of improved glycemic control. However, this progression is only temporary, and permanent control of glycemia is associated with less diabetic retinopathy. Patients with retinopathy are subject to preventive

photocoagulation when starting intensive therapy. Laser photocoagulation has proven to be very successful in sight maintenance. Proliferative retinopathy is treated with panretinal laser photocoagulation, while macular edema is usually treated with focal laser photocoagulation.

Proteinuria in patients with diabetic nephropathy causes high risk of cardiovascular disease and is associated with considerably reduced survival. Glomerular hyperperfusion and renal hypertrophy take place in the first years after the onset of DM and cause growth of the glomerular filtration rate (GFR). After 5-10 years of type 1 DM, ~40% of patients small amounts of albumin in the urine start to excrete. Microalbuminuria is defined as 30-300 mg/d in a 24-h collection or 30-300 μg/mg creatinine in a spot collection (preferred method). If there is found microalbuminuria (incipient nephropathy) in type 1 DM, it is an important sign of progression to evident proteinuria (>300 mg/d) or evident nephropathy. Blood pressure may grow insignificantly at this point but usually remains normal. If evident proteinuria occurs, there is a steady decline in GFR, and ~50% of individuals reach end-stage renal disease in 7-10 years.

It is easier to prevent diabetic nephropathy than to treat it. Effective measures for slowing progression of microalbuminuria to evident nephropathy are: (1) near normal level of glycemia, (2) thorough monitoring of blood pressure, (3) administration of ACE inhibitors or ARBs, and (4) treatment of dyslipidemia.

Approximately 50% of individuals have diabetic neuropathy with long-lasting type 1 and type 2 DM. It may be manifested as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy is connected with diabetes duration and control of glycemia; both myelinated and unmyelinated nerve fibers are lost.

Distal symmetric polyneuropathy, most often presented with distal sensory loss, is the most common form of diabetic neuropathy. Hyperesthesia, paresthesia, and dysesthesia also occur. Among the symptoms are: tingling sensation, numbness, sharpness, or a burning sensation starting from the feet and spreading proximally. Some of the patients may develop neuropathic pain, in some cases preceded by improvement in their glycemic control. Pain typically is felt in the lower extremities, is usually present at rest, and worsens at night.

Treatment of diabetic neuropathy has not proven to be effective. Glycemic control should be improved, which will enhance the velocity of nerve conduction, but the symptoms of diabetic neuropathy may not necessarily get better. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoiding neurotoxins (alcohol), enough of vitamins for possible deficiencies (B_{12}, B_6, folate) and symptomatic treatment are the main types of therapy. Inhibitors of aldose reductase do not provide any significant symptomatic relief. Although chronic, painful diabetic neuropathy is difficult to treat, it may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline),

gabapentin, nonsteroidal anti-inflammatory agents (should be avoided in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream).

Diabetes mellitus and as its result diabetic foot, is the main cause of nontraumatic lower extremity amputation in the world. The high occurrence of diabetic foot is due to the interaction of several pathogenic factors: neuropathy, peripheral arterial disease, abnormal foot biomechanics, and poor healing of wounds. The peripheral sensory neuropathy interferes with normal protective mechanisms, which allows the patient to sustain major or repeated minor trauma to the foot, often without even knowing about the injury. Disordered proprioception causes abnormal weight bearing during walking and subsequently forming of ulceration or callus. Motor and sensory neuropathy leads to abnormal mechanics of foot muscle and structural changes in the foot (claw toe deformity, hammer toe, prominent metatarsal heads, Charcot joint).

According to a recent consensus statement from the American Diabetes Association there are six interventions with evident efficacy in diabetic foot wounds: (1) off-loading, (2) debridement, (3) wound dressings, (4) proper use of antibiotics, (5) revascularization, and (6) limited amputation. Mild or non-limb-threatening infections are treated with oral antibiotics (clindamycin, cephalosporin, amoxicillin/clavulanate, and fluoroquinolones), surgical debridement of necrotic tissue, local wound care (avoidance of weight load over the ulcer), and careful monitoring for infection. More serious ulcers may need intravenous administering of antibiotics, bed rest and local wound care. Intravenous antibiotics used are to provide wide-range effect directed at Staphylococcus aureus, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial medications should include cefotetan, ampicillin/sulbactam, or the combination of clindamycin and a fluoroquinolone.

Diagnosis of gestational diabetes mellitus is given in Table 15.

Table 15

Diagnosis of gestational diabetes mellitus

Approach	Mg/dl	Mmol/l
100-g oral glucose load		
Fasting	95	5.3
1 hour	180	10.0
2 hour	155	8.6
3 hour	140	7.8
75-g oral glucose load		
Fasting	95	5.3
1 hour	180	10.0
2 hour	155	8.6

Classification of treatment approaches of gestational diabetes mellitus is summarized in Table 16.

Table 16

Classification of treatment approaches of gestational diabetes mellitus

Classification	Characteristics
Diet-controlled	Fasting capillary whole-blood glucose <90 mg/dl (5.3 mmol/l)
Insulin requirement	Trial of diet. Initiate insulin if normoglycemia is not maintained on diet alone. If the fasting capillary whole blood glucose level is >90 mg/dl and or postprandial glucose levels are >90 mg/dl (6.7 mmol/l) then insulin should be prescribed immediately.

Anesthesia and surgery lead to a stereotypical metabolic stress, which can influence homeostatic mechanisms in patients with previously existing abnormalities of glucose metabolism. The indicators of the metabolic stress response include secretion of the catabolic hormones: cortisol, epinephrine, norepinephrine, glucagons and growth hormone, and inhibition of insulin secretion and its action. In addition to insulin resistance, caused by circulating stress hormones, surgical stress has a negative impact on pancreatic β-cell function. Levels of plasma insulin drop and insulin secretory responses to glucose become impaired on surgery.
People with diabetes who control their diet and physical exercises may not require any special intervention for diabetes prior surgery. If surgery is minor (less 1 h), no specific therapy is needed. If surgery is major or if diabetes is not properly controlled (blood glucose >200 mg/dl), an intravenous infusion of insulin and dextrose is required, and hourly glucose check is recommended throughout operation.
Second-generation sulfonylureas should be stopped 1 day before surgery, and chlopropramide should not be given 2–3 days before surgery. Other oral agents can be taken until the day of surgery. Although metformin has a short half-life of ~6 h, it is expedient to avoid therapy temporarily 1–2 days before surgery, especially in sick patients and those undergoing procedures, which increase the risks for tissue hypoxia, renal hypoperfusion, and lactate accumulation. Patients using insulin of long action (e.g., ultralente, glargine, protamine zinc insulin) should choose intermediate-acting forms 1–2 days before elective surgery.
GM has a wide impact on health and disease. In recent years, attention has been drawn to the fact that *Actinobacteria* can also be used to diagnose the course of T2DM, since a direct correlation between glycated hemoglobin and Actinobacteria has been recorded. It should also be noted that in patients with type 2 diabetes mellitus and existing insulin resistance (European population), GM is characterized by the growth of representatives of the phylum *Bacteroidetes* and the impoverishment of genera of the phylum *Firmicutes*, which indicates early stages in pathogenesis. Upon receipt of test results reflecting such a structural and functional distribution in the GM structure, the patient should immediately be

advised to change his eating habits in the direction of increasing fiber, fresh plant products and natural fermentation products in the diet.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Male patient, aged 56, with type 2 diabetes mellitus for 10 years, takes gliburide regularly 5 mg 3 times a day, recently has lost weight, hasn't visited endocrinologist for the last 3 years. During inspection darkened nail on the right foot, cold foot, and weakened pulsation were detected. Fasting glucose in blood is 11.0 mmol/l, glucosuria is 2.0 %.

1. What is the patient's complication?
2. Choose the treatment method of this patient.

Case 2.

Patient C., 32 years old, was delivered unconscious to the intensive care unit. The patient has a medical history of diabetes. Insulin was not found. The breathing is noisy of Kussmaul's type; acetone breath, the skin is dry, turgor is lowered, the facial features are sharp, periosteal reflexes are absent, eyeball tone is lowered. Blood contains 1.2 mmol/l of lactic acid (norm - 0.62-1.3 mmol/l), glycemia - 29 mmol/l.

1. What kind of coma can be suspected?
2. How would you treat this patient?

Case 3.

Patient T., 26 years old, is in the intensive care unit with a ketoacidotic coma. Her consciousness is clouded; eyeball tone is lowered, arterial pressure - 90/60, pulse - 130 beats/minute, glycemia - 35 mmol/l, PH - 7.1. The content of ketone bodies is 18 mg %.

1. What is the differential diagnosis?
2. How would you treat this patient?

1.5 The iodine deficiency disorders. Hypothyroidism: classification, etiology, pathogenesis, clinical picture, laboratory diagnosis, therapy. Thyroiditis: classification, etiologies, pathogeneses, clinical presentation, laboratory evaluation, treatment approaches. Thyroid cancer: classification, etiology, diagnosis, treatment approach.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of common endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 5.

1. **Professional motivation**: Severe and moderate deficiency of iodine is common in many mountainous regions and in the central Africa, central South America, and northern Asia. In Europe mild deficiency is present. The World Health Organization (WHO) estimates based on urinary excretion analyses, that approximately 2 billion people are iodine-deficient. In regions of relative iodine deficiency, there is an increased incidence of goiter and, where deficiency is severe, hypothyroidism and cretinism are prevalent. Cretinism is characterized by mental and growth retardation and occurs in children living in iodine-deficient regions who are not treated with iodine or thyroid hormone to restore thyroid hormone levels to normal indices in the early life. These children are often born to mothers with iodine deficiency, and obviously thyroid hormone deficiency in mothers worsens the condition. India is the most common example, with 100 million people suffering from iodine deficiency (4 million from goiter, and 0.5 million from cretinism). Concomitant deficiency of selenium may also contribute to the neurologic signs of cretinism. Supplementation of salt, bread, and other food substances with iodine has significantly reduced the incidence of cretinism. Unfortunately, iodine deficiency is still the most common cause of preventable mental deficiency, often because of resistance to food supplements or the cost of additives. Besides obvious cretinism, mild iodine deficiency can cause subtle IQ reduction. Overdosage of iodine, either through supplements or foods enriched with iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The recommended average daily amount of iodine is 150 μg/d for adults, 90–120 μg/d for children, and 200 μg/d for pregnant women. Urinary iodine constitutes >10 μg/dL in iodine-sufficient populations.

Public health initiatives to lower the risk of cardiovascular disease have resulted in lower discretionary use of table salt, and with a tendency towards intake of more processed foods. The noniodized salt used in these foods also means that people are less likely to obtain iodine from adding salt during cooking. A low amount of thyroxine (one of the two thyroid hormones) in the blood, due to lack of dietary iodine, causes high levels of thyroid stimulating hormone TSH, which induces the thyroid gland to accelerate many biochemical processes; the cellular proliferation and growth can result in the characteristic swelling or hyperplasia of the thyroid gland, or goiter.

Early hypothyroidism is often asymptomatic and can show very subtle symptoms. Subclinical hypothyroidism is a condition of normal thyroid hormone levels, thyroxine (T4) and triiodothyronine (T3), with slight elevation of thyrotropin, thyroid-stimulating hormone (TSH). With higher TSH levels and low free T4 levels, symptoms become more evident in clinical (or overt) hypothyroidism. Hypothyroidism can be associated with infertility in females.

Thyroiditis is a group of disorders that cause inflammation of the thyroid. There are many symptoms for thyroiditis, none of which is only limited to this disease. Many of the signs are similar to the symptoms of other diseases, thus thyroiditis can sometimes be difficult to diagnose. Thyroiditis is usually caused by an attack of the thyroid, resulting in inflammation and damage to the thyroid cells. This disease is often regarded as a malfunction of the immune system. Antibodies that attack the thyroid cause most types of thyroiditis. It can also be caused by an infection, for example, virus or bacteria, which works in the same way as antibodies, causing inflammation in the glands. Certain people produce thyroid antibodies, thus thyroiditis can be considered an autoimmune disease, since the body acts as if the thyroid gland was foreign tissue. Some drugs, such as interferon and amiodarone, can cause thyroiditis because they have a tendency to impair thyroid cells.

Hashimoto's thyroiditis was first discovered by Japanese physician Hashimoto in 1912. The other name for Hashimoto's thyroiditis is lymphocytic thyroiditis, and patients with the disease often complain of difficulty swallowing. This condition may be so mild at the beginning that the disease goes unnoticed for years. The first symptom that shows signs of Hashimoto's thyroiditis is goitre in the front of the neck.

Thyroid cancer is usually found in euthyroid patient, but the symptoms of hyperthyroidism or hypothyroidism may be related to a large or metastatic well-differentiated tumor.

Thyroid nodules should be of particular concern when they are found in patients under the age of 20. The appearance of benign nodules at this age is less likely, and the potential for malignancy is far greater.

2. Study aim of this lesson.

To acquaint students with history and epidemiology of hypothyroidism, thyroiditis, thyroid cancer in he world (α=1)

In the study process students should know (α=2):

- the main etiological factors, pathogenesis, clinical appearance, laboratory findings, and treatment of hypothyroidism,
- etiology pathogenesis, clinical picture, laboratory evaluation, treatment of suppurative, subacute, Hashimoto's thyroiditis (autoimmune) and postpartum thyroiditis, Riedel thyroiditis,
- etiology and pathogenesis of endemic goiter and sporadic goiter, clinical features, treatment,
- classification of thyroid cancer, diagnosis, surgery, radioiodine therapy, thyroid hormone therapy, follow-up.

In the study process student should be able to (α=3):

- carry out the examination of the thyroid gland (technique for physical examination of the thyroid gland),
- note the gland texture, mobility, tenderness and the presence of nodules (in addition to palpation for size),
- evaluate thyroid gland function,
- interpret thyroid uptake and imaging, sonography, computed tomography,
- differentiate thyroid disorders,
- order replacement treatment in the case of hypothyroidism,
- prescribe preventive treatment of iodine deficiency.

3. Educational aim of this lesson

Is to focus attention on differential diagnosis of thyroid disorders, prevention of iodine deficiency, early recognition of thyroid cancer.

4. Interdisciplinary integration (see Table 17).

Table 17

Interdisciplinary integration

Discipline	To know	How to do
I. Previous General anatomy and physiology, histology, pathological anatomy, and physiology, pharmacology, radiology	Thyroid gland (location, morphology, regulation and hormone synthesis, embryogenesis). Synthetic preparations of L-T4. Thyroid sonography, computed tomography and magnetic resonance imaging	To estimate physiological function of the thyroid gland. To prescribe medications.

Discipline	To know	How to do
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology	Main clinical signs of thyroid disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment, prevention.	To make clinical observation, to recommend proper diagnostic assays, consultation of associative specialists for verification of diagnosis, to prescribe medications
III. Interdisciplinary integration	Contemporary methods of diagnosis and treatment	To administer adequate treatment

5. Contents of the lesson.

- Incidence of iodine deficiency (causative factors, outcomes).
- Iodine deficiency and pregnancy.
- Inborn iodine deficiency (clinical features, treatment, prognosis).
- Endemic and sporadic goiter (pathogenesis, clinical picture).
- Hypothyroidism (classification, etiology, pathogenesis, clinical picture, laboratory diagnosis, therapy).
- Thyroiditis (classification, etiologies, pathogeneses, clinical presentation, laboratory evaluation, treatment approaches).
- Thyroid cancer (classification, etiology, diagnosis, treatment approach).

6. Plan and organization structure of this lesson.

(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Which assertion is correct regarding the thyroid synthesis?
A) T_4 is derived from T_3 on periphery
B) Stimulated by corticotrophin
C) Depressed by hyperglycaemia
D) Disturbed following iodine deficiency
E) Thyroid synthesis 80% of T_3 and 20% of T_4

#2
All disorders, given below are symptoms of hyperthyroidism, except:

A) Increased heat production
B) Increased metabolism
C) Tachycardia
D) Exophthalmia
E) Weight gain

#3
Choose correct statement relative to detrimental action of increased thyroid hormone production.

A) T_3 and T_4 cause hyperprolactinemia
B) T_3 sensitizes myocardium to the effects of catecholamines
C) Weight gain is associated with thyroid overproduction
D) T_4 induces tachycardia directly
E) Excessive level of thyroid hormones predisposes constipation

#4
Choose the agent, inhibiting synthesis of thyroid hormones.

A) Thiamazole
B) Potassium perchlorate
C) Potassium iodide
D) Iopanoic acid
E) Dexamethasone

7.2. Recourses for the main stage of the lesson.

The thyroid hormones thyroxine and triiodotyronine contain iodine which is an essential trace element. If diet includes insufficient amount of iodine – for instance on remote inlands where no sea foods are consumed – iodine deficiency gives rise to goiter (the so-called endemic goiter), and cretinism, which causes developmental retardation and other health problems. The Lancet stated, "According to WHO, in 2007, nearly 2 billion individuals had insufficient iodine intake, a third being of school age. ... Thus iodine deficiency, as the single greatest preventable cause of mental retardation, is an important public-health problem".

Some places with low consumption of iodine saved the situation by adding small amounts of iodine to table salt in the form of sodium iodide, potassium iodide, and/or potassium iodate – this product is known as iodized salt. Iodine compounds may also be added to other food products, such as flour, water and milk in deficiency areas. Seafood is a major source of iodine. Thus, deficiency of iodine is more common in mountainous regions where food is cultivated in the soil poor in iodine.

Below is given a list of potential risk factors that may result in iodine deficiency:

1. Low iodine in diet
2. Selenium deficiency
3. Pregnancy
4. Exposure to radiation
5. Increased intake/plasma levels of goitrogens, such as calcium
6. Gender (higher occurrence in women)
7. Smoking
8. Alcohol (reduced prevalence in users)
9. Oral contraceptives (reduced prevalence in users)
10. Perchlorates
11. Thiocyanates
12. Age (for different types of iodine deficiency at different ages)

An enlarged thyroid is referred to as goiter. There is no direct connection between size and function- a person with goiter can be euthyroid, hypo- or hyperthyroid. Based on morphology, goitres can be grouped either according to the growth pattern or according to the size of the growth:

Growth pattern

- Uninodular (struma uninodosa) – can be either inactive or a toxic nodule
- Multinodular (struma nodosa) – can be inactive or toxic, the latter is called toxic multinodular goitre
- Diffuse (struma diffuse), with the entire thyroid appearing to be enlarged.

Size

- Class I – palpation struma – cannot be seen in normal position of the head; is only revealed on palpation.
- Class II – the struma is palpative and can also be easily seen.
- Class III – the struma is very large and is retrosternal; compression marks are left after pressure.

To the group of thyroiditis belong the following diseases: Hashimoto's thyroiditis, the most common cause of hypothyroidism, subacute thyroiditis, radiation-induced thyroiditis, silent thyroiditis, postpartum thyroiditis, drug-induced thyroiditis, and acute thyroiditis.

Each type of the disease possesses its own causes, clinical features, diagnoses, durations, resolutions, conditions and risks.

Common symptoms of hypothyroidism appear when the damage to the thyroid cell is slow and chronic, they include overweight, fatigue, feeling "fuzzy headed", dry skin, depression, and constipation. Additional, rarer symptoms include vague aches and pains, swelling of the legs, low concentration etc. When the condition progresses, depending on the thyroiditis type, the additional symptoms are swelling around the eyes, slowing of the heart rate, decreased body temperature, or even future heart failure. In case when the damage to the thyroid cell is severe, the thyroid

hormone within the gland leaks out into the bloodstream and causes the symptoms of thyrotoxicosis, which is similar to those of hyperthyroidism. These symptoms include irritability, weight loss, anxiety, high heart rate, insomnia, and fatigue. Elevated levels of the thyroid hormone in the bloodstream cause both conditions, but in the thyrotoxicosis the thyroid gland is not overactive, as in the case of hyperthyroidism.

Thyroid cancer is the condition with malignant thyroid neoplasm. It can be treated with radioactive iodine or surgical resection of the thyroid gland, chemotherapy or radiotherapy.

Commonly the early symptom of the thyroid cancer is a nodule in the thyroid area of the neck. However, many adults have small nodules in the thyroids, but usually less than 5% of these nodules are malignant. In some cases an enlarged lymph node is the first indicator of illness. Later the following symptoms are added: pain in the anterior region of the neck and changes in voice because of the involvement of recurrent laryngeal nerve.

According to histopathological characteristics the following variations of thyroid cancers can be distinguished (distribution over various subtypes may show regional variation):

- Papillary thyroid cancer (75% to 85% of cases) – excellent prognosis, often in young females
- Follicular thyroid cancer (10% to 20% of cases)
- Medullary thyroid cancer (5% to 8% of cases) – cancer of the parafollicular cells, part of MEN-2.
- Anaplastic thyroid cancer (Less than 5%). It is not responsive to treatment and can cause pressure symptoms.
- Others
    - Lymphoma
    - Squamous cell carcinoma, sarcoma

The follicular and papillary types together can be termed as "differentiated thyroid cancer". These types possess more favorable prognosis than the medullary and undifferentiated types.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Patient F., without any complains. After survey, following prevention program, enlarged thyroid gland was diagnosed. Patient lives in the Carpathians.

Objective review: Thyroid enlarged in all parts. Configuration of the neck was not changed. Consistency of the gland was tender. There was not feeling of pain.

1. What is the most likely diagnosis?
2. How would you manage this patient?

Case 2.
Patient R., 45 years old, has an enlargement of the right lobe of the thyroid gland, in which a round soft and elastic growth can be palpated; the growth is neither fused with the surrounding tissues nor painful. Lymphatic nodes are not palpated. Clinical examinations and laboratory tests show no disturbance of the thyroid function. What diagnosis can be suspected?

1. What is your diagnosis?
2. What are you going to do in this case?

Case 3.
N., a 66-year-old widow, complained "I can't hear well." Although she could not say the date of the onset of worsened hearing, she had experienced difficulty hearing over the telephone for at least a year. When a daughter who had not seen her mother for 2 years visited her, she noted several things that were unusual for her mother. The house was unkempt (her mother had been a compulsive housekeeper) and quite warm (the thermostat was set at 78-80°F during the winter months). Her mother's mood seemed to be more jovial and her voice huskier than the daughter had remembered. The patient, however, denied any real changes and had no specific complaints other than bad hearing. She occasionally had numbness in both hands early in the morning that cleared by 10 AM and sometimes had some cramping in the calves at night. She denied any constipation (bowel movement every 2-3 days), shortness of breath, use of any medications, or chronic pain. She had been treated with I-131 for hyperthyroidism 15 years ago; no other significant medical or family history was elicited.

1. Make your diagnosis.
2. Administer therapy.

1.6 Thyrotoxicosis: disorders that it can cause, clinical appearance, diagnosis, therapies. Thyroid storm. Hypoparathyroidism and hyperparathyroidism: clinical pictures, diagnostics, therapies.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of common endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 4.

1. **Professional motivation**: The causes of the thyrotoxicosis are: Hashimoto's thyroiditis, jod-Basedow thyrotoxicosis, pituitary tumor, postpartum thyroiditis, amiodarone use, choriocarcinoma, de Quervain thyroiditis, struma ovarii, teratoma, ovary, testicular cancer, thyroid adenoma, thyroid carcinoma, etc. Hyperthyroidism is the term for overactive tissue of the thyroid gland, which causes an overproduction of the thyroid hormones (thyroxine or "T4" and/or triiodothyronine or "T3"). Hyperthyroidism is the cause of thyrotoxicosis, a clinical condition of increased thyroid hormones in the blood.
Hyperthyroidism and thyrotoxicosis are not synonymous. For example, thyrotoxicosis can be caused by ingestion of exogenous thyroid hormone or inflammation of the thyroid gland, resulting in the release of the stores of thyroid hormones.
Graves' disease is the most common cause of thyrotoxicosis, and usually manifests during early adolescence. It has a strong hereditary component, affects up to 2% of the female population, and is five-ten times more frequent in females than in males. Graves' disease is an autoimmune disorder where the thyroid is overactive, secreting an excessive amount of thyroid hormones (a serious metabolic imbalance known as hyperthyroidism and thyrotoxicosis). It is caused by thyroid autoantibodies (TSHR-Ab) that activate the TSH-receptor (TSHR), thus stimulating synthesis and secretion of the thyroid hormone, and thyroid growth (causing a diffusely enlarged goiter). The resulting condition of hyperthyroidism can cause a severe combination of neuropsychological and physical signs and symptoms. Graves' disease is also the most common cause of serious hyperthyroidism, which is accompanied by more clinical manifestations and symptoms and laboratory abnormalities in comparison with milder forms of hyperthyroidism. Approximately 25-30% of people with

Graves' disease also suffer from Graves' ophthalmopathy (a protrusion of one or both eyes), caused by inflammation of the eye muscles by attacking autoantibodies.
Hyperparathyroidism is overactivity of the parathyroid glands causing excessive production of parathyroid hormone (PTH). The parathyroid hormone regulates levels of calcium and phosphate and helps maintain proper levels of these hormones. Excessive PTH secretion may be caused by the problems in the glands themselves; in this case it is called primary hyperparathryroidism which results in hypercalcemia (increased calcium levels). It may also occur in response to low levels of calcium, for example, vitamin D deficiency or chronic kidney disease; this is referred to as secondary hyperparathyroidism. In all cases, the elevated PTH levels are harmful to bones, and treatment is often required. Recent studies suggest that vitamin D deficiency plays a role in hyperparathyroidism development. Lithium is also associated with the increased incidence of hyperparathyroidism.
Hypoparathyroidism is decreased function of the parathyroid glands, evidenced by reduced levels of parathyroid hormone (PTH). PTH is necessary for maintaining proper calcium levels in the blood, thus low PTH levels can lead to hypocalcaemia (low calcium levels), which can have serious consequences.
Hypocalcemic crisis manifests itself with the classical symptoms of tetany and extrapyramidal symptoms, also a disordering of consciousness leading even to coma. It develops when the concentration of ionized serum calcium decreases rapidly, it very rarely occurs in chronic hypocalcemia. In terms of its etiology, different forms of parathyroid deficiency, and nonparathyrogenic diseases associated with hypocalcemia may be involved. Since in the latter the concentration of albumin is also diminished, and ionized calcium only slightly, hypocalcemic crisis in these conditions is rare. The most common clinical form is normocalcemic tetany that occurs within the framework of the hyperventilation syndrome. Here, the ionized calcium fraction is temporarily reduced by marked alkalosis. Today, laboratory findings render establishment of the diagnosis simple. Acute therapy takes the form of parenteral calcium administration, and for long-term treatment, vitamin D metabolites, possibly in combination with oral calcium replacement is employed.
Hypercalcemic crisis is a condition in which the decompensation of hypercalcemia, could have existed for longer periods or could be acute at the first appearance of this electrolyte disturbance. Compensated hypercalcemia is caused by malignancies in 70% of cases, by primary hyperparathyroidism (pHPT) in 20% of cases, and by other (rarer) conditions in 10%; and most cases of hypercalcemic crisis are caused by pHPT.

2. Study aim of this lesson.

To acquaint students with history and incidence of Graves' disease, hypoparathyroidism and hyperparathyroidism (α=1)

In the study process students should know (α=2):

- the main etiological factors, pathogenesis, clinical appearance, laboratory findings, and treatment of Graves' disease,
- etiology pathogenesis, clinical picture, laboratory evaluation, treatment of hyperparathyroidism,
- etiology and pathogenesis, clinical picture, laboratory evaluation, treatment of hypoparathyroidism.

In the study process student should be able to (α=3):

- carry out the examination of the thyroid gland (technique for physical examination of the thyroid gland),
- note the gland texture, mobility, tenderness and the presence of nodules (in addition to palpating for size),
- evaluate thyroid gland function, and parathyroid gland function,
- differentiate thyroid disorders,
- order adequate treatment in the case of Graves' disease, thyroid storm,
- perform differential diagnosis of parathyroid gland dysfunction,
- define treatment approach regarding hypoparathyroidism and hyperparathyroidism.

3. Educational aim of this lesson

Is to focus attention on differential diagnosis of parathyroid gland dysfunction, treatment of Graves' disease, prevention of thyroid storm.

4. Interdisciplinary integration (see Table 18).

Table 18

Interdisciplinary integration

Discipline	To know	How to do
I. Previous Normal anatomy and physiology, histology, pathological anatomy, and physiology, pharmacology, radiology	Thyroid gland, parathyroid glands (location, morphology, regulation and hormone synthesis, embryogenesis, calcium and bone metabolism), thyroid sonography, computed tomography and magnetic resonance imaging, thionamides, glucocorticoids, calcium salts (calcium supplements), vitamin D.	To estimate physiological function of the thyroid gland. To prescribe medications.
Discipline	**To know**	**How to do**
II. Future Internal medicine Pediatrics Surgery	Main clinical signs of thyroid disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment.	To make clinical observation, to recommend proper diagnostic assays, consultation of associative

Obstetrics & Gynecology Neurology, Traumatology **III. Interdisciplinary integration**	Main clinical signs of parathyroid gland dysfunction, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment. Contemporary methods of diagnostics and treatment	specialists for verification of diagnosis, to prescribe medications To prescribe adequate treatment. Differential diagnosis

5. Contents of the lesson.

- Etiology and pathogenesis of Graves' disease.
- Clinical appearance of Graves' disease, principles of treatment, prognosis.
- Thyroid storm (clinical picture, treatment, prevention).
- Differential diagnosis of hypercalcemia.
- Clinical presentation of hyperparathyroidism, laboratory evaluation, therapy.
- Hypoparathyroidism and other causes of hypocalcemia.
- Clinical presentation of hypoparathyroidism, laboratory evaluation, therapy.
- Hypercalcemic crisis (etiology, clinical presentation, treatment).

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Choose agent, which inhibits synthesis of thyroid hormones
A) Thiamazole
B) Potassium perchlorate
C) Potassium iodide
D) Iopanoic acid
E) Dexamethasone

#2
Choose agent, which decreases thyroid hormone release
A) Thiamazole

B) Potassium perchlorate
C) Potassium iodide
D) Propylthiouracil
E) Dexamethasone

#3
Choose agent, which diminishes sympathetic reactions in the treatment of Graves' disease
A) Propylthiouracil
B) Potassium perchlorate
C) Thiamazole
D) Propranolol
E) Potassium iodide

#4
Average duration of symptomatic treatment of thyrotoxicosis is
A) 2-4 weeks
B) 1-2 weeks
C) 1 week
D) 10-12 days
E) 1-2 months

7.2. Recourses for the main stage of the lesson.

Etiologies of thyrotoxicosis are listed in Table 19.

Table 19

Etiologies of thyrotoxicosis

Thyrotoxicosis caused by hyperthyroidism	
Entity	Pathogenesis
Graves' disease	TSH receptor-stimulating antibodies
Toxic adenoma	Somatic gain-of-function mutations in the TSH receptor or αGs
Toxic multinodular goiter	αSomatic gain-of-function mutations in the TSH receptor or Gs
Thyroid carcinoma in hyperthyroidism	Somatic gain-of-function mutations in the TSH receptor
Familial non-autoimmune hyperthyroidism	Germline gain-of-function mutations in the TSH receptor
Thyrotoxicosis caused by hyperthyroidism	
Sporadic non-autoimmune hyperthyroidism	Germline gain-of-function mutations in the TSH receptor
TSH-secreting pituitary adenoma	Increased stimulation by inappropriate TSH secretion

hCG-induced gestational hyperthyroidism	Increased stimulation of the TSH receptor by hCG
Familial hypersensitivity to hCG	TSH receptor mutation with increased sensitivity to hCG
Trophoblast tumors (hydatiform mole, choriocarcinoma)	Increased stimulation of the TSH receptor by hCG
Struma ovarii	Autonomous function of thyroid tissue in ovarian teratoma
Iodine-induced hyperthyroidism	Increased synthesis of thyroid hormone in autonomously functioning thyroid tissue after exposure to excessive amounts of iodide
Thyrotoxicosis without hyperthyroidism	
Subacute thyroiditis	Release of stored thyroid hormone
Silent thyroiditis	Release of stored thyroid hormone
Drug-induced thyroiditis	Release of stored thyroid hormone
Exogenous thyroid hormone (iatrogenic, thyrotoxicosis factitia)	Thyroid hormone

Signs and symptoms of thyrotoxicosis are listed in Table 20.

Table 20

Signs and symptoms of thyrotoxicosis

Organ system	Symptoms	Signs
Neuropsychiatric/Neuromuscular	Emotional lability	Muscle wasting
	Anxiety	Hyperreflexia
	Confusion	Fine tremor
	Coma	Periodic paralysis
Gastrointestinal	Hyperdefecation	
	Diarrhea	
Reproductive	Oligomenorrhea	Gynecomastia
	Decreased libido	Spider angiomas
Thyroid gland	Neck fullness	Diffuse enlargement
	Tenderness	Bruit
Cardiorespiratory	Palpitations	Atrial fibrillation
	Dyspnea	Sinus tachycardia
	Chest pain	Hyperdynamic precordium
		Congestive heart failure
Dermatologic	Hair loss	Pretibial myxedema
		Warm, moist skin
		Palmar erythema
Ophthalmologic	Diplopia	Exophthalmos
	Eye irritation	Ophthalmoplegia
		Conjunctival injection

Iodine-containing compounds that may be associated with iodine-induced thyrotoxicosis are given in Table 21.

Table 21

Iodine-containing compounds potentially associated with iodine-induced thyrotoxicosis

Radiological contrast agents
Diatrizoate
Ipanoic acid
Ipodate
Iothalamate
Metrizamide
Diatrozide
Topical iodine preparations
Diiodohydroxyquinolone
Iodine tincture
Povidone iodine
Iodochlorohydroxyquinolone
Iodoform gauze
Solutions
Saturated potassium iodide (SSKI)
Lugol solution
Iodinated glycerol
Echothiopate iodide
Hydriodic acid syrup
Calcium iodide
Drugs
Amiodarone
Expectorants
Vitamins containing iodine
Iodochlorohydroxyquinolone
Diiodohydroxyquinolone
Potassium iodide
Benziodarone
Isopropamide iodide
Food components
Kelp, Kombu and other algae
Food colors: Erythrosine
Iodine containing food: Hamburger thyroiditis

Amiodarone-induced hyper- and hypothyroidism is quite important in clinical practice. Amiodarone-induced thyrotoxicosis has higher occurrence in iodine-deficient areas, but also occurs in patients with adequate nutritional consumption of iodine. Amiodarone-induced hypothyroidism is usually found in regions with lack of iodine in diet.

Incidences of amiodarone-induced thyrotoxicosis range from 0.003% to 11.5%. Study showed that 30 patients from 1448, to whom amiodarone has been administered, developed amiodarone-induced thyrotoxicosis. There are two forms of smiodarone-induced thyrotoxicosis. Amiodarone-induced thyrotoxicosis Type I is caused by increased hormone synthesis due to consumption of large amounts of iodine, and amiodarone-induced thyrotoxicosis Type II is caused by cytotoxic destruction of thyrocytes. Hypothyroidism is usually diagnosed in patients with preexisting thyroid autoimmune disease and in the regions of normal iodine consumption. Men are more prone to have amiodarone-induced thyrotoxicosis than women.

The indicators of thyrotoxicosis may not be seen in all patients with amiodarone-induced thyrotoxicosis. They may be mistaken due to the underlying cardiac condition. Also some patients have a nodular goiter.

The total or free levels of T4 are increased in euthyroid, hypothyroid and hyperthyroid patients using amiodarone because of its suppression of 5'-monodeiodination. In hyperthyroid patients, TSH is decreased and T3 is elevated. It may not be easy to differentiate between type I and II amiodarone-induced thyrotoxicosis on clinical grounds. The radioiodine uptake is usually low to normal in amiodarone-induced thyrotoxicosis Type I, and low to decreased in amiodarone-induced thyrotoxicosis Type II. Serum interleukin 6 levels are normal to high in amiodarone-induced thyrotoxicosis Type I and extremely high in amiodarone-induced thyrotoxicosis Type II, but there is a marked overlap and the test is not sufficiently sensitive. On Doppler ultrasound, amiodarone-induced thyrotoxicosis Type I is associated with normal to increased vascularity with patchy distribution, while Type II shows absent vascularity.

The process of amiodarone-induced thyrotoxicosis treatment is really complicated (see Table 23). If possible, amiodarone should be eliminated. Patients diagnosed with type 1 amiodarone-induced thyrotoxicosis should be administered methimazole (starting with 40 – 60 mg/day, followed by gradual dose adjustment), but the response to thionamides is moderate. For some patients, treatment with potassium perchlorate (1 g/day for 4 to 6 weeks) can be used. Potassium perchlorate may cause aplastic anemia and its use should be limited to patients who cannot be treated with methimazole, or who have allergy to thionamides. Prednisone (0.5 – 0.7 mg/kg body weight per day) can be used for several months for patients with amiodarone-induced thyrotoxicosis Type II. Since the distinction between amiodarone-induced thyrotoxicosis Type I and II is vague, and some patients have mixed forms of amiodarone-induced thyrotoxicosis, these types of treatment are sometimes combined. Patients with a history of amiodarone-induced thyrotoxicosis type II tend to develop hypothyroidism if they consume large amounts of iodide.

An algorithm for the treatment of patients with amiodarone-induced thyrotoxicosis is given below (Fig.2).

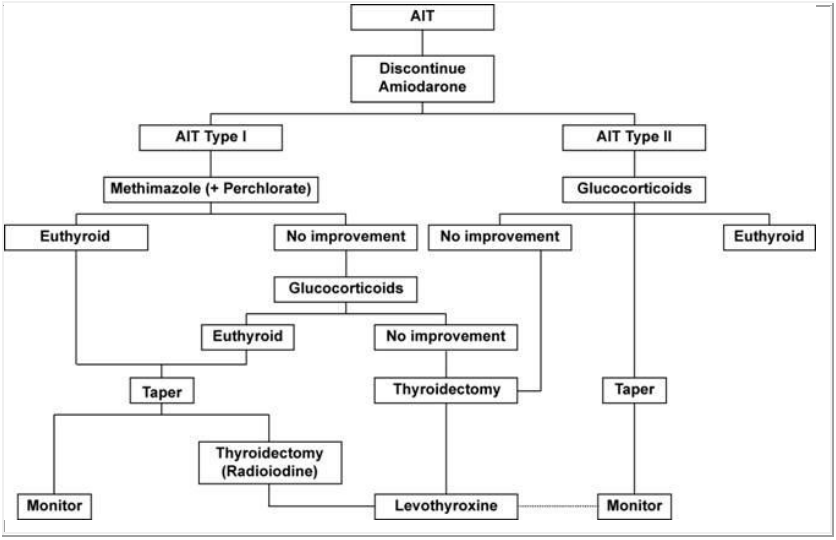


Figure 2. Management of patients with amiodarone-induced thyrotoxicosis (AIT)

Symptoms of the hypercalcemic syndrome, organ manifestations of pHPT, and typical indications for other causes of hypercalcemia are listed in Table 22.

Table 22

Symptoms of the hypercalcemic syndrome, organ manifestations of pHPT, and typical indications for other causes of hypercalcemia

Organ	Components of Hypercalcemic Syndrome				
	Disturbance (Reversible)	Resulting Symptom or Complication	Destabilization to Hypercalcemic Crisis	Organ Manifestation of pHPT	Pathognomonic Findings for Other Hypercalcemic Diseases
Kidney	Hyposthenuria, hypercalciuria, sodium and potassi m loss → hypokalemia	Polyuria, polydipsia, exsiccosis, muscle weakness, arrhythmia	Oliguria, anuria, azotemia	Nephrolithiasis (recurrent), nephrocalcinosis	FHH: hypocalciuria
Organ	Components of Hypercalcemic Syndrome				
	Disturbance (Reversible)	Resulting Symptom or Complication	Destabilization to Hypercalcemic Crisis	Organ Manifestation of pHPT	Pathognomonic Findings for Other Hypercalcemic Diseases

Intestine	Increased gastric acid secretion, pancreatic enzyme secretion, delaye intestinal transport	Loss of appetite, nausea, vomiting, weight loss, constipation	Increase	Peptic ulcer (recurrent), pancreatitis (calcifying), cholelithiasis	Hyperthyroidism: weight loss
Central nervous system	Endocrine psychologic syndrome, EEG changes	Weakness, tiredness, loss of initiative, depression, dizziness, loss of appetite	Somnolence, coma		
Musculature	Increases in level of neuromuscular excitability	Muscle weakness, weakened reflexes	Increase		Hypercortisolism Cushing myopathy
Cardiovascular system	ECG: shortened QT time	Arrhythmia (hypertension)	Cardiac arrest (avoid digitalis)	Rare calcinosis	Hyperthyroidism tachycardia, hypertension (large amplitude)
Skeleton				Osteoporosis, ostitis fibrosa cystica generalisata (von Recklinghausen)	Malignancies: bone metastases
Ankles				Chondrocalcinosis (pseudogout)	
[a]pHPT, primary hyperparathyroidism; FHH, familial hypocalciuric hypercalcemia; EKG, electrocardiogram; EEG, electroencephalography.					

Symptomatic treatment of hypercalcemia is presented in Table 23.

Table 23

Symptomatic treatment of hypercalcemia

Type	Measure/ Substance	Dosage	Specific Indication	Mode of Action	Side Effects, Complications
Fast-acting					
diuretic	Drinking of fluids low in calcium	2 to 3 liters/d	Universal	Increase in calciuria	None
	IV infusion of saline	4 to 6 (10) liters/d	Universal	Increase in calciuria (via natriuresis)	Volume expansion, hypokalemia, hypomagnesemia

	Furosemide	20 to 40 to 500 mg/d	Universal in cases of fluid retention	Increase in diuresis and calciuria	Hypomalemia, hypomagnesemia
		100 mg/hr → 24 h	Same	Direct stimula-tion of calciuria	Same
antiresorptive	Bisphosphonates clodronate	300 mg iv in 6 to 8 h for 2 to 6 days	Universal (in preference in HHM)	Inhibition of osteolysis	In cases of too fast administration, renal insufficiency
		400 to 3200 mg orally for days or weeks	Same	Same	Rarely gastrointestinal complaints
	pamidronate	15 to 90 mg iv in 4 to 6 h	Same	Same	Same, occasionally feverish reaction
	ibandronate	2 to 6 mg iv in 2 h	Same	Same	None
	Calcitonin	200 to 500 IU/d	Universal (adjuvant drug)	Inhibition of osteolysis	Nausea, vomiting, escape phenomenon
	Mithramycin, mostly replaced by bisphosphonates	25 µg/kg iv daily for 3 to 4 d	In preference in HHM, parathyroid carcinoma	Inhibition of osteolysis	Thrombopenia, leukopenia, liver and kidney damage
extractive	Hemodialysis	Ca^{2+} -free dialysate	Hypercalcemic crisis and renal insufficiency	Dialysis of Ca^{2+} from the circulation	Dialysis-related
Slow-acting					
anti-absorptive	Diet low in Ca^{2+} and vitamin D	<100 mg Ca^{2+}/d	Universal	Decrease in Ca^{2+} supply and absorption	None
	Prednisone	40 to 100 mg/d	Vitamin D intoxication, sarcoidosis (rarely HHM)	Decrease in Ca^{2+} absorption, increase in calciuria	Iatrogenic Cushing's syndrome

[a]HHM, humoral hypercalcemia of malignancy; iv, intravenous. Digitalis and hydrochlorothiazides are contraindicated during hypercalcemia.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Patient M., 33 years old, after a stressful incident, presented with weakness, a 10 kg weight loss despite good appetite, feeling of inner tension, irritability, emotional lability, sweating, tachycardia, tremor, menstrual irregularity, diarrhea. Objective review: pulse 110 per min. BP 130/65, cardiac tones normal, skin is moist, warm, thyroid gland enlarged, with a firm and homogenous mass.

1. What is this patient's suspected diagnosis?
2. Choose the way of treatment of this patient.

Case 2.

Patient C., 56 y/o, complains of weakness, muscle ache, loss of appetite, nausea, vomiting, aching bones, worsening of memory and cramps. Anamnesis contains a record of the ulcerous gastric disease, frequent pathological bone fractures. Objectively: the consciousness is clouded, the skin is dry of ashy gray color, present deformity of the vertebrae bodies, "goose-stepping" gait, X-ray shows systemic osteoporosis. Heart sounds are dull, rhythmical, arterial pressure – 160/100, pulse 56/minute. The level of calcium in the blood – 3.9mmol/l; hypophosphatemia, hyperphophaturia; glycemia – 4.8mmol/l.

1. What is your diagnosis?
2. What are you going to do in this case?

Case 3.

D., a 26-year-old school teacher, presented complaining of itchy skin and of being excessively nervous and jittery. Her symptoms started about two months ago. She was "short-tempered", easily angered, and tremulous. She lost 3 kg despite a voracious appetite, perspired much more than normal, and preferred a cool room. She didn't experience diarrhea, polyuria, cough, headache, medication use, or change in menses. She could not seem to sit still during the examination. Her pulse was 98/min; BP 110/60. Her hands were red, warm, and moist, presented onycholysis. HEENT: No exophthalmos or stare was observed. The thyroid was easily visible. On palpation the total thyroid width was 7 cm, with each lobe measuring 5 cm in height. The gland was moderately firm and symmetrically enlarged without any palpable nodules. A venous hum was heard at the base of the right lobe of the thyroid. The heart, lung, and abdominal examinations were normal. A fine tremor of outstretched fingers, brisk deep tendon reflexes, and lid lag were noted.

1. What is the diagnosis?
2. What therapies are available to manage this problem?

1.7 Primary adrenal insufficiency (Addison disease): etiology, pathogenesis, clinical presentation, diagnosis, therapy. Acute adrenal insufficiency. Itsenko-Cushing syndrome. Primary aldosteronism. Pheochromocytoma.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of the endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 5.

1. **Professional motivation**: Addison's disease (also called hypocortisolism, chronic adrenal insufficiency or chronic primary adrenocortical insufficiency, or hypoadrenalism) is a rare chronic endocrine disorder in which the adrenal glands do not produce sufficient amount of steroid hormones (glucocorticoids and often mineralocorticoids). It is characterised by a number of relatively nonspecific symptoms, in particular, weakness and abdominal pain, but under certain conditions they may progress to Addisonian crisis, a severe illness characterized by very low blood pressure and coma. The condition is caused by the problems in the adrenal gland itself, a condition referred to as "primary adrenal insufficiency" and can be due to the damage by the body's own immune system, certain infections or other rarer causes. Addison's disease should also be distinguished from secondary and tertiary adrenal insufficiency which are caused by deficiency of ACTH (produced by the pituitary gland) and CRH (produced by the hypothalamus) respectively. However, Addisonian crisis can occur in all forms of adrenal insufficiency.
Cushing's syndrome is caused by excess cortisol of any etiology. One of the causes of Cushing's syndrome is a cortisol-secreting adenoma in the cortex of the adrenal gland. This adenoma causes increased cortisol levels in the blood, and negative feedback on the pituitary gland from the high levels of cortisol causes ACTH levels to be very low. Adults may experience symptoms of extreme weight gain, excessive hair growth in women, high blood pressure, diabetes, and skin problems. Untreated Cushing's syndrome can result in heart disease and increased mortality.
Primary aldosteronism, also known as primary hyperaldosteronism, is the overproduction of the mineralocorticoid hormone aldosterone by the adrenal glands, not a result of excessive secretion of renin. Aldosterone causes retention of sodium and water and also potassium excretion in the kidneys, causing arterial hypertension (high blood pressure). An increase in the production of mineralocorticoid by the

adrenal gland is obvious. It is one of the most common causes of secondary hypertension after renal disease.

Primary hyperaldosteronism has many causes, among them are adrenal hyperplasia and adrenalcarcinoma. When it occurs as a result of a solitary aldosterone-secreting adrenal adenoma (a type of benign tumor), it is known as Conn's syndrome. In the absence of appropriate treatment, individuals with hyperaldosteronism often suffer from difficulty with controlling high blood pressure, which may be associated with increased incidence of heart disease, stroke, and kidney failure.

A pheochromocytoma is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells), or extra-adrenal chromaffin tissue that failed to involute after birth and secretes excess amounts of catecholamines, usually noradrenaline (norepinephrine), and rarer adrenaline (epinephrine). Extra-adrenal paragangliomas (often referred to as extra-adrenal pheochromocytomas) are closely related, though less common, tumors that originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of their origin.

2. Study aim of this lesson.

To acquaint students with the following problems: adrenal insufficiency, hypercortisolism, primary aldosteronism and pheochromocytoma and their relation to other concurrent disorders (hypertension, diabetes) (α=1)

In the study process students should know (α=2):

- the main etiological factors, pathogenesis, clinical appearance, laboratory findings and treatment of Addison's disease,
- etiology, pathogenesis, clinical presentation, laboratory evaluation, treatment of Addisonian crisis,
- etiology and pathogenesis, clinical picture, laboratory measurements, treatment of primary aldosteronism.
- causative factors, pathogenesis, clinical appearance, laboratory findings, and treatment of pheochromocytoma

In the study process student should be able to (α=3):

- evaluate adrenal function following hormone analyses,
- differentiate adrenal disorders,
- order adequate treatment in the case of Addison's disease, Addisonian crisis,
- perform differential diagnosis of adrenal dysfunction,
- define treatment approach regarding primary aldosteronism and pheochromocytoma.

3. Educational aim of this lesson

Is to focus attention on differential diagnosis of adrenal dysfunction, early diagnosis, and treatment of Addison's syndrome and Addisonian crisis as well as primary aldosteronism and pheochromocytoma.

4. Interdisciplinary integration (see Table 24).

Table 24

Interdisciplinary integration

Discipline	To know	How to do
I. Previous		
Normal anatomy and physiology, histology, pathological anatomy, and physiology, pharmacology.	Adrenal glands, (location, morphology, regulation and hormone synthesis), adrenal sonography, computed tomography and magnetic resonance imaging. Main clinical signs of adrenal disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment. Contemporary methods of diagnosis and treatment	To estimate functional condition of the adrenal glands. To prescribe medications.
II. Future		
Internal medicine, Surgery, particular specialities.		To make clinical observation, to recommend proper diagnostic assays, consultation of associative specialists for verification of diagnosis, to prescribe medication To prescribe adequate treatment.
III. Interdisciplinary integration		Differential diagnosis

5. Contents of the lesson.

- Addison's disease: etiology, pathogenesis, clinical picture, laboratory investigations, diagnosis and differential diagnosis, replacement hormone therapy.
- Acute adrenal insufficiency: development, symptoms and signs, laboratory findings, diagnosis, treatment.
- Cushing's syndrome: etiology, pathogenesis, clinical presentations, diagnosis, therapy.
- Primary aldosteronism: etiology, pathogenesis, clinical features, diagnosis and differential diagnosis, treatment

- Pheochromocytoma: clinical manifestations, diagnosis, localization, treatment

6. Plan and organization structure of this lesson.
(See preface)

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Choose factor, which can cause Addison's disease.
A) Hormone acting tumour of adrenals
B) Tuberculosis
C) Pneumonia
D) Autoimmune thyroiditis
E) Diabetes mellitus

#2
Main clinical signs of acute adrenal failure are:
A) Acetone breath, aggressiveness
B) Loud breathing, bradycardia
C) Vomiting, diarrhoea
D) Polydipsia, polyuria
E) Neck pain, hypertension

#3
Which statement is correct according to low-dose Liddle's test?
A) In the diagnostic approach to determine hypercortisolism
B) To differentiate Cushing's syndrome from Cushing's disease
C) Total 4 mg of dexamethasone per day
D) Total 6 mg of dexamethasone per day
E) 0.5 mg of dexamethasone once a day

#4
Prominent effect of the cardiovascular system in patient with hypercortisolism is:
A) Sinus bradycardia
B) Bacterial endocarditis
C) Bundle-branch block
D) Hypertension
E) Respiratory arrhythmia

7.2. Recourses for the main stage of the lesson.

Addison's disease.

Addison's disease is named after Dr. Thomas Addison, the British physician who first described this condition in 1849. The term "Addisonian" refers to signs of the condition, as well as patients suffering from Addison's disease.

In order to diagnose Addison's disease and other forms of hypoadrenalism blood tests and medical imaging are used. Treatment includes replacing the absent hormones (oral hydrocortisone and fludrocortisone). Lifelong, permanent treatment with steroid replacement therapy is required, with regular check-up and monitoring for other problems with health.

Since the symptoms of Addison's disease are not vivid, it may take time to recognize it. The most common symptoms are: fatigue, lightheadedness upon standing or while upright, fever, muscle weakness, weight loss, difficulty in standing up, anxiety, nausea, vomiting, diarrhea, sweating, headache, changes in mood and personality, and joint and muscle aches. Some patients may have cravings for salt or salty food because of the sodium loss with the urine. Increased tanning may be observed, particularly in the areas exposed to sun, as well as darkening of the palmar creases, friction sites, recent scars, the vermilion border of the lips, and skin in the genital region. These symptoms are absent in secondary and tertiary hypoadrenalism.

Medical conditions such as type I diabetes, autoimmune thyroid disease (Hashimoto's thyroiditis and goiter) and vitiligo often occur in combination with Addison's (often in the setting of Autoimmune polyendocrine syndrome). Thus, the patients with Addison's may also have symptoms and manifestations of any of the mentioned conditions. The occurrence of Addison's disease in a person with Hashimoto's thyroiditis is called Schmidt syndrome.

Acute adrenal insufficiency.

Adrenal crisis is a potentially fatal condition usually with an acute deficiency of the glucocorticoid cortisol and, sometimes, the mineralocorticoid aldosterone. Crisis takes place when the physiological need in these hormones exceeds the ability of adrenal glands to secrete them, in particular, in patients with chronic adrenal insufficiency who suffer intercurrent illness or stress:

- Major or minor infections
- Injury
- Burns
- Surgery
- Pregnancy
- General anaesthesia
- Hypermetabolic conditions

The most common reason is sudden steroid withdrawal; secondary adrenocortical deficiency occurs when steroids administered as therapy suppress the hypothalamic-pituitary-adrenal axis. Bilateral haemorrhage in the adrenal gland may lead to

adrenal crisis because of severe physiological stress factors such as myocardial infarction, septic shock or complicated pregnancy, concomitant coagulopathy or thromboembolic disorders. To other causes belong autoimmune Addison's disease, adrenoleukodystrophy, tuberculosis, HIV, congenital adrenal hypoplasia, etc.

Risk factors:

- Long-term steroids:
  - A few cases caused by inhaling high-dose of fluticasone occurred and it may cause suppression at lower doses also.
  - A case has been recorded following intra-articular steroid injection.
- There have also been cases following ketoconazole, phenytoin and rifampicin.

Presentation

- The patients suffer from strong hypotension, especially postural; they may also be very emaciated and confused.
- Circulatory collapse may be severe with feeble rapid pulse and soft heart sounds.
- Pyrexia is common and may be the result of underlying infection.
- Anorexia, vomiting, nausea and severe abdominal pain are common. The symptoms may be severe and present as obvious acute abdomen.
- The patient may have high motor activity progressing to delirium or seizures.

Investigations

- Sodium is usually slightly low, but may be normal.
- Potassium is usually slightly high or normal – rarely, markedly increased (risk of arrhythmias).
- Hypoglycaemia, possibly severe, is characteristic.
- Concentrations of serum cortisol are normally the highest in the early morning (04:00 hours – 08:00 hours) and increase further in case of stress. Concentrations of serum cortisol at this time less than 80 nmol/L are high indicators of adrenal insufficiency.
- A short ACTH stimulation test should be taken by all patients who are suspected of having adrenal insufficiency:
  - Determine the baseline serum cortisol, and then administer ACTH 250 mcg intravenously.
  - Serum cortisol measurements are done in 30 and 60 minutes after ACTH administration.
  - An increase in serum cortisol concentration in 30 or 60 minutes to 500-550 nmol/L or more is considered to be a normal reaction.

- ECG may show continuous QT interval:
    - This may cause ventricular arrhythmias.
    - Deep negative T waves have been described in acute adrenal crisis.

Treatment

General principles

- Therapy should begin immediately based on clinical manifestations and should not be postponed for confirmation of adrenal function.
- The only definitive treatment is the use of glucocorticoids in supraphysiological or stress doses.
- Dexamethasone does not interfere with serum cortisol assay and thus may be the starting medication of choice.
- Since dexamethasone has little mineralocorticoid activity, fluid and electrolyte replacement is required.

Resuscitation

- ABCDs which may include:
    - Oxygen.
    - IV Normal saline fluid boluses (500-1000 mL for adult, 10-20 mL/kg for a child).
    - IV dextrose (25-50 mL 50% dextrose for an adult, 2-5 mL/kg 10% dextrose for a child) as needed.
- Constant intravenous replacement of estimated dehydration:
    - Usually 5%+ over 8+ hours.
    - Using 5% dextrose in normal saline.
    - Taking into consideration age, volume, heart and kidneys functions.
    - Not likely to require added potassium initially.
- 200 mg hydrocortisone - 100 mg/m^2 or approximately 4 mg/kg for a child - IV stat:
    - Then 100 mg hydrocortisone (2 mg/kg for a child) IV every 6 hours during the first 24 hours.
    - Later the dose of hydrocortisone can usually be halved again.
    - With high doses of glucocorticoid, mineralocorticoids are not needed.
    - When dosage is lowered, add fludrocortisone 0.05-0.2 mg/day, implying normotension, normokalaemia and a plasma renin activity in the upper normal range.
- If there is still hypotension, additionally use corticosteroids and also consider vasopressors, e.g. dopamine.
    - Attention should be paid to adrenal haemorrhage, especially if anticoagulants are administered.

    - Reversal of coagulopathy should be attempted with fresh frozen plasma.
- Underlying precipitating disorder, e.g. infection, is treated with antibiotics.
- If testing for adrenal insufficiency and treatment are carried out at the same time, hydrocortisone should be replaced with dexamethasone added to the infusion together with corticotropin.
- Urine and blood analysis of cortisol and urinary – OH-CS levels – should be provided.

Prevention

- Early dose adjustments (e.g. increasing the usual maintenance dose twice) are essential to cover the growing demand in glucocorticoid during stress.
- Constant thorough education of patients and their partners is the best measure to avoid this serious life-threatening condition.
- Contact with patients with chickenpox or measles should be avoided. If there was one, medical consultation is required immediately.
- Patients do not need cover for general dentistry. If patients require general anaesthesia for procedures they may need additional steroids depending on the dose and duration of steroid treatment.

Associations

The underlying associated endocrinopathies, which should be excluded:

- Hypothyroidism may mask the Addison's disease and the thyroxine replacement may be present in an acute adrenal crisis.
- In course of steroid replacement therapy the "hypothyroidism" may resolve.

Lethal outcome may be the result of circulatory collapse and arrhythmias with contributing hypoglycaemia. Prognosis is the same as for patients without adrenal insufficiency if the precipitating condition is diagnosed and treated in a proper way.

Cushing syndrome

The symptoms are rapid weight gain, especially on the face and the trunk with sparing of the extremities (central obesity). Also fat pads near the collar bone and on the back of the neck (buffalo hump) and a round face often called a "moon face" are common. Among other symptoms may be hyperhidrosis (profuse sweating), telangiectasia (dilation of capillaries), thinning of the skin (leading to dryness and easy bruising, especially of the hands) and mucous membranes, red or purple striae (the overweight in Cushing's syndrome stretches the skin, which is thin and weakened, causing bleeding) on the trunk, buttocks, arms, legs or breasts, proximal muscle weakness (hips, shoulders), and hirsutism (facial male hair growth), baldness

and/or extremely dry and brittle hair. In rare cases, Cushing's can cause hypercalcemia, leading to skin necrosis. The excess cortisol may also affect other endocrine systems and cause, for instance, insomnia, inhibited aromatase, impotence, reduced libido, amenorrhoea/oligomenorrhea and infertility due to increased androgens. Patients often have various psychological disturbances, ranging from euphoria to psychosis, as well as depression and anxiety.

Other evident and distressing skin changes that may occur in Cushing's syndrome include facial acne, tendency to superficial dermatophyte and malassezia infections, and also the characteristic purplish, atrophic striae on the abdomen.

The symptoms also include polyuria (and accompanying polydipsia), persistent hypertension (resulting from cortisol's enhancement of epinephrine's vasoconstrictive effect) and insulin resistance (especially common in ectopic ACTH production), which leads to hyperglycemia and insulin resistance and can cause diabetes mellitus. Insulin resistance is accompanied by skin changes such as acanthosis nigricans in the axilla and around the neck, also skin tags in the axilla. Hyperpigmentation may also be the result of Cushing's syndrome caused by excessive ACTH. This happens because of Melanocyte-Stimulating Hormone production as a byproduct of ACTH synthesis from Pro-opiomelanocortin (POMC). Cortisol may also possess mineral corticoid activity in high concentrations, aggravating the hypertension and leading to hypokalemia (common in ectopic ACTH secretion). Moreover, opportunistic infections, gastrointestinal disturbances, and slow wound healing (cortisol is a stress hormone, which depresses the immune and inflammatory responses).Osteoporosis also is the result of Cushing's syndrome due to depression of osteoblasts activity. In addition, Cushing's syndrome can cause sore and aching joints, particularly in shoulders, the hip and lower back.

When it comes to diagnosing Cushing's syndrome, either a dexamethasone suppression test (dexamethasone administration and frequent detection of cortisol and ACTH levels), or a 24-hour urinary count for cortisol are equally effective. Dexamethasone is a glucocorticoid and simulates the effects of cortisol, including negative feedback on the pituitary gland. High coristol in test blood samples during the use of dexamethasone indicates Cushing's syndrome because there is an ectopic source of cortisol or ACTH (e.g. adrenal adenoma) that is not inhibited by the dexamethasone. A new method recently cleared by the US FDA, is sampling cortisol in saliva for 24 hours, which may be equally efficient, since late night levels of salivary cortisol are high in patients with Cushing's syndrome. Other levels of the pituitary hormone may need to be ascertained. Conducting a physical examination to determine visual field defect may be necessary if the pituitary disturbance is suspected, which may squeeze the optic chiasm leading to typical bitemporal hemianopia.

If any of these tests are positive, CT scanning of the adrenal glands and MRI of the pituitary gland should be carried out to detect the presence of adrenal or pituitary

adenomas or incidentalomas (incidental discovery of harmless lesions). Scintigraphy of the adrenal glands with iodocholesterol scan is sometimes required. In rare cases, determining the ACTH levels in veins throughout the body by means of venous catheterization, working towards the pituitary (petrosal sinus sampling) is necessary.

Primary aldosteronism

Aldosterone enhances exchange of sodium for potassium in the kidney so that increased aldosteronism causes hypernatremia and hypokalemia. If the level of potassium is considerably reduced by aldosterone, a sodium/hydrogen pump in the nephron becomes more active causing increased excretion of hydrogen ions and further hypernatremia exacerbation. The hydrogen ions that are exchanged for sodium are produced by carbonic anhydrase in epithelium of the renal tubule causing increased production of bicarbonate. The increased bicarbonate and the excreted hydrogen combine to generate a metabolic alkalosis. The high pH of the blood prevents calcium from the tissues and causes symptoms of hypocalcemia (low levels of calcium).

Expansion of plasma volume and high blood pressure are caused by the retention of sodium. The increased blood pressure leads to increased glomerular filtration rate and causes a decrease in renin release from the granular cells of the juxtaglomerular apparatus in the kidney. If there is a primary hyperaldosteronism, the decreased renin (and subsequent decreased angiotensin II) will not result in a decrease in aldosterone levels (an effective clinical sign in primary hyperaldosteronism diagnosis).

Apart from elevated blood pressure, such symptoms as signs of muscle cramps (due to hyperexcitability of neurons secondary to hypocalcemia), muscle weakness (due to hypoexcitability of skeletal muscles secondary to hypokalemia), and headaches (caused by hypertension or hypokalemia) may be observed.

Secondary hyperaldosteronism is commonly connected with decreased cardiac output which is due to high renin levels.

Only the measuring of aldosterone is not sufficient to diagnose primary hyperaldosteronism. Rather, both renin and aldosterone should be measured, and a resultant aldosterone-to-renin ratio should be used for proper diagnosis. A high aldosterone-to-renin ratio indicates presence of primary hyperaldosteronism.

If there is a possibility of hyperaldosteronism due to plasma levels of renin and aldosterone, CT scanning can be used to confirm the presence of an adrenal adenoma. In case when the clinical manifestation primarily involves elevated blood pressure and increased levels of catecholamines, CT or MRI scanning can confirm a tumor in the adrenal medulla, as a rule, an aldosteronoma.

The choice of treatment for hyperaldosteronism depends on the underlying cause. Laparoscopical surgical removal (adrenalectomy) is effective in patients with a single benign tumor (adenoma). For patients with hyperplasia of both glands, use of

drugs that block the effect of aldosterone (spironolactone or eplerenoneis) is successful. Due to its antiandrogen effect, spironolactone medication therapy may have various results in males, sometimes causing gynecomastia. Such symptoms usually do not occur with eplerenone drug therapy.

Pheochromocytoma

The symptoms of pheochromocytoma include those related to sympathetic nervous system hyperactivity:

- Skin sensitivity
- Flank pain
- Increased heart beat
- Hypertension, including paroxysmal (sporadic, episodic) elevated blood pressure, which may be more difficult to detect; another sign of pheochromocytoma is orthostatic hypotension (a drop in systolic blood pressure more than 20 mmHg or a drop in diastolic blood pressure more than 10 mmHg while standing)
- Palpitations
- Anxiety often resembling that of a panic attack
- Diaphoresis (excessive sweating)
- Headaches
- Pallor
- Weight loss
- Localized amyloid deposits found microscopically
- Increased blood glucose level (caused by catecholamine stimulation of lipolysis (breakdown of stored fat) leading to high levels of free fatty acids and the subsequent inhibition of glucose uptake by muscle cells. Further, stimulation of beta-adrenergic receptors causes glycogenolysis and gluconeogenesis and thus an increase in blood glucose levels).
-

A pheochromocytoma can also cause resistant arterial hypertension. A pheochromocytoma can lead to death if it causes malignant hypertension, or severely high blood pressure. Standard blood pressure medications are not able to control this hypertension effectively.
The mentioned symptoms are present not in all patients. The most common symptoms are headache, excessive perspiration, and increased heart rate, the attack subsiding in less than one hour.
Tumors can grow quite large, but most are less than 10 cm.
The diagnosis can be made by measuring catecholamines and metanephrines in blood plasma or a 24-hour urine collection. Other causes of adrenergic (adrenalin-like) excess, for example, hypoglycemia, stress, exercise, and drugs affecting the

catecholamines such as stimulants, methyldopa, dopamineagonists, or antihypertensives blocking ganglion should be handled with precaution. Various types of food (e.g. vanilla ice cream) can also influence the levels of urinary metanephrine and VMA (vanillylmandelic acid). Computed tomography or a T2weighted MRI of the head, neck, thorax, and abdomen can help localize the tumor. Tumors can also be located using an MIBG scan, which is scintigraphy using iodine-123-marked metaiodobenzylguanidine.
Patients with pheochromocytomas are most often young adults to mid-adults.
The combined formation of these tumors with other endocrine gland cancers is referred to as multiple endocrine neoplasia (MEN).
The treatment of the first choice is surgical resection of the tumor either by open laparotomy or other laparoscopy.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
L.K., a 30-year-old clerk, presented with hematuria. He had been in exellent health until he woke up with severe right flank pain associated with red-colored urine. The pain radiated to his right groin. He had no previous history of kidney stones or genitourinary infection. There was no family history of gout. Physical exam revealed a healthy appearing white male in moderate distress. Vital signs: BP 130/80 mm Hg, pulse 95/min; tempetature 37°C, weight 70 kg, height 160 cm. The only remarkable finding was flank tenderness. Urine analysis: red tinged; many erythrocytes (too numerous to count); trace protein; negative glucose; urine culture, pending. An intravenous pyelogram was ordered. The right ureter had a small filling defect which did not totally obstruct the flow of contrast media. Because suprarenal mass was a contradictory issue, CT of the abdomen was ordered. The ST scan shows a 3-cm mass in the left adrenal gland. The mass does not enhance with contrast medium and appears homogeneous with well-defined margins. Thus, an adrenal mass is found incidentally on CT scan.
1. What is the differential diagnosis for such a finding and what further studies are indicated for this patient?
2. Choose the way of treatment of this patient.

Case 2.
Patient D., 38 years old, presents with complaints of general weakness, weight loss, dizziness, nausea, vomiting, diarrhea, pain in the cord. Objective status: height 163 cm, weight 153 kg. Skin was grayish-brown. Tones were rhythmical, muffled. BP – 90/60, pulse – 90/min. The melanosis was accentuated over the sun-exposed areas,

the scrotum and perineum, nipple areola, and in the skin creases. Several small hyperpigmented areas over the gingival and buccal mucosa were found.

1. What is your diagnosis?
2. What are you going to do in this case?

Case 3.

Patient B., 46 years old, complains of onsets of high blood pressure, which appear spontaneously, accompanied by headache, disturbance of eyesight, sense of anxiety and fear, trembling of extremities, overwhelming sweating, irritability, shortness of breath, nausea, vomiting, pain over the abdomen and chest, pallor or ruddy face. All of which rapidly end with profuse urination and sweating. The history of this illness is that all symptoms appeared within 6 months.

1. What is the diagnosis?
2. What therapies are available to manage this problem?

1.8 Acromegaly and gigantism. Itsenko-Cushing disease. Diabetes insipidus. Prolactin and its disorders. Growth and development disorders in children and adolescents. Obesity.

Instructive module 1: "Fundamentals of diagnosis, management, and prevention of common endocrine disorders" in the module 1: "The fundamentals of internal medicine"

Year of study: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 4.

1. Professional motivation: Acromegaly/Gigantism is a very rare disease (incidence: 3/1.000.000 a year). The syndrome is caused by a chronic exposure to GH (Growth Hormone) leading to the classic clinical characteristics that the diagnosis seems to be easy.
High exposure to GH causes gigantism in young patients prior to epiphyseal fusion and acromegaly in adults. The early diagnosis and treatment may prevent irreversible changes related to chronic overproduction of GH (as well IGF-1) and may also normalize life expectancy. Such patients have an increased mortality incidence due to systemic consequences of hypersomatotrophism in 2-4 times greater than in the healthy population. Especially over the age 45 years, an increase in mortality rate from cardiovascular and cerebrovascular atherosclerosis (36-62%), respiratory diseases (0-25%) and malignancies (9-25%) is recorded. Death incidence tends to be higher when diabetes mellitus or hypertension is present.
Itsenko-Cushing's disease (after the names of the Ukrainian neuropathologist N. M. Itsenko, 1889–1954, and the American neurosurgeon H. W. Cushing, 1869–1939), is a disorder caused by excess secretion of the pituitary adrenocorticotropic hormone (ACTH) with a resultant increase in adrenal function.
Excessive function of the pituitary may be caused by a tumor (basophilic adenoma) or by damage to the hypothalamic region in the brain, where a special substance (corticotropin releasing factor), that intensifies the synthesis and liberation of adrenocorticotropic hormone (ACTH), is produced. The syndrome of Itsenko-Cushing's disease is caused due to the elevated level of secretion of adrenocortical hormones (glucocorticoids, mineralocorticoids, and ketosteroids); signs include adiposis (basically in the region of the pectoral girdle, abdomen, trunk, and face), hypertension, hirsutism (in women), osteoporosis, diabetes mellitus, decreased sexual function, and dryness of the cutaneous integuments.
Diabetes insipidus is a condition characterized by excess thirst and excretion of large amounts of extremely diluted urine, the reduction of fluid intake does not have any

effect on the concentration of the urine. There are several types of diabetes insipidus, each of them having a different cause. The most common type in humans is central diabetes insipidus, caused by a lack of arginine vasopressin, also known as antidiuretic hormone. The second type of diabetes insipidus in nephrogenic diabetes insipidus, caused by insensitivity of the kidneys to antidiuretic hormone. It can also be an iatrogenic artifact of medication use.

Diabetes mellitus and diabetes insipidus are two completely different conditions with unrelated mechanisms. Both of them cause production of large amounts of urine (polyuria), and the term diabetes is derived from the Greek name for this symptom. Diabetes insipidus is either a problem with the production of antidiuretic hormone (cranial diabetes insipidus) or response of the kidneys to antidiuretic hormone (nephrogenic diabetes insipidus), while diabetes mellitus causes polyuria through a process called osmotic diuresis, when the high blood sugar leaks into the urine and takes excess water with it.

The incidence of diabetes insipidus in the general population is 3 in 100,000. The term refers to the inability of fluid retention (diabetes = passing [water] through) and the lack of sugar in the urine (insipidus = tasteless).

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. Though the clinical syndrome which is the result of hyperprolactinemia has been recognized in females since ancient times, the biochemical condition is a relatively new disorder, since human prolactin was purified and verified to differ from human growth hormone only in 1971.

Hyperprolactinaemia can be a part of ordinary body changes during pregnancy and breastfeeding. It can also result from the diseases affecting the hypothalamus and the pituitary gland. It can also be caused by disturbance of the normal regulation of prolactin levels under the influence of drugs, medicinal herbs and heavy metals. Hyperprolactinaemia may also be the result of the problems of other organs such as the liver, kidneys, ovaries and the thyroid gland.

In women, a high level of prolactin in the blood often results in hypo-oestrogenism with anovulatory infertility and a decreased menstruation. In some women, menstruation may disappear completely (amenorrhoea). In others, it may become irregular or menstrual flow may change. Women who are not pregnant or nursing may begin producing breast milk. Some women may experience a loss of libido (interest in sex) and breast pain, especially when prolactin levels begin to rise for the first time, because the hormone provokes changes in the breast tissue. Sexual intercourse may become painful because of vaginal dryness.

In men, the most common symptoms of hyperprolactinaemia are lowered libido, infertility, erectile dysfunction and gynaecomastia. Since men have no evident indicator such as menstruation to signal a problem, many men with hyperprolactinaemia, which is caused by an adenoma, may not go to the doctor until they have headaches or eye problems, caused by the enlarged pituitary which presses

against adjacent optic nerves. They may not notice a gradual loss of sexual function or libido. Often after treatment some men understand that they had a problem with sexual function. Hyperprolactinaemia can lead to osteoporosis because of hypoestrogenism and hypogonadism (low testosterone).

Pituitary disorders in children are the following: hypopituitarism, hormone-producing brain tumors (adenomas with secretion of such hormones: GH, TSH, FSH, ACTH), tall stature, precocious puberty, and diabetes insipidus.

For example, hypopituitarism is the reduced secretion of one or more of the eight hormones produced by the pituitary gland at the base of the brain. The term panhypopituitarism is used when there is decreased secretion of most pituitary hormones. The signs and symptoms of hypopituitarism range, and depend on which hormones are undersecreted and the underlying cause of the abnormality.

Obesity is a medical condition in which excessive body fat accumulates to the extent that it may have an adverse impact on health, leading to shorter life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) if their BMI is between 25 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2.

Obesity increases the possibility of various diseases, especially heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most often caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, drugs or mental illness. Evidence to support the view that some obese people eat little but put on weight because of a slow metabolism is contradictory; because commonly obese people have a greater energy expenditure than thin people due to the energy needed to maintain an increased body mass.

2. Study aim of this lesson.

To acquaint students with the following: differences between acromegaly and gigantism, between diabetes insipidus and diabetes mellitus, differential diagnosis of Itsenko-Cushing's disease, features of hyperprolactinemia, various pituitary disorders in children, obesity, as a current problem (α=1)

In the study process students should know (α=2):

- the main etiological factors, pathogenesis, clinical appearance, laboratory findings, and treatment of acromegaly and gigantism,
- etiology, pathogenesis, clinical presentation, laboratory evaluation, treatment of Itsenko-Cushing's disease,
- etiology and pathogenesis, clinical picture, laboratory measurements, treatment of diabetes insipidus,
- causative factors, pathogenesis, clinical appearance, laboratory findings, and treatment of hyperprolactinemia,

- the main pathologies, that provoke growth and development disorders in children and adolescents
- causes and variants of obesity

In the study process student should be able to (α=3):
- evaluate pituitary function following hormone analyses,
- differentiate pituitary disorders,
- administer adequate treatment in the case of acromegaly and gigantism,
- perform differential diagnosis of Itsenko-Cushing's syndrome,
- define treatment approach regarding diabetes insipidus,
- treat patient with hyperprolactinemia,
- discern causes of hypoglycaemia growth and development disorders in children and adolescents,
- manage patients with obesity.

3. Educational aim of this lesson

Is to focus attention on differential diagnosis of Itsenko-Cushing's syndrome, early diagnosis, and treatment of diabetes insipidus, syndrome of hyperprolactinemia, main pathologies that provoke growth and development disorders in children and adolescents as well as be aware on obesity.

4. Interdisciplinary integration (see Table 25).

Table 25

Interdisciplinary integration

Discipline	To know	How to do
I. Previous General anatomy and physiology, histology, pathological anatomy, and physiology	Pituitary gland (morphology, regulation and hormone synthesis, regulation, negative feedback effect, participation in metabolism),	To estimate physiological function of the pituitary gland. To prescribe medications.
Discipline	**To know**	**How to do**
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology, Ophthalmology	Main clinical signs of pituitary disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment.	To make clinical observation, to recommend proper diagnostic assays, consultation of associative specialists for verification of diagnosis, to prescribe medication

III. Interdisciplinary integration	Contemporary methods of diagnosis and treatment	To order adequate observation and treatment.

5. Contents of the lesson.

- Physiology and pathophysiology of the endocrine part of the brain and hypothalamus.
- Adenohypophysis: classification.
- Acromegaly and gigantism: etiology, pathogenesis, clinical picture, laboratory investigations, diagnosis and differential diagnosis, therapy.
- Itsenko-Cushing's disease: development, symptoms and signs, laboratory findings, diagnosis, treatment.
- Diabetes insipidus: etiology, pathophysiology, classification, clinical presentations, differential diagnosis, therapy.
- Hyperprolactinemia: etiology, pathogenesis, clinical features, diagnosis and differential diagnosis, treatment
- Hypopituitarism: etiology, pathogenesis, clinical manifestations, laboratory investigations, diagnosis and differential diagnosis, therapy.
- Obesity: variants, causes (underlying pathologies), diagnosis, treatment.

6. Plan and organization structure of this lesson.

(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*

Choose the correct answer/statement. One answer/statement is correct.

#1

Which statement is correct according to high-dose Liddle's test?

A) In the diagnostic approach to determine hypercortisolism
B) To differentiate Cushing's syndrome from Cushing's disease
C) Total 4 mg of dexamethasone per day
D) Total 6 mg of dexamethasone per day
E) 0.5 mg of dexamethasone once a day

#2
Anterior part of pituitary gland secretes the following hormones, except:

A) Somatotropin
B) Vasopressin
C) Corticotropin
D) Thyrotropin
E) Prolactin

#3
Development of gigantism is conditioned by:

A) Excessive secretion of GH in adolescence
B) Excessive secretion of GH in old age
C) Excessive secretion of GH in adults
D) Excessive secretion of somatostatin in adults
E) Inborn sensitivity lack in tissues to GH

#4
Physiological influence of vasopressin is evidenced by:

A) Intensification of Na excretion
B) Increased diuresis
C) Increased water reabsorption in distal tubules
D) Spasm of uterus
E) Increased glucose reabsorption

7.2. Recourses for the main stage of the lesson.

Acromegaly/Gigantism.
Acromegaly/Gigantism is the second most common of pituitary adenomas, accounting for about 17% of them. It often occurs as the result of pituitary adenoma GH secreting (99%), but other causes are also described such as a rare form induced by oversecretion of GHRH from an ectopic source (pancreatic islet or carcinoid tumors) or from the central nervous system such as ganglyoneuroma (called eutopic). Even rarer form is a nonpituitary GH secreting tumor recorded in a few lung tumors and in those called ectopic pituitary tumor.
GH secreting pituitary adenomas usually already extend more than 1cm in diameter at the time of diagnosing. They come from the lateral wings of the anterior pituitary, and in rare cases are caused by microadenoma.
About 15% of GH secreting tumors also secrete excess prolactin, which explains the clinical manifestations of hyperprolactinemia observed in these patients.
The pituitary adenomas are classified on microscopy as shown in Table 26.

Table 26

Classification of pituitary adenomas

Incidence	Adenoma type	A/B/C *	Hormone
5%	Plurihormonal	C - A	GH – Prl
5%	Acidophil Stem Cell	C	GH - Prl
5%	Mammosomatotroph	A	GH - Prl
15%	Mixed GH Cell – Prl Cell	A - C	GH - Prl
10 – 20%	Somatotrophic - Densely Granulated Cell	A	GH
20 – 30%	Somatotrophic - Sparsely Granulated Cells	C - A	GH

Notes. * A – Acidophilic; B – Basophilic; C –Chromophobic.

The excessive production of GH in acromegaly has an abnormal dynamic control. Secretion remains episodic, however the duration, amplitude and the number of secretory episodes increase. There is no characteristic night surge and abnormal reactions to inhibition and stimulation are found. TRH and GnRH may cause GH secretion while these substances do not stimulate normal release. (These factors help a lot to make a correct diagnosis).

Characteristic features and pathologic data associated with GH overproduction usually start in the third or fourth decade and unexpectedly begin to progress. The patients diagnosed with this disease are in average of age of 42 and equally of both sexes. Commonly the appearance of symptoms lasts usually 5–10 years before the diagnosis.

One of the early manifestations is soft tissue proliferation. The common features are: enlargement of the hands, feet and facial features, of which the patients most often complain.

In adults, the syndrome is characterized by overgrowth of local bone (skull, mandible). There is no linear growth because of prior fusion of the epiphyses of long bones. Hypogonadism associated with delays of epiphyseal closure may occur in many younger patients. The combination of elevated IGF-1 and hypogonadism results in a strong acceleration of linear growth.

These changes in bone and soft tissues are also connected with other systemic disorders of cardiovascular, endocrine and respiratory systems.

The main problem of the treatment is the timing when the patients start to seek medical attention. The tumor is typically in a very advanced phase causing headache, changes in visual field and/or hypopituitarism (resulting from the mass effect). Signs and symptoms of GH overproduction are given in Table 27.

Table 27

Chronic GH excess exposure

Facial changes	Coarsening of features Prognathism Diastema (widely spaced teeth)
Acral enlargement	Increased ring and shoe sizes Hands become enlarged, moist and soft. Tufting of distal phalanges
Skin changes	Generalized thickening Increased sweating and oiliness – an important sign of activity of the disease. Hypertrichosis, Acanthosis nigricans, acne
Visceromegaly	
Neuropathies and Arthropathy	Carpal Tunnel Syndrome Peripheral neuropathy, paresthesias Spinal Cord or nerve root compression from bony overgrowth Enlargement of bone
Local Effects of Pituitary (mass effect)	Headache; visual impairment, hypopituitarism, rhinorrhea
Cardiovascular disease	Cardiomyopathy left ventricular diastolic function decreased; Left ventricular mass increased; arrhythmia Hypertension
Respiratory Disease	Upper Airway Obstruction (Caused by Soft Tissue Overgrowth) Sleep Apnea
Malignancy	Colon, Esophagus, Stomach, Polyps Melanoma Lymphoma
Endocrinopathy (due either to GH excess or to mechanical effects of the adenoma)	Hyperprolactinemia Diabetes Mellitus/Carbohydrate intolerance Hypogonadism; Hypothyroidism; Hypoadrenalism Decreased libido or impotence
General Systemic Manifestations	Fatigue or lethargy Weight Gain Heat intolerance Photophobias Increased sleep requirement

The norm of serum GH is 3 to 5 ng/ml. More than 10 ng/ml is detected in 90% of patients with acromegaly. However, children and younger adults can have normal levels of GH or even up to 50 ng/ml.

Nevertheless, doctors should not rely on single measurement, as GH is secreted by the pituitary in spurts and its concentration can vary greatly. At some moment, an acromegalic patient may have normal GH levels, whereas a GH level in a healthy person may be 5 times higher especially in such conditions as: stress, sleeping time, exercise.

Taking into consideration these aspects, more accurate diagnosis can be made when GH is measured under conditions in which GH secretion is normally suppressed.

The common methods used are: oral glucose tolerance test (OGTT), IGF-1 measurement, TRH and GnRH tests.
OGTT is the most effective test to confirm the disease, because it is the simplest and most specific dynamic test.
IGF-1 Measurement: (normal ranges vary in different laboratories) is an indirect measurement of GH. IGF-1 levels are usually more reliable in the measurements of GH levels during the day, as they are more stable then. This exam also gives the opportunity to monitor thoroughly the disease.
TRH & GnRH Tests: after 500μg I.V. of TRH or 100μg I.V. of GnRH, GH increases in most patients with acromegaly. TRH can release GH in 70-80% of acromegalic patients. It is most effective when the OGTT shows a borderline response. Its reaction needs TRH receptor in the tumor.
If after GH or IGF-1acromegaly has been diagnosed, other exams may also be done:

1. Tumor Localization

As 90% of patients have tumors more than 1cm in diameter, it is possible to see its localization and size on MRI. Normal MRI finding is very rare, however in this case an extrapituitary ectopic source of GHRH or GH should be considered. If the scans show diffuse pituitary enlargement or hyperplasia, there is a possibility of ectopic GRH. Typical skull RX (thickening of the calvarium) of an acromegalic patient is pituitary macroadenoma (MRI).

2. Heel Pad Measurement

Its size is commonly more than 22mm and it must be measured with lateral RX
GH-secreting tumors are quite aggressive, thus surgical therapy should the primary choice in all patients unless there are serious surgical risks. The surgical modality can be transsphenoidal (preferred) or craniotomy (if adenoma is enlarged)
The effectiveness of this treatment, using a value of 10 ng/ml or less, was 73%, and it is more successful when the tumor is restricted to sella.
Patients in whom surgery proved ineffective in reaching normal GH levels or patients at high risk of surgical treatment should be subject to radiation therapy. Therapy may also be used in some cases to shrink large tumors prior to surgery.

- Dopaminergic Analogues

These medications come from ergoline family: bromocriptine, pergolide. In at least 50% of acromegalic patients, dopamine action is presumably through a dopamine D2 receptor-mediated mechanism, thus inhibiting GH secretion.
This being the main precaution of this therapy, 15% have the coexistence of prolactin hypersecretion, since D2 are not so dense as in the prolactinomas. Thus, the aim at shrinking the tumor with the help of these drugs is just 10-15% in comparison with 70-80% of the prolactinomas. Furthermore, this kind of treatment is the 3rd choice.
Bromocriptine is divided into 2-3 doses of about 15-60mg daily and reduces GH release from some pituitary tumors. Side effects include GH upset, nausea, vomiting, light-headedness during standing and nasal congestion. To avoid or reduce these side

effects the drug should first be administered in a very low dose before going to bed, during meal, and gradually increased to the full therapeutic dose.

- Somatostatin analogues (Octreotide)

As it is explained below with the use of dopaminergic analogues, the use of octreotide also depends on somatostatine receptors in the adenoma. However in 10-30% of acromegalic patients the density of these receptors is not high. This drug should be administered through subcutaneous injection every 8 hours approximately 300 μg/daily for effective treatment. In 50% reduction of GH levels < 5ng/ml occurs. Also the patients who initially had GH < 20ng/ml, the levels of GH and IGF-1 normalized in 95%.

Very often GH levels get lower within one hour and headaches improve within minutes after the injection. Several studies have shown that octreotide is effective for long-term treatment. And it has proven to be efficient for patients with acromegaly caused by non-pituitary tumors.

Because suppression of gastrointestinal and pancreatic function, long-term use causes digestive problems such as decreased gastrointestinal motility, nausea, bloating, abdominal pain, fat malabsorption, acholic stools, colelithiasis in one third of patients, about 25% of patients develop gallstones. It may also cause glucose intolerance, although studies have revealed that in some acromegalic patients with diabetes, the drug improves control of blood sugar.

Nowadays the effective treatment is surgery. Pharmacotherapy can not be adequately sufficient. It is administered when neither surgery nor radiotherapy was successful and/or there were contraindications for the patient.

Brief information about Itsenko-Cushing's syndrome is presented in Table 28.

Table 28

Features of Itsenko-Cushing syndrome

Etiologies	**Symptoms**
Iatrogenic Steroid therapy (most common cause) *Central Cause* Pituitary adenoma *Adrenal Cause* Adrenal Adenoma Adrenal Hyperplasia Adrenal Malignancy (15%) *Ectopic Source* Malignancy (Small Cell Carcinoma of the lung: 15%)	Mood changes (depression and euphoria) Easy bruising Weakness Weight gain Amenorrhea Back pain

Features of Itsenko-Cushing syndrome

Signs	**Labs**
Truncal Obesity (90%) Hypertension (85%) Glucose Intolerance (80%)	Screening Test 24-hour Urinary free cortisol level (preferred)

Hirsutism (70%) Wide, purple abdominal and thigh striae (65%) Osteoporosis (55%) Moon faces Buffalo hump (Thoracic kyphosis) Myopathy Plethoric face Supraclavicular fat pad development Hypertrichosis Peripheral Edema Hypertension	Urine 17-Ketosteroid excretion Urine 17-Hydroxysteroid excretion Serum Cortisol Low dose Dexamethasone Suppression Test Dexamethasone 1 mg at 11pm Plasma Cortisol in following 8 AM Night-time salivaryry cortisol testing Distinguish between pituitary, adrenal or ectopic cause Plasma ACTH High dose Dexamethasone Suppression Test (8 mg)
Radiology CT or MRI Cone down Sella Turcica Pituitary adenoma CT abdomen Adrenal tumor	**Management** Exogenous Cushing's Stop steroids or decrease dose Change steroid dosing or use drug holiday Endogenous Cushing's Surgically excise adenoma (in pituitary or adrenal)

1. Distinguishing ACTH-induced hypercortisolism from adrenal neoplasm
An undetectable or very low normal baseline plasma ACTH level combined with hypercortisolism is a vivid indicator of an adrenal tumor.
A high or high normal baseline plasma ACTH level combined with hypercortisolism shows either pituitary or ectopic production of excessive ACTH. Usually, ACTH levels of patients with Cushing's disease are much lower than of patients with ectopic ACTH production. However, there may be so many coincidences that the ACTH level cannot be the reliable indicator for distinction between the two conditions in a given case. If the ACTH level is low, a high-dose dexamethasone test should be done to confirm the presence of an adrenal neoplasm.
High-dose dexamethasone suppression test.
The goal of this test is to confirm the diagnosis of autonomous adrenal neoplasia when hypercortisolism with a low or low-normal plasma ACTH has been diagnosed. Lack of suppression confirms the diagnosis.
Overnight 8-mg test. A baseline 8 a.m. plasma cortisol determination is the best for high-dose dexamethasone suppression test. 8 mg of dexamethasone are administered at 11 p.m. and a 6-8 a.m. plasma cortisol is taken the next morning. A decrease in plasma cortisol to less than 50% of the baseline value is considered significant suppression.
Two-day test. The 2-day high-dose dexamethasone suppression test may be the alternative. Although it is not so convenient and accurate as the overnight test, it can be used in difficult diagnostic cases when more data are needed. A baseline 24-hour urine is collected for 17-OHCS, free cortisol, and creatinine. After that dexamethasone should be used, 2 mg orally every 6 hours for 2 days (20 μg/kg every 6 hours for children). On the second day a repeated 24-hour urine collection should

be done; a reduction of 17-OHCS and free cortisol excretion to less than 50% of the baseline value is considered significant suppression.
The high-dose dexamethasone suppression test is not able to effectively distinguish between ectopic and pituitary sources of ACTH secretion. About 15% of ectopic tumors are suppressible, especially carcinoid tumors of the lung; about 90% of pituitary tumors are suppressible. Thus, considerable cortisol suppression with high-dose dexamethasone shows pituitary Cushing's disease but the diagnosis can not be considered accurate without further testing.
2. Distinguishing adrenal adenomas from hyperplasia.
Plasma 18-hydroxycorticosterone (18-OHB). If there is decreased plasma potassium and renin and a high 24-hour urinary aldosterone excretion, the patient needs further examination to exclude an adrenal adenoma or hyperplasia. In order to do this it is required to check both plasma 18-OHB and aldosterone levels: a single plasma level of 18-OHB is obtained; levels higher than 85 ng/dl indicate adrenal neoplasm. Accurate 18-OHB determinations are now available. If plasma aldosterone level is more than 20 ng/dl, it is additional proof for an adrenal neoplasm.
Cushing's disease refers to hypercortisolism secondary to increased production of ACTH from a corticotrophic pituitary adenoma. Such rise in the blood ACTH levels occurs in combination with cortisol from the adrenal gland. The ACTH levels remain elevated as a tumor causes the pituitary to be unresponsive to negative feedback due to high cortisol levels.
X-irradiation of the pituitary region is used for treatment. Symptomatic treatment includes the administration of agents that decrease blood pressure, antidiabetic preparations, and medications inhibiting adrenal function (amphenone, metopyrone). Subtotal or total adrenalectomy may be followed by administration of adrenal hormones.

Diabetes insipidus

Central diabetes insipidus

Central diabetes insipidus is the most common form of severe diabetes insipidus, and it is caused by damage to the pituitary gland, which damages the normal storage and release of ADH. The pituitary gland may be harmed by different diseases, head injuries, neurosurgery, or genetic disorders. For treatment a synthetic hormone desmopressin can be injected, a nasal spray, or a pill for the treatment of the ADH deficiency that results from any kind of damage to the hypothalamus or the pituitary. During treatment with desmopressin, a patient should not drink fluids unless thirsty, since the drug prevents water excretion, and it can accumulate so that the kidneys are producing less urine and are less responsive to changes in body fluids.

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus is caused by the failure of the kidneys to respond to ADH. The ability of the kidneys to respond to ADH can be affected by medication such as lithium, and by chronic disorders including polycystic kidney disease, sickle

cell disease, kidney failure, partial obstruction of the ureters, and inherited genetic disorders. In some cases it is impossible to find the cause of nephrogenic diabetes insipidus.

Desmopressin is not effective for this type of diabetes insipidus. Thus, a person with nephrogenic diabetes insipidus may be administered hydrochlorothiazide (HCTZ) or indomethacin. HCTZ is sometimes combined with amiloride, and this combination is produced under the brand name Moduretic. With This medication, a patient should also drink fluids only when thirsty.

Dipsogenic diabetes insipidus

Dipsogenic diabetes insipidus is caused by a defect in or damage to the thirst mechanism, which is located in the hypothalamus. This defect leads to an abnormal increase in thirst and fluid intake that suppresses ADH secretion and increases urine output. Desmopressin or other drugs should not be administered to treat this disease, since they may decrease urine output but not thirst and fluid intake. This can lead to water intoxication, a condition that decreases the concentration of sodium in the blood and can severely damage the brain. An effective treatment for dipsogenic diabetes insipidus has not been found yet.

Gestational diabetes insipidus

Gestational DI occurs only during pregnancy when an enzyme produced by the placenta destroys ADH of the mother. The placenta is the system of blood vessels and other tissues that develops with the fetus and provides the exchange of nutrients and waste products between the mother and the fetus.

In most cases desmopressin is effective for the treatment of this disease. Rarely, however, an abnormality in the thirst mechanism causes gestational diabetes insipidus, and desmopressin should not be used.

Prolactin and its disorders (see Fig.3)

There are 2 groups of prolactin-secreting adenomas: (1) microadenomas (likely to occur in premenopausal women), which are smaller than 10 mm and (2) macroadenomas (more common in men and postmenopausal women), which are 10 mm or even larger.

If the prolactin level is higher than 100 ng/mL or lower than 250 ng/mL, the decision should be taken whether a radiographic study is required. MRI scanners being available, imaging is carried out earlier and at lower prolactin levels to manage a non-prolactin-producing tumor.

Idiopathic hyperprolactinemia is diagnosed when the underlying cause (physiologic, medical, pharmacologic) cannot be detected and an MRI does not help to find adenoma.

Macroprolactinemia may also lead to hyperprolactinemia. Most prolactin in the bloodstream is monomeric (approximately 85%), however, dimeric and polymeric forms may also be possible. Macroprolactinemia is the obvious increase in serum prolactin without evident symptoms. In this condition, serum prolactin molecules

can polymerize and eventually bind to immunoglobulin G (IgG). This form of prolactin is unable to bind to prolactin receptors and doesn't show a systemic response. So if the patient with hyperprolactinemia does not have vivid symptoms, this condition should be considered. If macroprolactinemia is diagnosed, this could spare the patient from thorough examination for a microadenoma. Laboratory personnel should be consulted for any special collecting requirements. Women with macroprolactinemia are able to conceive, this condition generally requires no treatment (Fig. 4).

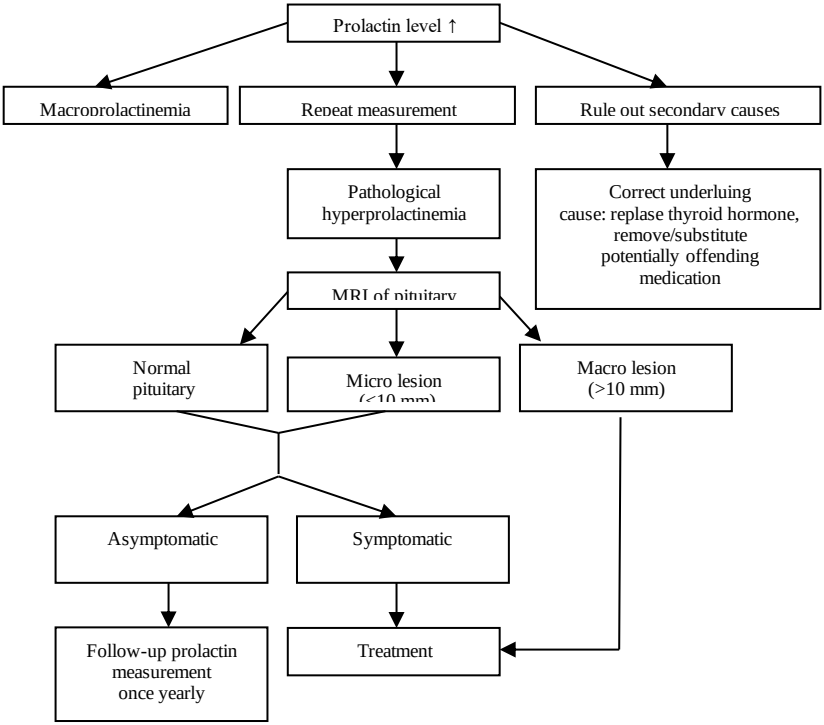


Figure 3. Approach to diagnosis of hyperprolactinemia.

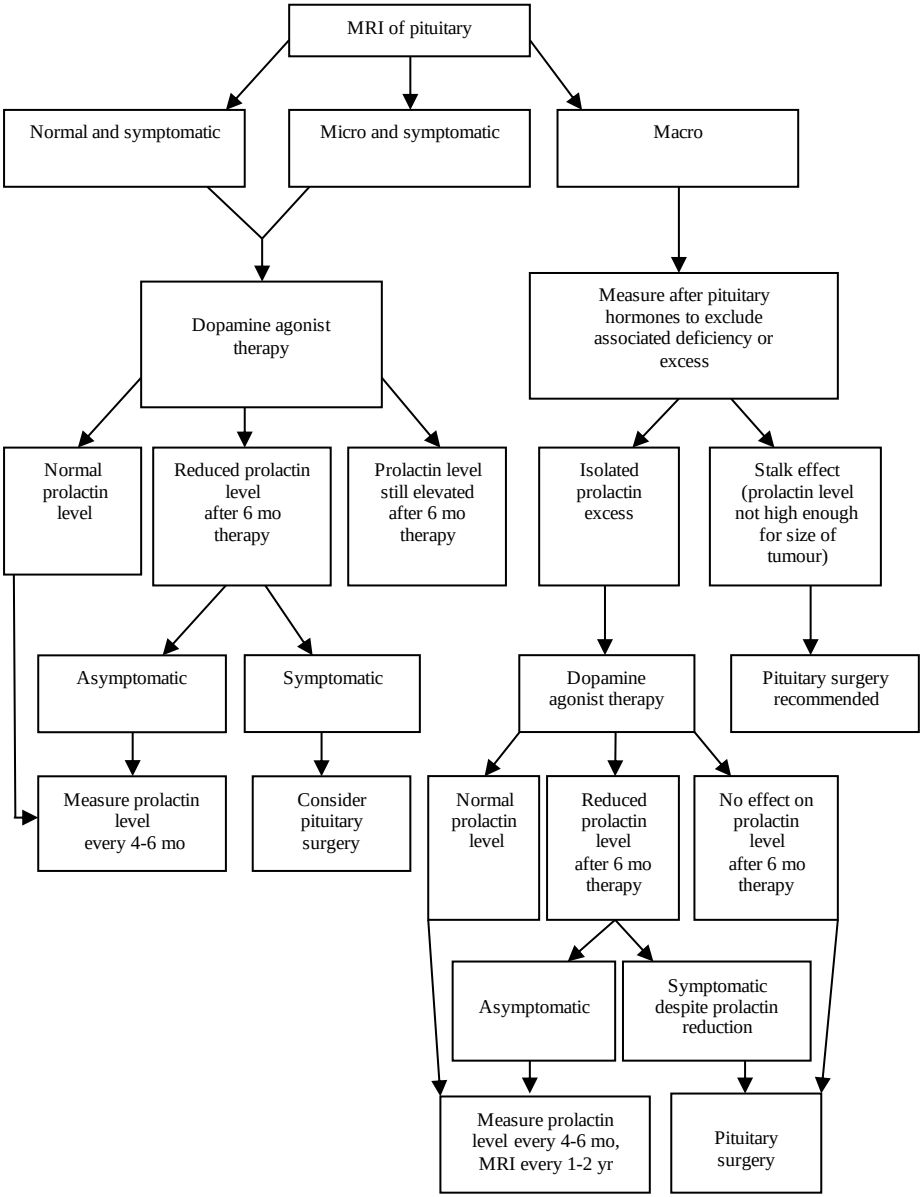


Figure 4. Approach to management of hyperprolactinemia.

Drugs with dopamine agonists such as cabergoline, bromocriptine (often preferred when pregnancy is likely), and less frequently lisuride are used for treatment. A new drug in use is norprolac with the active ingredient quinagolide.

In cases of mild hyperprolactinaemia vitex agnus-castus extract can be used.

Peculiarities of hyperprolactinemia in pregnancy

- There is no evidence of elevated teratogenicity associated with bromocriptine or cabergoline use during gestation
- As well as there is no proof of high risk of abortion or multiple pregnancies with dopamine agonist use
- If the size of the tumour before pregnancy is < 10 mm, dopamine agonist therapy is stopped during gestation, since there is no high risk of tumour expansion
- If the tumour size before pregnancy is ≥ 10 mm, it is recommended to use bromocriptine during pregnancy to avoid considerable tumour expansion
- All patients should be examined every 2 months during pregnancy
- Formal visual field testing is recommended in patients with symptoms or a history of macroadenoma
- If visual field defects develop in spite of dopamine agonist treatment, the risk of early delivery or pituitary surgery should be considered.

METABOLIC SYNDROME

The term "metabolic syndrome" refers to a combination of risk factors of specific cardiovascular diseases (CVD), underlying pathophysiology of which is considered to be related to insulin resistance.

Table 29 shows the ATP III (Third Report of the National Cholesterol Education Program's Adult Treatment Panel, 2004) and WHO (World Health Organization, 1999) definitions of the metabolic syndrome.

Table 29

Definitions of metabolic syndrom

ATP III definition
Any three or more of the following criteria:
1) Waist circumference >102 cm in men and >88 cm in women
2) Serum triglycerides ≥1.7 mmol/l
3) Blood pressure ≥130/85 mmHg
4) HDL cholesterol <1.0 mmol/l in men and <1.3 mmol/l in women
5) Serum glucose ≥6.1 mmol/l (≥5.6 mmol/l may be applicable)

Definitions of metabolic syndrom
WHO definition
Diabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
1) Waist-to-hip ratio >0.90 in men or >0.85 in women
2) Serum triglycerides ≥1.7 mmol/l or HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women
3) Blood pressure ≥140/90 mmHg
4) Urinary albumin excretion rate >20 μg/min or albumin-to-creatinine ratio ≥30 mg/g

Though the WHO and ATP III definitions generally refer to the same individuals, there are significant differences. So patients may be classified as having the syndrome according to one definition but not according to the other one.
Taking this into consideration, ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) advise the following:

1. Patients should not be labeled with the term "metabolic syndrome," as this may create the impression that this syndrome means a greater risk than its components, or that it is more serious than other cardiovascular disease risk factors, or that the underlying pathophysiology is clear.
2. All cardiovascular disease risk factors should be treated individually and aggressively.
3. There is no efficient pharmacological treatment for the metabolic syndrome, nor should it be considered that pharmacological therapy to reduce insulin resistance will be proper for patients with the metabolic syndrome before randomized controlled tests have been completed.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
Patient, 37 years old, complains of general weakness, headache, weight gain, menstrual irregularity, hirsutism, frequent urination and thirst. Objective status: Height – 167 cm, weight – 89 kg. Localization of fat tissue is disproportional, found mostly on the face, neck and trunk with relatively thin extremities. Face is ruddy, "moon face". There are dark red striae under her arms, on the inner surfaces of the hips and on the belly. Skin is normal, moist, pulse is rhythmic, 72/min, BP – 170/110. Over her upper lip and chin large amount of hair growth (patient shaves). Laboratory exam: 17-OHCS is elevated, oral glucose tolerance test (OGTT) – 6.2-10.2-8.4 mmol/l, glucose in urine – 0.5%.

1. What is the differential diagnosis for such a finding and what further studies are indicated for this patient?
2. Choose the way of treatment of this patient.

Case 2.
Patient M., 23 years old, complains of a tiresome thirst (drinks 10-15 l/day), mouth dryness, frequent urination, headache and weight loss. Six months ago the patient had a trauma to the skull. Objective status: Height – 178 cm, weight – 56 kg, skin is dry, turgor decreased. BP – 115/70, pulse – 70/min. Additional investigations: specific gravity 1002-1005, oral glucose tolerance test – 4.7-7.1-5.5 mmol/l. Rtg of the skull – normal, vision fields – normal.

1. What diagnosis would you suggest?
2. What additional investigations should you order to confirm the diagnosis?

Case 3.
Patient H., 40 years old, complains of absence of libido, dizziness, feeling of cold, constipation, frequent urination, paresthesias, worsening of eyesight and memory, increased disability, thirst with 3-4 l/day of fluids being consumed. The disease commenced approximately 4-5 years previously, with an ophthalmological consultation because of a narrowing of vision fields and a consequent diagnosis of pituitary tumor. Patient has undergone a surgical operation to ablate the tumor. Objective status: Height – 158 cm, weight – 67 kg, skin is dry and cool, turgor is normal. BP – 90/55, pulse – 56/min. 17-OHCS is decreased, OGTT, T_3, T_4, TSH, LH levels are decreased.

1. What is the most likely diagnosis?
2. What additional investigations should you order to confirm the diagnosis?

Part 2
(for sixth year of study in "Endocrine emergencies")

2.1 Chronic complications in Diabetes Mellitus. Hypoglycemic coma.

Year of study: 6.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 6.

1 Professional motivation: The complications of diabetes mellitus are less common and less serious in patients who have sensibly controlled blood sugar levels. Additional health problems accelerate the effects of diabetes. They include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise. The damage to small blood vessels results in a microangiopathy, which can cause one or more of the following problems:

- Diabetic cardiomyopathy, damage to the heart, leading to diastolic dysfunction and subsequently heart failure.
- Diabetic nephropathy, damage to the kidneys which can result in chronic renal failure, subsequently requiring dialysis. Diabetes mellitus is the most common cause of kidney failure in adults worldwide in the developed countries.
- Diabetic neuropathy, abnormal and lowered sensation, usually in a "glove and stocking" region starting with the feet but affecting other nerves, finally often fingers and hands. This can lead to diabetic foot when combined with damage to the blood vessels. Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Diabetic amyotrophy is muscle weakness caused by neuropathy.
- Diabetic retinopathy, growth of fragile and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula) can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) is the most common cause of blindness among non-elderly adults in the US.

Macrovascular disease causes cardiovascular disease, though accelerated atherosclerosis is also a contributor:

- Coronary artery disease, leading to angina or myocardial infarction ("heart attack")
- Diabetic myonecrosis ("muscle wasting")
- Peripheral vascular disease contributes to intermittent claudication (exertion-related pain in the leg and foot) as well as diabetic foot.

- Stroke (usually the ischemic one)

Diabetic foot, often caused by a combination of sensory neuropathy (numbness or insensitivity) and vascular damage, increases incidence of skin ulcers (diabetic foot ulcers), infection and, in serious cases, necrosis and gangrene. That is why diabetics are prone to leg and foot infections and it takes longer for them to heal leg and foot wounds. It is the most common cause of non-traumatic amputation in adults, usually of toes and/or feet, in the developed countries.

Carotid artery stenosis does not occur more often in diabetes, and there is a lower incidence of abdominal aortic aneurysm. However, diabetes causes higher morbidity, mortality and surgical risks associated with these conditions.

Diabetic encephalopathy is the increased cognitive risk of dementia-including (but not limited to) the Alzheimer's type, observed in diabetes. Various mechanisms are suggested, including alterations in the vascular supply of the brain and the influence of insulin on the brain itself.

In the developed countries, diabetes is the most common cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis, for example in the United States.

From the study of type 1 diabetes it is seen that despite modern treatment, women with diabetes are at increased risk of infertility, which is reflected by delayed puberty and menarche, menstrual irregularities (especially oligomenorrhoea), mild hyperandrogenism, polycystic ovarian syndrome, fewer live born children and possibly earlier menopause. Experiments on animals show that abnodmalities on the molecular level, caused by diabetes, include defective leptin, insulin and kisspeptin signalling.

Diabetic hypoglycemia represents a special case concerning the correlation of measured glucose and hypoglycemic symptoms for several reasons. First, although home glucose meter readings are often misleading, the probability that a low index, whether accompanied by symptoms or not, represents real hypoglycemia is much higher in a person who takes insulin than in someone who does not. Second, since injected insulin cannot be "turned off", diabetic hypoglycemia has a greater chance of advancing to a serious impairment if untreated, in comparison with most other forms of hypoglycemia. Third, since glucose levels are often above normal for prolonged periods of time (hours, days, or months) in patients with diabetes, hypoglycemic symptoms may sometimes occur at higher thresholds than in people whose blood sugar is usually within normal limits.

2 Study aim of this lesson.

To acquaint students with natural history of diabetes and its complications that face contemporary society, as well as with classification, etiology, pathogenesis of diabetic complications (α=1)

In the study process students should know (α=2):

- the incidence of diabetes mellitus and associated risk factors,
- main chronic complications of diabetes mellitus,
- treatment approach,
- causative factors of hypoglycemic coma development,
- treatment of hypoglycemic coma

In the study process student should be able to (α=3):

- manage patients with chronic complications,
- make an analysis by express method (glucose in blood, glucose and acetone in urine),
- interpret glucose in urine, acetone in urine, level of fasting glucose, HbA1c (glycated hemoglobin), and C-peptide in blood,
- carry out physical examination,
- discern hypoglycaemia from other acute complications,
- organise therapeutic approach.

3 Educational aim of this lesson

Is to pay attention to classification, treatment approach, and evaluation of metabolic control in diabetes mellitus.

4 Interdisciplinary integration (see Table2).

Table 2

Interdisciplinary integration

Discipline	To know	How to do
I. Previous General anatomy and physiology, histology, pathological anatomy and physiology, pharmacology	Pancreas (location, morphology, function); hormones, regulation	To estimate physiological reserve of pancreas in order to prescribe proper treatment (doses and methods) To prescribe medications.
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology, Nephrology Ophthalmology.	Main clinical signs of Diabetes Mellitus, its types, differential diagnosis, treatment Emergency states and late diabetic complications	To make clinical observation, prescribe proper diagnostic assays, consultation of associative specialists for verification of diagnosis.

Discipline	To know	How to do
III. Interdisciplinary integration	Contemporary methods of diagnostics and treatment of diabetic emergencies.	To prescribe adequate treatment of diabetes mellitus and hypoglycemic coma.

5 Contents of the lesson.

- Definition of diabetic complications.
- Natural history and distribution of late diabetic complications, prognosis.
- Evaluation of metabolic control in diabetes.
- Cardiovascular diseases in diabetes and their classification.
- Management of diabetic ischemic heart disease (diet plan, exercise, drug therapy, surgical approaches such as balloon angioplasty and coronary artery bypass surgery).
- Diabetic neuropathy: classification, clinical picture, pathogenesis and therapeutic implications.
- Diabetic nephropathy: classification, clinical course, laboratory abnormalities and treatment.
- Diabetic retinopathy: classification and characteristics of each stage, management. Other eye disorders in diabetes (diabetic cataract, diabetic ophthalmoplegia, glaucoma) and their management.
- The diabetic foot: pathophysiology (neuropathy, ischemia, infection), management and threatening factors (foot ulcer, limb-threatening infections, osteomyelitis).
- Hypoglycemic coma (etiology, clinical picture, laboratory, tretment)

6 Plan and organization structure of this lesson.
(See preface)

7 Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Please, choose the best therapy for treatment of diabetes in a patient with coexisting coronary artery disease:
A) Glimepiride
B) Acarbose
C) Rosiglitazone

D) Glibenclamide
E) Metformin

#2
All of the following are possible side effects of insulin use, except:
A) Hypoglycemic coma
B) Insulin resistance
C) Weight loss
D) Weight gain
E) Lipodystrophy at injection sites

#3
One of the main causes of hypoglycaemia is:
A) Diarrhoea
B) Stress
C) Weight loss
D) Weight gain
E) Unaccustomed exercise

#4
Which of the following drugs may precipitate cardiovascular complications?
A) Glyburide
B) Gliclazide
C) Glimepiride
D) Acarbose
E) Nateglinide

#5
Macroangiopathy in diabetes mellitus, most often destroys vessels of:
A) Lung
B) Brain
C) Retina
D) Kidneys
E) Liver

7.2. Recourses for the main stage of the lesson.

The chronic complications of DM affect multiple organ systems and lead to the majority of morbidity and fatal cases associated with the disease. There are vascular and nonvascular chronic complications. The vascular complications are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and

macrovascular complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Nonvascular complications encompass gastroparesis, infections, and skin changes. The longer a patient suffers from hyperglycemia the higher the risk for chronic complications, which usually are vividly manifested in the second decade of hyperglycemia. Many patients with type 2 DM already have complications at the time of diagnosis, since in case of 2 DM there is often a long asymptomatic period of hyperglycemia (see Table 3).

Table 3

Chronic Complications of Diabetes Mellitus

Microvascular
Eye disease
Retinopathy (nonproliferative/proliferative)
Macular edema
Neuropathy
Sensory and motor (mono- and polyneuropathy)
Autonomic
Nephropathy
Macrovascular
Coronary artery disease
Peripheral vascular disease
Cerebrovascular disease
Other
Gastrointestinal (gastroparesis, diarrhea)
Genitourinary (uropathy/sexual dysfunction)
Dermatologic
Infectious
Cataracts
Glaucoma

Although chronic hyperglycemia is an important etiologic cause of complications of diabetes mellitus, the mechanisms by which it leads to such various cellular and organ dysfunction are unknown. There are four parallel basic theories explaining how hyperglycemia may cause the chronic complications of diabetes mellitus.

One theory suggests that elevated intracellular glucose causes the formation of advanced glycosylation end products (AGEs) through the nonenzymatic glycosylaton of intra- and extracellular proteins. Non-enzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs cross-link proteins (e.g. collagen, extracellular matrix proteins), accelerate atherosclerosis, induce glomerular dysfunction, lower nitric oxide synthesis, promote endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with glycemia levels and these products accumulate as glomerular filtration rate falls.

The second hypothesis was drawn from the observation that hyperglycemia enhances glucose metabolism through the sorbitol pathway. Intracellular glucose is

usually metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol under the effect of the enzyme aldose reductase. Elevated sorbitol concentration changes redox potential, increases cellular osmolality, generates reactive oxygen species, and may cause other types of cellular dysfunction. However, testing of this theory in humans by means of aldose reductase inhibitors has not been efficient on clinical endpoints of retinopathy, neuropathy, or nephropathy.

The third theory argues that hyperglycemia increases the formation of diacylglycerol causing activation of protein kinase C (PKC). PKC also changes the gene transcription for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons.

The fourth theory states that hyperglycemia enhances the flux via the hexosamine pathway, generating fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. The hexosamine pathway may alter the function by glycosylation of proteins, for instance, endothelial nitric oxide synthase or by changes in gene expression of transformation of growth factor β (TGF-β) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors are crucial in DM-associated complications, and they are increased by most of the suggested pathways. Vascular endothelial growth factor (VEGF) increases locally in diabetic proliferative retinopathy and decreases after administering laser photocoagulation. TGF-β is high in case of diabetic nephropathy and stimulates basement membrane to produce collagen and mesangial cells to produce fibronectin. Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and insulin, may often take part in DM-related complications. What is possibly unifying them all is that hyperglycemia causes increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may launch all the above-mentioned pathways. Although hyperglycemia is considered to be the trigger for complications of diabetes, it has not been proven that the same pathophysiological processes are involved in all complications or that some pathways prevail in certain organs.

OPHTHALMOLOGIC COMPLICATIONS OF DIABETES MELLITUS

DM is the main cause of blindness at the ages of 20-74 in the United States alone. The research reveals that patients with DM are 25 times more likely to lose vision than individuals without DM. Blindness is caused by progressive diabetic retinopathy and clinically significant macular edema. There are two stages of diabetic retinopathy: nonproliferative and proliferative. Nonproliferative diabetic retinopathy often takes place late in the first decade or early in the second decade of the disease and is characterized by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots. Mild nonproliferative retinopathy develops into more extensive disease, accompanied by alterations in venous vessel caliber,

intraretinal microvascular abnormalities, and numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms associated with nonproliferative retinopathy include loss of retinal pericytes, elevated retinal vascular permeability, changes in retinal blood flow, and abnormal retinal microvasculature, all of them causing retinal ischemia.

Neovascularization in response to retinal hypoxia is the indicator of proliferative diabetic retinopathy. These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and finally retinal detachment. Non-proliferative retinopathy does not develop into proliferative retinopathy in all individuals, but if the non-proliferative disease is serious, there are all chances of progression to proliferative retinopathy within 5 years. Thus, it is crucial to reveal and treat diabetic retinopathy on early stages. Clinically significant macular edema is possible when only non-proliferative retinopathy is present. To detect macular edema, which is responsible for 25% chance of moderate visual loss over the next 3 years, fluorescent angiography is used.

Duration of DM, degree of glycemic control and high blood pressure are the important factors of the development of retinopathy. Almost all patients suffering from diabetes mellitus for over 20 years develop non-proliferative retinopathy (25% incidence with 5 years, and 80% incidence with 15 years of type 1 DM). Although there may be genetic predisposition to retinopathy, it does not play such an important role as either the duration of diabetes mellitus or the degree of glycemic control.

TREATMENT

Prevention is the most effective treatment for diabetic retinopathy. Thorough glycemic and blood pressure control can delay or slow the development of retinopathy in individuals with both types 1 and 2 diabetes mellitus. Paradoxically, diabetic retinopathy condition may deteriorate during the first 6 to 12 months of improved glycemic control. However, it is a temporary process, and in the long term, improved glycemic control is associated with less diabetic retinopathy. Patients with diagnosed retinopathy may be subject to preventive photocoagulation while starting intensive therapy. In case of advanced retinopathy, improved glycemic control is less effective, but proper ophthalmologic care can prevent most blindness.

All patients with DM should undergo regular, thorough eye examinations. Most diabetic eye diseases can be effectively treated if they are detected on time. Routine, nondilated eye examinations by the primary physician or diabetes specialist are not enough to reveal diabetic eye disease, which requires a consultation of an ophthalmologist for optimal care of these disorders. Laser photocoagulation is a very successful way of treatment. Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation. Most patients with advanced diabetic eye disease are advised to refrain from physical activities associated with repeated Valsalva maneuvers, although exercise has not been proven to worsen proliferative diabetic retinopathy .

RENAL COMPLICATIONS OF DIABETES MELLITUS

The main cause of DM-related morbidity and mortality is diabetic nephropathy. Proteinuria in patients with DM leads to very low survival and high risk of cardiovascular disease. Almost all individuals with diabetic nephropathy have as well diabetic retinopathy.

The course of diabetic nephropathy development is fairly predictable and was initially defined for individuals with type 1 diabetes mellitus but is also similar in type 2 DM. Glomerular hyperperfusion and renal hypertrophy are common in the first years after the occurrence of DM and lead to high glomerular filtration rate (GFR). Thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur during the first 5 years of DM as the GFR returns to normal. ~40% of individuals begin to excrete small amounts of albu min in the urine in 5 to 10 years of type 1 DM. Microalbuminuria is defined as 30-300 mg/d in a 24-h collection or 30-300 μg/mg creatinine in a spot collection (preferred method). A crucial indicator of progression to overt proteinuria (>300 mg/d) or overt nephropathy is the appearance of microalbuminuria (incipient nephropathy) in type 1 DM. There might be also a possibility of slightly increased blood pressure at this point. If evident proteinuria occurs, there is a constant decline in GFR, and ~50% of individuals reach ESRD in 7-10 years. The early pathologic changes and albumin excretion abnormalities may go back to norm with normalization of plasma glucose. However, in case of evident nephropathy, the pathologic changes are likely irreversible.

The nephropathy that occurs in type 2 diabetes mellitus differs from that of type 1 diabetes mellitus in the following ways: (1) microalbuminuria or overt nephropathy may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension is more likely together with microalbuminuria or overt nephropathy in type 2 DM; and (3) microalbuminuria may be less indicating diabetic nephropathy and progression to evident nephropathy in type 2 DM. It is also worth noting that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as congestive heart failure, hypertension, prostate disease, or infection. Diabetic nephropathy and ESRD secondary to this occur more commonly in African Americans, Native Americans, and Hispanic individuals than in Caucasians with type 2 DM.

Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) also may accompany type 1 or 2 DM. These individuals are prone to hyperkalemia, which may be exacerbated by medications [especially angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)]. Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Risk factors for radiocontrast-induced nephrotoxicity are preexisting nephropathy and volume depletion. Patients with DM who are subject to radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be

monitored for several days after the procedure. Treatment with acetylcysteine (600 mg bid) on the day before and the day of the dye study is an effective protection for high-risk patients [creatinine, >212 μmol/L (>2.4 mg/dL)] from radiocontrast-induced nephrotoxicity.

TREATMENT

The best treatment for diabetic nephropathy is prevention. In diabetes care it is crucial to detect microalbuminuria at an early stage when effective therapies can be administered. Efficient measures delaying progression from microalbuminuria to overt nephropathy include: (1) near normalization of glycemia, (2) strict control of blood pressure, and (3) administration of ACE inhibitors or ARBs, and (4) treatment of dyslipidemia.

Many individuals with type 1 or type 2 DM suffer from hypertension. It is important to maintain blood pressure at the level <130/80 mmHg in diabetic patients without proteinuria. A slightly lowered blood pressure (125/75) should be maintained for individuals with microalbuminuria or overt nephropathy.

ACE inhibitors and ARBs are administered in case of type 1 or type 2 DM and microalbuminuria to reduce the progression of overt nephropathy in patients with type 1 or type 2 DM.

A consensus panel of the ADA suggests modest restriction of protein ingestion in diabetic patients with microalbuminuria (0.8 g/kg per day) or overt nephropathy (<0.8 g/kg per day, which is the adult Recommended Daily Allowance, or about 10% of the daily caloric intake).

The diagnosis of early incipient nephropathy should be followed by the consultation of nephrologist. Unlike with nondiabetic individuals, hemodialysis in patients with diabetes mellitus may be accompanied with more frequent complications, such as low blood pressure (due to autonomic neuropathy or loss of reflex tachycardia), more difficult vascular access, and accelerated retinopathy progression. Hyperlipidemia requires aggressive treatment since atherosclerosis is the main cause of death in diabetic individuals on dialysis. Renal transplantation from living donor is the preferred treatment, but requires chronic immunosuppression. Combined pancreas-kidney transplant provides normoglycemia but needs substantial expertise.

DIABETIC NEUROPATHY

About 50% of individuals with continuous type 1 and type 2 DM suffer from diabetic neuropathy. It may have the forms of mononeuropathy, polyneuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy depends on the duration of diabetes and glycemic control; both myelinated and unmyelinated nerve fibers are lost. Diabetic neuropathy can be diagnosed only after the exclusion of other possible etiologies, because the clinical features of diabetic neuropathy are similar to those of other neuropathies.

Polyneuropathy/Mononeuropathy

Distal symmetric polyneuropathy is the most common form of diabetic neuropathy. It most often is manifested by distal sensory loss, hyperesthesia, paresthesia, and dysesthesia. With the progress of the disease any combination of these symptoms may develop. Symptoms include feeling of numbness, tingling, sharpness, or burning which begins in the feet and spreads proximally. Some of the patients develop neuropathic pain, occasionally preceded by improvement in their glycemic control. Pain in the lower extremities is usually present at rest, and worsens at night. An acute (lasting over 12 months) and a chronic form of painful diabetic neuropathy have been recorded. The pain eases and eventually disappears as diabetic neuropathy progresses, but a sensory deficit in the lower limbs remains. Physical examination reveals sensory loss, loss of ankle reflexes, and the sense of abnormal position. Diabetic polyradiculopathy is a syndrome which causes severe disabling pain in the area of one or more nerve roots, which may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain throughout the chest or abdomen. Pain in the thigh or hip may be the result of involvement of the lumbar plexus or femoral nerve, and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). However, diabetic polyradiculopathies are commonly self-limited and resolve over the period 6 to 12 months.

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) causes pain and motor weakness in the distribution of a single nerve and is less common than polyneuropathy in DM. The etiology of the disease is presumably vascular, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Ptosis and opthalmoplegia with normal constriction of pupils in reaction to light are found during physical examination. There may also be peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex). Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected.

Autonomic Neuropathy

Patients with continuous type 1 or 2 DM may have signs of autonomic dysfunction including the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can influence numerous systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic ones. Autonomic neuropathies influencing the cardiovascular system cause a tachycardia on rest and orthostatic hypotension. Cases of sudden death have also been connected with autonomic neuropathy. Gastroparesis and dysfunction of bladder emptying are frequently caused by the autonomic neuropathy present in DM (discussed below). Sympathetic nervous system dysfunction causes hyperhidrosis of the upper extremities and anhidrosis of the lower extremities. The risk of foot ulcers is caused by anhidrosis of the feet and dry skin with cracking. Autonomic neuropathy may reduce counterregulatory hormone release, causing inability to sense hypoglycemia

properly, thus, exposing the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

TREATMENT

Treatment of diabetic neuropathy has not proven to be successful. Improved glycemic control has to be carried out, which enhances velocity of nerve conduction, but that does not guarantee the improvement of the symptoms of diabetic neuropathy. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. The basic principles of therapy are elimination of neurotoxins (alcohol), vitamin supplementation for possible deficiencies (B_{12}, B_6, folate), and symptomatic treatment. Aldose reductase inhibitors do not help to significantly relieve symptoms. Loss of sensation in the foot provokes a risk for ulceration and its consequences; thus, prevention of such problems is crucial. Analgesics may be discontinued as progressive neuronal damage from DM occurs, the pain of acute diabetic neuropathy may disappear within the first year. Chronic, painful diabetic neuropathy is difficult to treat but may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, nonsteroidal anti-inflammatory agents (should be avoided in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream). There may be a need to refer to a pain management center.

Treatment of orthostatic hypotension after autonomic neuropathy is quite difficult. Various agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine) but each of them has significant side effects. Nonpharmacologic choices (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity supporting hose) may be somewhat helpful.

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

The motility and function of gastrointestinal (GI) and genitourinary systems may be affected by continuous type 1 and 2 DM. To the common GI symptoms belong delayed gastric emptying (gastroparesis) and alterations in small- and large-bowel motility (constipation or diarrhea). Gastroparesis may be accompanied with anorexia, nausea, vomiting, early satiety, and bloating of the abdomen. The best study to document delayed gastric emptying is nuclear medicine scintigraphy after ingestion of a radiolabeled meal, but noninvasive “breath tests” following ingestion of a radiolabeled meal are being developed. Though parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also damages gastric emptying. Nocturnal diarrhea, alternating with constipation, is the usual indicator of DM-related GI autonomic neuropathy. If these symptoms are present in type 1 DM, examination for celiac sprue has to be carried out because of its increased frequency. Esophageal dysfunction in long-standing diabetic autonomic neuropathy may cause genitourinary dysfunction including cystopathy, erectile dysfunction, and female

sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication).

TREATMENT

Modern therapy for these complications of DM is not sufficient. Improved glycemic control should be a primary goal, because some aspects (neuropathy, gastric function) may improve. To relieve the symptoms of gastroparesis it may be recommended to have smaller, frequent meals that are easier to digest (liquid) and low in fat and fiber. Cisapride (10 to 20 mg before each meal) is probably the most effective drug, but has been removed from administration in the United States, and allowed only under special conditions. Other effective agents include dopamine agonists (metoclopramide, 5-10 mg, and domperidone, 10-20 mg, prior to each food intake) and bethanechol (10-20 mg prior to each food intake). Erythromycin interacts with the motilin receptor and may faciliate gastric emptying. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically with loperamide but may respond to clonidine at higher doses (0.6 mg tid) or octreotide (50 to 75 μg subcutaneously). Treatment of bacterial overgrowth with antibiotics is sometimes beneficial.

Diabetic cystopathy should be treated with timely urination or self-catherization. Drugs (bethanechol) are inconsistently effective. The medicine of choice for erectile dysfunction is sildenafil, however the efficiency in patients with DM is slightly lower than in the nondiabetic patients. Vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement may improve sexual dysfunction in women.

CARDIOVASCULAR MORBIDITY AND MORTALITY

Patients with diabetes may have no chest pain ("silent ischemia"), and a thorough cardiac examination is required in individuals undergoing major surgical procedures. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors common for the diabetic patients include microalbuminuria, gross proteinuria, an increased creatinine, and abnormal platelet function. Insulin resistance, indicated by elevated serum insulin levels, is associated with an increased risk of cardiovascular complications in individuals with and without DM. Diabetes is also connected with endothelial, vascular smooth muscle, and platelet dysfunction. Besides coronary artery disease, patients with DM are likely to suffer from cerebrovascular disease (threefold increase in stroke). There is high incidence of congestive heart failure (diabetic cardiomyopathy) in individuals with DM. The etiology of this disorder includes factors such as myocardial ischemia due to atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

TREATMENT

Usually there are no peculiarities of treatment of coronary disease for the diabetic individuals. Revascularization procedures for coronary artery disease, in particular, percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG) are not so efficient for the diabetic individuals. Initial success rates of PCI in diabetic patients are similar to those in the nondiabetic individuals, but diabetic patients have higher rates of restenosis and lower long-standing patency and survival rates. The use of stents and a GPIIb/IIIa platelet inhibitor proved effective for diabetic patients. Perioperative death rates from CABG are not altered in DM, but both short- and long-term survival are reduced. Recent experiments indicate that diabetic individuals with multivessel coronary artery disease or recent Q-wave MI have better long-term survival rate with CABG than PCI.

The ADA is crucial in glycemic control and modification of aggressive cardiovascular risk in all individuals with DM. Past trepidation about using beta blockers in individuals with diabetes should not prevent use of these agents since they are effective for diabetic patients after MI. ACE inhibitors may also be especially beneficial and should be administered for patients with type 2 DM and other risk factors (smoking, dyslipidemia, microalbuminuria, history of cardiovascular disease).

Antiplatelet therapy reduces cardiovascular problems in individuals with DM suffering from coronary artery disease. It is recommended by ADA to use aspirin for secondary prevention of coronary problems. Although there is no sufficient data proving effectiveness in primary prevention of coronary events in DM, antiplatelet therapy should be strongly considered, especially in diabetic individuals with other coronary risk factors such as hypertension, smoking, or dyslipidemia. The dose of aspirin (81-325 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not affect negatively the renal function or hypertension, nor does it influence the course of diabetic retinopathy.

Cardiovascular Risk Factors

DYSLIPIDEMIA

The majority of diabetic dyslipidemia studies have been carried out in individuals with type 2 DM due to high frequency of dyslipidemia in this form of diabetes. Interventional studies have revealed that the positive effects of LDL reduction are similar in the diabetic and nondiabetic populations. The course of the treatment of hyperlipidemia, based on the guidelines provided by the ADA and the American Heart Association, is: (1) decrease the LDL cholesterol, (2) raise the HDL cholesterol, and (3) lower the triglycerides. A treatment method depends on the range of lipoprotein abnormalities. Primary therapy for all forms of dyslipidemia includes diet and life-style changes advised for the nondiabetic individuals (smoking cessation, blood pressure control, weight loss, increased physical activity). The dietary recommendations for patients with DM correspond to those suggested by the National Cholesterol Education Program and encompass an increase in

monounsaturated fats and carbohydrates and a decrease in saturated fats and cholesterol. The effect of dietary alterations is usually modest [<0.6-mmol/L (<25-mg/dL) reduction in the LDL], though not less important. Improvement in glycemic control lowers triglycerides and has a slight positive effect on raising HDL. HMG CoA reductase inhibitors are efficient for lowering the LDL. Recent data show that an HMG CoA reductase inhibitor has been successful in all patients over 40 with diabetes and total cholesterol >135 mg/dL. When the HDL is low, fibric acid derivatives should be considered as they have certain efficacy. The combination of an HMG CoA reductase inhibitor and fibric acid derivative may be helpful but increases the probability of myositis. Nicotinic acid raises HDL effectively, but in high doses (>2 g/d) may worsen glycemic control and increase insulin resistance. In case of hypertriglyceridemia bile acid-binding resins are not to be used.

HYPERTENSION

Hypertension can worsen other complications of DM, especially cardiovascular diseases and nephropathy. The treatment of hypertension should first of all include life-style changes such as weight loss, exercise, stress management, and sodium restriction. Antihypertensive agents should be selected based on the advantages and drawbacks of the therapeutic agent taking into consideration an individual patient's risk factor profile. DM-related considerations are the following:

- ACE inhibitors are either glucose- and lipid-neutral or glucose- and lipid-beneficial and thus are beneficial in case of cardiovascular risk profile.
- α-Adrenergic blockers slightly improve insulin resistance and have a positive effect on the lipid profile, while beta blockers and thiazide diuretics can enhance insulin resistance and negatively influence the lipid profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid- and glucose-neutral.
- Beta blockers may slightly increase the risk of type 2 DM development. There are no restrictions for beta blockers in most patients with diabetes and they reduce cardiovascular conditions, though often their use is questioned because of the potential masking of hypoglycemic symptoms.
- Sympathetic inhibitors and α-adrenergic blockers may enhance orthostatic hypotension in the diabetic patients with autonomic neuropathy.
- Equivalent decrease in blood pressure with the help of various classes of agents may not assure equivalent protection against cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs positively influence cardiovascular consequences (MI or stroke). ACE inhibitors (in types 1 and 2 DM) and ARBs (in type 2 DM) slow the development of diabetic renal disease.
- It is advised to use non-dihydropyridine calcium channel blockers (verapamil and diltiazem), rather than dihydropyridine agents (amlodipine and nifedipine), in diabetics.

Most prefer ARBs to ACE inhibitors in type 2 DM with hypertension and microalbuminuria. In case of normal excretion of albumin, an ACE inhibitor is commonly prescribed initially. Non-dihydropyridine calcium channel blockers, α-adrenergic blockers, and central adrenergic antagonists may be additional or second-line agents. Since it is not easy to control hypertension with a single medication (especially in type 2 DM), multiple antihypertensive agents are usually administered when blood pressure goals (<130/80 mmHg) are not achieved.

LOWER EXTREMITY COMPLICATIONS

DM is the leading cause of nontraumatic lower extremity amputation all over the world. Foot ulcers and infections are also a major cause of morbidity in individuals with DM. The combination of several pathogenic factors: neuropathy, damaged foot biomechanics, peripheral arterial disease, and poor wound healing are the reasons of the high probability of these disorders in DM. The peripheral sensory neuropathy inhibits normal protective mechanisms and enables the patient to sustain major or repeated minor trauma to the foot, often without being aware of the injury. Disordered proprioception causes abnormal weight bearing while walking and further formation of callus or ulcers. Motor and sensory neuropathy cause abnormal foot muscle mechanics and structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint). Autonomic neuropathy leads to anhidrosis and damaged superficial blood flow in the foot, which cause dry skin and fissure formation. Peripheral arterial disease and poor wound healing inhibit resolution of minor breaks in the skin, thus they grow and become infected.

Approximately 15% of patients with DM suffer from a foot ulcer, and many of them ultimately need amputation (14 to 24% risk with subsequent ulceration). Risk factors for foot ulcers or amputation are the following: male sex, diabetes >10 years duration, peripheral neuropathy, abnormal structure of foot (bone abnormalities, callus, and thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation, and poor glycemic control.

TREATMENT

The most effective therapy for foot ulcers and amputations is prevention by identification of high-risk patients, educating them, and taking measures to prevent ulceration. High-risk patients should be detected during the routine foot examination performed on all patients with DM. Instruction of the patient should emphasize: (1) careful choice of footwear, (2) daily examination of the feet to detect early indicators of poor-fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and (5) immediate consultation with a physician if an abnormality arises. Patients at high risk for ulceration or amputation have the possibility to consult a foot care specialist. Preventive measures for risk factor modification include orthotic shoes and devices, callus management, nail care, and lowering increased skin pressure from abnormal bone architecture. Attention to other

risk factors of vascular diseases (smoking, dyslipidemia, and hypertension) and constant glycemic control are also important.

Since lower extremity lesions have multifactorial pathogenesis, treatment of these ulcers is multidisciplinary and often requires expertise in orthopedics, vascular surgery, endocrinology, podiatry, and infectious diseases. The plantar surface of the foot is the most common risk area of ulceration. Ulcers may be initially neuropathic (no accompanying infection) or may have surrounding cellulitis or osteomyelitis. Cellulitis without ulceration is common and should be treated with wide-spectrum antibiotics, including anaerobes.

An infected ulcer is a clinical diagnosis, since superficial culture of any ulceration is likely to find various bacterial pathogens. The infection surrounding the foot ulcer is often the result of various organisms (gram-positive and gram-negative organisms and anaerobes), gas gangrene may also develop in the absence of clostridial infection. The most helpful cultures are those taken from the debrided ulcer base or from purulent drainage. Wound depth should be determined with inspection and probing with a blunt-tipped sterile instrument. Simple radiographs of the foot should be carried out to identify the risk of osteomyelitis in chronic ulcers that have not responded to treatment.

Osteomyelitis is successfully treated with a combination of prolonged antibiotics (IV then oral) and also the debridement of infected bone. Peripheral arterial bypass procedures often enhance wound healing and decrease the need for amputation of the ischemic limb.

There are also numerous other possible therapies for diabetic foot ulcers, but they have yet to prove high efficiency in future, controlled tests. A recent consensus statement from the ADA identified six evidently effective interventions in diabetic foot wounds: (1) off-loading, (2) debridement, (3) wound dressings, (4) appropriate use of antibiotics, (5) revascularization, and (6) limited amputation.

INFECTIONS

Patients with DM are prone to higher incidence and severity of infection, the reasons include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization. Hyperglycemia enhances the colonization and growth of a various organisms (Candida and other fungal species). Many common infections are more frequent and severe in the diabetics, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of the latter category include rhinocerebral mucormycosis, emphysematous infections of the gall bladder and urinary tract, and “malignant” or invasive otitis externa.

DERMATOLOGIC MANIFESTATIONS

The most common skin indicators of DM are protracted wound healing and skin ulcerations. Diabetic dermopathy, also known as pigmented pretibial papules, or “diabetic skin spots,” begins as an erythematous area and develops into an area of

circular hyperpigmentation. These lesions are caused by minor mechanical trauma in the pretibial region and are more common in elderly men with DM. Bullous diseases (shallow ulcerations or erosions in the pretibial region) are also seen. Necrobiosis lipoidica diabeticorum is a rare disorder of DM that commonly affects young women with type 1 DM, neuropathy and retinopathy. Acanthosis nigricans (hyperpigmented velvety plaques on the neck, axilla, or extensor surfaces) may indicate severe insulin resistance and accompanying diabetes.

HYPOGLYCEMIA

People with type 1 diabetes mellitus, taking insulin in full replacement doses, are most prone to hypoglycemia episodes. It is usually mild enough to reverse by eating or drinking carbohydrates, but blood glucose occasionally can drop quickly enough and quite low to provoke unconsciousness before hypoglycemia can be diagnosed and reversed. Severe hypoglycemia may cause unconsciousness during sleep, due to prolonged exercise earlier in the day or eating less than usual. Sometimes it is difficult to recognize the symptoms of early hypoglycemia.

Unconsciousness caused by hypoglycemia can occur within 20 minutes to an hour after onset of early symptoms and is not usually preceded by other illness or symptoms. It may be accompanied by twitching or convulsions. A person unconscious from hypoglycemia is usually pale, has a rapid heart rate, and perspires heavily: all signs of the adrenaline reaction to hypoglycemia. The patient is not usually dehydrated and breathing is normal or shallow. The blood sugar level, measured with a glucose meter or laboratory measurement at the time of discovery, is usually low but not always severe, and in some cases may have already risen from the nadir that caused the unconsciousness.

Hypoglycemia induced unconsciousness is treated by raising the blood glucose with intravenous glucose or injected glucagon.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Male patient, aged 56, with type 2 diabetes mellitus during 10 years, takes gliburide regularly 5 mg 3 times a day, recently lost weight, haven't visited endocrinologist for the last 3 years. During inspection there were detected: blackened nail on the right foot, cold foot, and weakened pulsation. Fasting glucose in blood is 11.0 mmol/l, glucosurea is 2.0 %.

1. What is this patient's complication?
2. Choose the way of treatment of this patient.

Case 2.

Child, 11 years old presents with relapse of furunculosis. Fasting blood glucose is 8.5mmol/l, glucose and acetone in urine are absent.

1. What is the most likely diabetic complication?
2. What treatment will you order?

Case 3.

Male patient, aged 56, with type 2 diabetes mellitus during 10 years, takes gliburide regularly 5 mg 3 times a day, recently lost weight, haven't visited endocrinologist for the last 3 years. During inspection blackened nail on the right foot, cold feet, and weakened pulsation were detected. Fasting glucose in blood is 11.0 mmol/l, glucoseurea is 2.0 %.

1. What is this patient's complication?
2. Choose the way of treatment of this patient.

Case 4.

Patient M., 36 y/o, was found in the street unconscious. The patient has a medical history of diabetes. There is a smell of alcohol from the mouth. The skin is moist, warm, arterial pressure – 145/90 mm column of mercury, convulsive twitching of muscles. Breathing is shallow, eye ball tone is retained, pupils are dilated, hyperflexion.

1. What kind of coma can be suspected?
2. How would you treat this patient?

2.2 Decompensation state in Diabetes Mellitus. Diabetic ketoacidosis.

Year of study: 6.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 6.

1 Professional motivation: Acute diabetic complications can be considered as a variety of diabetic metabolic abnormalities. The most common acute diabetic comorbidities are: (1) diabetic ketoacidosis, (2) hyperosmolar non ketotic diabetic coma, (3) hypoglycemia, (4) lactic acidosis.
Diabetic ketoacidosis (DKA) is a potentially life-threatening condition in patients with diabetes mellitus. It occurs predominantly in patients with type 1 diabetes, but it can occur in individuals with type 2 diabetes under certain conditions. DKA results from a lack of insulin; in response the body starts burning fatty acids and producing acidic ketone bodies that provoke most of the symptoms and complications. DKA may be the first symptom of previously undiagnosed diabetes, but it may also occur in people diagnosed with diabetes as a result of a variety of causes, such as opportunistic illness or poor compliance with insulin therapy. The typical symptoms are vomiting, dehydration, deep gasping breathing, confusion and occasionally coma. DKA is diagnosed by means of blood and urine tests; it is distinguished from other, rarer forms of ketoacidosis by the presence of high blood sugar levels. Treatment includes intravenous fluids to correct dehydration, insulin to inhibit the production of ketone bodies, treatment for any underlying causes such as infections, and close monitoring to prevent and identify complications. DKA is a medical emergency, and if untreated, it can lead to death. DKA was first described in 1886; until the introduction of insulin therapy in the 1920s it was almost universally fatal. The mortality now constitutes less than 1% due to proper and timely treatment. Diabetic ketoacidosis occurs in 4.6–8.0 per 1000 people with type 1 diabetes every year. The risk is increased in individuals with an ongoing risk factor, for example, eating disorder, and in those who cannot afford insulin. There has been a reported increasing trend to hospital admissions. About 30% of children with type 1 diabetes are diagnosed after an episode of DKA.

2 Study aim of this lesson.
To acquaint students with modern therapy of type 2 diabetes mellitus, side effects of insulin treatment (α=1)

In the study process students should know (α=2):

- stages of diabetic compensation, and diagnostic criteria of each stage, as well as setting goals of therapy,
- clinical picture of the main endocrine emergencies,
- treatment of acute diabetic states,
- prevention of acute diabetic complications.

In the study process student should be able to (α=3):

- establish a stage of compensation,
- differentiate variant of acute complication,
- prescribe agents IV and oral drugs, used to treat acute diabetic complications,
- discern ketoacidosis from other acute complications,

3 Educational aim of this lesson

Is to focus attention on modern treatment of diabetic ketoacidosis.

4. Interdisciplinary integration (see Table 4).

Table 4

Interdisciplinary integration

Discipline	To know	How to do
I. Previous general anatomy and physiology, histology, pathological anatomy and physiology, pharmacology	Pancreas (location, morphology, function); hormones, regulation	To estimate physiological reserve of pancreas in order to prescribe proper treatment (doses and methods) To prescribe medications.
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology, Nephrology Ophthalmology.	Main clinical signs of Diabetes Mellitus, its types, differential diagnosis, treatment	To make clinical observation, prescribe proper diagnostic assays, consultation of associative specialists for verification ofdiagnosis.
III. Interdisciplinary integration	Contemporary methods of treatment of diabetic emergencies	To prescribe adequate treatment of diabetes mellitus and diabetic ketoacidosis.

5. Contents of the lesson.

- Stages of diabetic compensation and diagnostic criteria of each stage.
- Diabetic acidosis: pathophysiology, precipitating factors, signs and symptoms, diagnosis, initial laboratory investigations, treatment, prevention.
- Hyperosmolar coma: pathophysiology, precipitating factors, presentation, diagnosis, treatment.
- Lactic acidosis: pathophysiology, presentation, diagnosis, treatment.
- Diabetes mellitus and pregnancy: diagnostic strategies, treatment.
- Differential diagnostics of emergency states.

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Patient K., suffering from diabetes mellitus during the last 8 years, is in coma. The skin is dry, Kussmaul's respiration, acetone breath is evidenced. What type of coma is it?

A) Hypoglycemic coma
B) Lactic acidosis
C) Hyperosmolar state
D) Ketoacidosis
E) Brain coma

#2
Metformin is contraindicated in all of the following situations, except:

A) Increased BMI
B) Tendency to develop lactic acidosis
C) Diarrhea and other gastrointestinal disturbances
D) Pregnancy
E) Breast feeding

#3
Which of the following medications does not have hypoglycemic effects (does not augment insulin activity)?

A) Loop diuretics
B) Somatostatin analogues
C) MAO inhibitors
D) ACE inhibitors
E) Beta- blockers

#4
What insulin dose is used for coma secondary to diabetic ketoacidosis?

A) 0.1 U/кg/hr
B) 1 U/кg/hr
C) 80-100 U/24 hours
D) 40-60 U/24 hours
E) 100-200 U/24 hours

7.2. Recourses for the main stage of the lesson.

SIGNS AND SYMPTOMS

The symptoms of diabetic ketoacidosis commonly appear within about 24 hours. The major symptoms are nausea and vomiting, severe thirst, excessive urine production and abdominal pain that may be acute. Individuals who measure their glucose levels themselves may notice elevated blood sugar levels – hyperglycemia. In severe cases of DKA, breathing is difficult, deep and of gasping character (a condition known as "Kussmaul respiration"). The abdomen may be tender to the point that an acute abdomen may be suspected, such as acute pancreatitis, appendicitis or gastrointestinal perforation. Coffee ground vomiting (vomiting of altered blood) occurs in some patients; this is caused by an erosion of the esophagus. Confusion, lethargy, stupor or even coma (a marked decreased consciousness) may be the result of severe DKA.

Physical examination usually reveals clinical evidence of dehydration, such as a dry mouth and decreased skin turgor. If the dehydration is severe enough to cause a decrease in the circulating blood volume, tachycardia and hypotension may be observed. Often, a "ketotic" or "fruity" odor is present, compared to the smell of pear drops scent of which is a ketone. Kussmaul respiration is reflected in an increased respiratory rate.

Young children with DKA are relatively susceptible to cerebral edema (swelling of the brain tissue), which may lead to headache, coma, loss of the pupillary light reflex, and even death. It occurs in 0.3–1.0% of children with DKA, and has been recorded

in young adults, but is generally very rare in adults. It accounts for a 20–50% mortality rate.

CAUSE

Patients with diabetes are most often prone to DKA, but it may also be the first manifestation in someone who had not previously been diagnosed with diabetes. There is often a certain underlying cause that has led to the DKA episode; this may be intercurrent illness (pneumonia, influenza, gastroenteritis, a urinary tract infection), pregnancy, inadequate insulin administration (e.g. faulty insulin pen device), myocardial infarction (heart attack), stroke or cocaine abuse. Young patients with recurrent episodes of DKA may have an underlying eating disorder, or may be using insufficient insulin not to gain weight.

Diabetic ketoacidosis may be diagnosed in individuals previously known to have diabetes mellitus type 2 or in those who on further examinations turned out to have features of type 2 diabetes (e.g. obesity, strong family history); African, African-American and Hispanic people are more likely to have this problem. Their condition is known as "ketosis-prone type 2 diabetes".

MECHANISM

Diabetic ketoacidosis is caused by insufficiensy of insulin in the body. The lack of insulin and subsequent increase of glucagon leads to elevated release of glucose by the liver (a process that is normally suppressed by insulin) from glycogen and through glyconeogenesis. High glucose levels leak into the urine, taking water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. This results in polyuria, dehydration, and compensatory thirst and polydipsia. The lack of insulin also causes the release of free fatty acids from adipose tissue (lipolysis), which are converted in the liver, into ketone bodies (acetoacetate and β-hydroxybutyrate). β-Hydroxybutyrate can serve as an energy source in absence of insulin-mediated glucose delivery, and is a protective mechanism in case of starvation. However, the ketone bodies have a low pKa and turn the blood acidic (metabolic acidosis). The body initially buffers the change with the bicarbonate buffering system, but this system is soon exhausted and other mechanisms must work to compensate for the acidosis. One such mechanism is hyperventilation to decrease the bloodcarbon dioxide levels (a form of compensatory respiratory alkalosis). Such severe hyperventilation may be observed as Kussmaul respiration. In some situations such as infection, insulin demands rise but are not matched by the failing pancreas. The level of sugar in blood rises, dehydration ensues, and resistance to the normal effects of insulin increases further by way of a vicious circle.

Thus, the above-described mechanisms cause a total body water shortage of about 6 liters (or 100 mL/kg) in the average adult DKA patient, besides substantial shortages

in sodium, potassium, chloride, phosphate, magnesium and calcium occur. Levels of glucose usually exceed 13.8 mmol/L or 250 mg/dL.

Although β-hydroxybutyrate chemically contains a carboxylic acid instead of a ketone, it is the principal "ketone body" in diabetic ketoacidosis. DKA is frequent in type 1 diabetes, because this form of diabetes is characterized by an absolute deficiency of insulin production by the islets of Langerhans. In type 2 diabetes, insulin is produced but it is not sufficient to meet the body's requirements as a result of end-organ insulin resistance. Commonly, these amounts of insulin are enough to inhibit ketogenesis. If a patient with type 2 diabetes suffers DKA, the condition is called "ketosis-prone type 2 diabetes". The exact mechanism for this phenomenon has not been discovered, but there is evidence both of impaired insulin secretion and insulin action. Insulin is still produced and often the patient may be able to resume diet or tablet treatment as normally recommended in type 2 diabetes if the condition has been treated.

The clinical condition of DKA is characterised, besides the above-mentioned, by the production of various counterregulatory hormones such as glucagon and adrenaline as well as cytokines, the latter leading to increased inflammation markers, even in the absence of infection. The most dangerous complication of DKA is cerebral edema, which is the result of numerous factors. Some authors suggest that it is the result of excessive fluid replacement, but the complication may develop prior to treatment. Patients with more severe DKA and with the first occurrence of DKA are more prone to it. Possible causes of the cerebral edema development are dehydration, acidosis and low carbon dioxide levels; additionally, the increased level of inflammation and coagulation may, in combination with these factors, lead to decreased blood flow to parts of the brain, which swells when fluid replacement has been commenced. The swelling of the brain tissue leads to increased intracranial pressure which is eventually fatal.

DIAGNOSIS. INVESTIGATIONS

Diabetic ketoacidosis may be diagnosed when the combination of hyperglycemia (high blood sugar), ketones in the blood or on urinalysis and acidosis are present. Arterial blood gas measurement of a sample of blood from an artery is usually the way to detect the acidosis. Further measurements (to ensure treatment is successful), may be taken from a normal blood test from a vein, as there is little difference between the arterial and the venous pH.

In addition, blood samples are usually taken to measure urea and creatinine (measures of kidney function, which may be damaged in DKA as a result of dehydration) and electrolytes. Infection markers (complete blood count, C-reactive protein) and acute pancreatitis (amylase and lipase) may also be measured. In order to exclude infection chest radiography and urinalysis are usually carried out.

Computed tomography may be required to evaluate the severity of cerebral edema if it is suspected because of confusion, recurrent vomiting or other symptoms in order to exclude other causes such as stroke.

CRITERIA

Diabetic ketoacidosis is distinguished from other diabetic emergencies by the presence of large amounts of ketones in the blood and urine, and evident metabolic acidosis. Hyperosmolar hyperglycemic state (HHS, sometimes termed "hyperosmolar non-ketotic state" or HONK) occurs more often in type 2 diabetes and is associated with increased plasma osmolarity (above 320 mosm/kg) due to severe dehydration and concentration of the blood; mild acidosis and ketonemia may be present in this condition, but not to the extent observed in DKA. In DKA the osmolarity may also be increased, since there is a degree of overlap between DKA and HHS.

Ketoacidosis is not always associated with diabetes, it may also be caused by alcoholism and starvation; in both conditions the glucose level is normal or low. Patients with diabetes may have metabolic acidosis for other reasons, such as poisoning with ethylene glycol or paraldehyde.

The American Diabetes Association categorizes DKA in adults into one of three stages of severity:

- *Mild:* blood pH mildly falls to between 7.25 and 7.30 (normal 7.35–7.45); serum bicarbonate decreased to 15–18 mmol/l (normal above 20); the patient is alert
- *Moderate* pH 7.00–7.25, bicarbonate 10–15, the patient may feel mild drowsiness
- *Severe:* pH below 7.00, bicarbonate below 10, stupor or coma may occur

A 2004 statement by the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (for children) uses slightly different criteria, where mild DKA is defined by pH 7.20–7.30 (bicarbonate 10–15 mmol/l), moderate DKA by pH 7.1–7.2 (bicarbonate 5–10) and severe DKA by pH<7.1 (bicarbonate below 5).

PREVENTION

Attacks of DKA can be prevented in patients with diabetes to an extent by adherence to "sick day rules"; these are instructions to patients how to treat themselves when unwell, namely, how much extra insulin to take when sugar levels are uncontrolled, an easily digestible diet rich on salt and carbohydrates, means to suppress fever and treat infection, and recommendations when to search medical help.

MANAGEMENT

The main goals in the treatment of diabetic ketoacidosis are replacement of the lost fluids and electrolytes while suppressing the high blood sugars and ketone

production with insulin. Hospitalisation to an intensive care unit or similar high-dependency area or ward for close monitoring may be required.

FLUID REPLACEMENT

The amount of fluid depends on the degree of dehydration. If dehydration is so severe that it leads to shock (considerably lowered blood pressure with insufficient blood supply to the body organs), or a depressed consciousness, rapid infusion of saline (1 liter for adults, 10 ml/kg in repeated doses for children) is recommended to restore circulating volume. Slower rehydration based on calculated water and sodium lack take place if the dehydration is moderate, and saline is also the recommended fluid. Very mild ketoacidosis not accompanied by vomiting and mild dehydration may be treated with oral rehydration and subcutaneous rather than intravenous insulin under observation for indicators of worsening. A special but not very common measure is cardiogenic shock, where the blood pressure is decreased not due to dehydration, but because of inability of the heart to push blood through the blood vessels. Such situation requires ICU admission, observation of the central venous pressure (by insertion of a central venous catheter into a large upper body vein), and the administration of medication that amplifies the heart pumping action and increases blood pressure.

INSULIN

Some guidelines suggest a bolus (initial large dose) of insulin in the dose of 0.1 unit of insulin per kilogram of body weight. It can be administered immediately after the potassium level is higher than 3.3 mmol/l; if the level is lower, use of insulin could cause a dramatically low level of potassium (described below). Other guidelines recommend delaying the onset of insulin until fluids are administered. Commonly, insulin is used at 0.1 unit/kg per hour to decrease the blood sugars and suppress ketone production. Recommendations differ as to which dose to use when blood sugar levels start falling; some advise reducing the dose of insulin when glucose falls below 16.6 mmol/l (300 mg/dl), but some recommend administering glucose in addition to saline to allow for ongoing infusion of higher doses of insulin.

POTASSIUM

Potassium levels can fluctuate considerably in the process of DKA treatment, since insulin decreases potassium levels in the blood by redistributing it into the cells. A large part of the shifted extracellular potassium would have been lost in urine because of osmotic diuresis. Hypokalemia (low blood potassium concentration) often occurs after treatment and this increases the risk of dangerous abnormalities in the heart rate. Thus, constant observation of the heart rate is recommended, as well as repeated measurement of the potassium levels and addition of potassium to the intravenous fluids if levels fall below 5.3 mmol/l. If potassium levels are lower than

3.3 mmol/l, it may be necessary to discontinue insulin use in order to allow correction of the hypokalemia.

BICARBONATE

The used of sodium bicarbonate solution to rapidly improve the acid levels in the blood is controversial. It has not been proven clearly that it improves the result beyond standard therapy, and really some evidence exists that it may improve the acidity of the blood, but may also worsen acidity inside the body cells and increase the risk of certain complications. Therefore its use is not advised, although some guidelines recommend it in extreme acidosis (pH<6.9), and smaller amounts for severe acidosis (pH 6.9–7.0).

CEREBRAL EDEMA

Cerebral edema, if associated with coma, often requires admission to intensive care unit, artificial ventilation, and close observation. The administration of fluids is slowed. The perfect treatment of cerebral edema in DKA is not defined, but intravenous mannitol and hypertonic salines (3%) are used – as well as in other forms of cerebral edema – in order to reduce the swelling.

RESOLUTION

Resolution of DKA is a general improvement in the symptoms, such as the ability to sustain oral nutrition and fluids, normalization of blood acidity (pH>7.3), and absence of ketones in the blood (<1 mmol/l) or urine. If the patient has reached this condition, in one hour the intravenous administration can be stopped and insulin may be administered in the usual subcutaneous regimen.

If a patient is suspected to have ketosis-prone type 2 diabetes, it is necessary to determine antibodies against glutamic acid decarboxylase and islet cells to help in the decision whether to continue insulin use long-term (if antibodies are detected), or stop insulin and try treatment with oral agents as in type 2 diabetes.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.

Patient C., 32 y/o, was delivered unconscious to the intensive care department. The patient has a medical history of diabetes. Insulin was not found. The breathing is noisy, of Kussmaul's type; acetone breath, the skin is dry, turgor is lowered, the facial features are sharp, periosteal reflexes are absent, eye ball tone is lowered. Blood contains 1.2 mmol/l of lactic acid (norm – 0.62-1.3 mmol/l), glycemia – 29 mmol/l.

3. What kind of coma can be suspected?
4. How would you manage this patient?

Case 2.
Patient T., 66 y/o, complains of stomach ache, nausea, vomiting and muscle ache. Objectively: evident symptoms of dehydration, Kussmaul's breathing, arterial pressure – 90/50 mm column of mercury, anuria, temperature – 35.9 ºC, glycemia – 12.9 mmol/l, no acetonuria, blood PH – 6.8, lactic acid content – 1.7 mmol/l (norm – 0.62 – 1.3 mmol/l).

1. What is your diagnosis?
2. What are you going to do in this case?

Case 3.
Patient M., 57 y/o, complains of nausea, vomiting and muscle ache. Objectively: evident symptoms of dehydration, Kussmaul's respiration, arterial pressure – 90/50 mm column of mercury, anuria, temperature – 35.9 ºC, glycemia – 12.9 mmol/l, no acetonuria, blood PH – 6.8, lactic acid content – 1.7mmol/l (norm – 0.62 – 1.3 mmol/l). Hyperlactacidemic coma has been diagnosed.

1. What is the differential diagnosis?
2. What therapeutic measures should be taken first of all?

Case 4.
Patient M., 72 y/o, is in the intensive care unit with the symptoms of dehydration, oliguria, hypothermia and hypoxia. In anamnesis there is a record of type 2 diabetes mellitus, the patient was treated with biguanides. Her condition began to deteriorate after she had a myocardial infarction one month ago. Objectively: the skin is dry; turgor is lowered, arterial pressure – 80/40 mm column of mercury, pulse – 136 beats/minute. The breathing is shallow, eye ball tone is lowered.

1. What is your diagnosis?
2. What are you going to do in this case?

2.3 Thyroid goiter. Thyroid storm.

Year of study: 6.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 6.

1 Professional motivation: Thyroid storm, also termed thyrotoxic crisis, is an acute, life-threatening, hypermetabolic condition induced by excessive production of the thyroid hormones (THs) in individuals with thyrotoxicosis. Thyroid storm may be the initial manifestation of thyrotoxicosis in undiagnosed children, especially in neonates. The clinical signs are fever, tachycardia, hypertension, and neurological and GI abnormalities. Hypertension may be followed by congestive heart failure that is associated with low blood pressure and shock. Early diagnosis and aggressive treatment are very important, because thyroid storm is almost always fatal if left untreated. Fortunately, this condition is extremely rare in children.

Diagnosis is primarily clinical, and there are no specific laboratory tests. Several factors may precipitate the progression of thyrotoxicosis to thyroid storm. In the past, thyroid storm was commonly observed during thyroid surgery, especially in older children and adults, but improved preoperative management has markedly decreased the incidence of this complication. Today, thyroid storm is more commonly as a medical crisis rather than a surgical crisis.

The incidence of thyrotoxicosis increases with age. Thyrotoxicosis may affect approximately 2% of older women, children constitute less than 5% of all thyrotoxicosis cases. Grave's disease is the most common cause of childhood thyrotoxicosis and, it affects 0.2-0.4% of children and adolescents. Nearly 1-2% of neonates, born to mothers with Graves's disease, experience thyrotoxicosis.

Thyroid storm is an acute, life-threatening condition. The mortality rate among adults is extremely high (90%) if early diagnosis is not made and the patient is left untreated. Because of better thyrotoxicosis control and early management of thyroid storm, adult mortality rates have droped to less than 20%. Thyrotoxicosis is 3-5 times more common in females than in males, especially among pubertal children. Thyroid storm affects a small percentage of patients with thyrotoxicosis. The incidence is reported to be higher in females; however, no specific records concerning sex-related incidence are available. Neonatal thyrotoxicosis occurs in 1-2% of neonates born to mothers with Grave's disease. Infants under 1 year constitute only 1% of childhood thyrotoxicosis. More than two thirds of all cases of thyrotoxicosis occur in children aged 10-15 years. In general, thyrotoxicosis occurs most commonly during the third and fourth decades of life. Thyroid storm is more common in this adolescents, although it can occur in patients of all ages.

2. Study aim of this lesson.
To acquaint students with therapy of thyroid emergency – thyroid storm, management and treatment strategies, as well as to understand diagnostics and treatment of goiter (α=1).

In the study process students should know (α=2):
classification of thyroid disorders, diagnosis, therapy, follow-up.

In the study process student should be able to (α=3):

- carry out the examination of the thyroid gland (technique for physical examination of the thyroid gland),
- note the gland texture, mobility, tenderness and the presence of nodules (in addition to palpating for size),
- evaluate thyroid gland function,
- interpret thyroid uptake and imaging, sonography, computed tomography,
- differentiate thyroid disorders,
- order replacement treatment in the case of hypothyroidism,
- prescribe preventive treatment on iodine deficiency?
- treat thyroid storm.

3. Educational aim of this lesson.
To focus attention on differential diagnosis of thyroid disorders, prophylaxis of iodine deficiency, early recognition of thyroid storm.

4. Interdisciplinary integration (see Table 5).

Table 5

Interdisciplinary integration

Discipline	To know	How to do
I. Previous General anatomy and physiology, histology, pathological anatomy, and physiology, pharmacology, radiology	Thyroid gland (location, morphology, regulation and hormone synthesis, embryogenesis). Synthetic preparations of L-T4. Thyroid sonography, computed tomography and magnetic resonance imaging	To estimate physiological function of the thyroid gland. To prescribe medications.
II. Future Internal medicine Pediatrics		To make clinical observation, to recommend proper diagnostic

Surgery Obstetrics & Gynecology Neurology	Main clinical signs of thyroid disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment, prophylactics.	assays, consultation of associative specialists for verification of diagnosis, to prescribe medication
Discipline	**To know**	**How to do**
III. Interdisciplinary integration	Contemporary methods of diagnosis and treatment	To prescribe adequate treatment

5. Contents of the lesson.

- Endemic and sporadic goiter (pathogenesis, clinical picture).
- Inborn iodine deficiency (clinical features, treatment, prognosis).
- Iodine deficiency and pregnancy.
- Incidence of iodine deficiency (causative factors, outcomes).
- Treatment and management goiter
- The main etiological factors, pathogenesis, clinical appearance, laboratory findings, and treatment of thyrod storm.
- Prevention of thyroid storm.

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.
7.1. Recourses for preliminary stage of the lesson
Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Symptoms of hyperthyroidism are, except:
A) Increased heat production
B) Increased metabolism
C) Tachycardia
D) Exophthalmia
E) Weight gain

#2
Choose correct statement relatively to the detrimental action of increased thyroid hormone production.
A) T_3 and T_4 cause hyperprolactinemia
B) T_3 sensitises the myocardium to the effects of catecholamines

C) Weight gain is related with thyroid overproduction
D) T_4 directly induce tachycardia
E) Excessive level of thyroid hormones predisposes to constipation

#3
Choose the agent, which inhibits synthesis of thyroid hormones.
A) Thiamazole
B) Potassium perchlorate
C) Potassium iodide
D) Iopanoic acid
E) Dexamethasone

#4
What potential adverse effect may be expected following long-term use of ^{131}I for the treatment of hyperthyroidism?
A) Thyroid storm
B) Suppurative thyroiditis
C) Hypothyroidism
D) Toxic multinodular goiter
E) Autoimmune thyroiditis

7.2. Recourses for the main stage of the lesson.

A goitre or goitre (Latin *gutteria, struma*), is a swelling of the thyroid gland, which can lead to swelling of the neck or larynx (voice box). Goitre is a term that refers to an enlargement of the thyroid (thyromegaly). Iodine deficiency causes 90% cases of goitre all over the world.

SIGNS AND SYMPTOMS
Goitre accompanied with hypothyroidism or hyperthyroidism may be present with symptoms of the underlying disorder. In hyperthyroidism, the usual symptoms are weight loss despite high appetite, and heat intolerance. However, these symptoms are often vague and hard to diagnose.

MORPHOLOGY
Concerning their morphology, goitres are classified either according to the growth pattern or to the size of the growth:
Growth pattern
- Uninodular (struma uninodosa): can be either inactive or a toxic nodule
- Multinodular (struma nodosa): can likewise be inactive or toxic, the latter called known as multinodular goitre

- Diffuse (struma diffuse): the whole thyroid appearing to be enlarged.

Size

- Class I (palpation struma): can not be seen in normal posture of the head, is only found by palpation.
- Class II: the struma is palpative and can be easily seen.
- Class III: the struma is very large and is retrosternal; pressure results in compression marks.

CAUSES

The most common cause for goitre worldwide is iodine deficiency, usually in countries where salt is not iodized. Insufficiency of selenium is also considered a contributing factor. In countries where iodized salt is used, Hashimoto's thyroiditis is the most common cause.

Table 6

Causes of goiter

Cause	Pathophysiology	Resultant thyroid activity	Growth pattern	Treatment	Incidence and prevalence	Prognosis
Iodine deficiency	Hyperplasia of thyroid to compensate for decreased efficacy	Can cause hypothyroidism	Diffuse	Iodine	Constitutes over 90% cases of goitre worldwide	Increased size of thyroid may be permanent if untreated for about five years
Congenital hypothyroidism	Inborn pathologies of thyroid hormone synthesis	Hypothyroidism				
Goitrogenigestion						
Adverse drug reactions						
Hashimoto's thyroiditis	Autoimmune disease in which the thyroid gland	Hypothyroidism	Diffuse and lobulated	Thyroid hormone replacement	Prevalence: 1 to 1.5 in a 1000	Remission with treatment

Cause	Pathophysiology	Resultant thyroid activity	Growth pattern	Treatment	Incidence and prevalence	Prognosis
	is gradually destroyed					
Pituitary disease	Hypersecretion of thyroid stimulating hormone, almost always by a pituitary adenoma[5]		Diffuse	Pituitary surgery	Very rare	
Grave's disease-also called Basedow syndrome	Autoantibodies (TSHR-Ab) that activate the TSH-receptor (TSHR)	Hyperthyroidism	Diffuse	Antithyroid agents, radioiodine, surgery	1 to 2 cases per 1,000 population per year	Remission with treatment, but still lower quality of life for 14 to 21 years after treatment, with lower mood and lower vitality, regardless of the choice of treatment[6]
Thyroiditis	Acute or chronic inflammation	Can be hyperthyroidism initially, but progress to hypothyroidism				
Thyroid cancer			Usually uninodular			Overall relative5-year survival rate of 85% for females and 74% for males[7]

Cause	Pathophysiology	Resultant thyroid activity	Growth pattern	Treatment	Incidence and prevalence	Prognosis
Benign thyroid neoplasms		Usually hyperthyroidism	Usually uninodular			Mostly harmless
Thyroid hormone insensitivity		Secretional hyperthyroidism, Symptomatic alhypothyroidism	Diffuse			

Females are more prone to goitre, but there are also many types of goitre caused by autoimmune problems, and not only those caused by simple deficiency of iodine.

TREATMENT

The treatment of goitre depends on its cause. If the thyroid gland is secreting too much T3 and T4, radioactive iodine is administered to the patient to shrink the gland. If goitre is the result of insufficient iodine, small doses of iodide in the form of Lugol's Iodine or KI solution are used. If the goitre is caused by an underactive thyroid, thyroid supplements are administered in the treatment. In severe cases, a partial or complete thyroidectomy is required.

THYROID STORM

Malignant or critical thyrotoxicosis, thyroid storm, is a medical condition in which excessive concentrations of thyroid hormone lead to organ dysfunction threatening the life of the patient. It does not often accompany hyperthyroidism, less than 10% of patients hospitalized with thyrotoxicosis suffer fom it. However, it may be the indicator of the condition and, if untreated, is associated with 80% to 90% fatal cases. Despite the treatment the mortality from thyroid storm is still more than 20%. Diagnosis and immediate treatment is crucial in preventing the high morbidity and mortality caused by this disease. Hyperthyroidism, or thyrotoxicosis, is caused be the disorders that result from excessive production and release of hormone from the thyroid. Thyrotoxicosis is due to any cause of excessive thyroid hormone concentration, whereas malignant thyrotoxicosis, or thyroid storm, is a vivid sign of thyrotoxicosis leading to end-organ dysfunction. Men and women at any age can suffer from thyroid storm, but teenagers or young adult women are more prone to it. Although a history of hyperthyroidism is common, thyroid storm may be the starting manifestation in a significant number of cases. Thyroid storm can be precipitated by a variety of factors, including severe infection, diabetic ketoacidosis, surgery,

trauma, and pulmonary thromboembolism. Direct trauma or surgery performed on the thyroid gland can also precipitate thyroid storm. Thyroid storm may be triggered by iodine, either from excessive consumption, intravenous administration, or radiotherapy. It can also occur after antithyroid medications have been ceased to be used. Salicylates cause thyroid storm by increasing the concentration of circulating free thyroid hormones to critical levels.

CLINICAL PICTURE

The clinical indicators of thyroid storm are connected with evident hypermetabolism resulting in multiorgan system dysfunction. The differential diagnosis of the thyroid storm encompasses sepsis, central nervous system infections, anticholinergic or adrenergic intoxication, other endocrine dysfunctions, and acute mental illness. To the symptoms also belong thermoregulatory dysfunction (high fever, warm moist skin, diaphoresis), neurologic features (changes in mental condition, seizure, coma, psychosis, hyperreflexia, lid lag), cardiovascular irregulation (atrial fibrillation, tachycardia, hypertension, congestive heart failure), respiratory distress (dyspnea, tachypnea), and gastrointestinal problems (diarrhea, abdominal pain, nausea, vomiting). Clinical suspicion is the major reason for the diagnosis of the thyroid storm. It is strongly suspected by the combination of these symptoms and is confirmed by means of thyroid function tests (TFT). However, therapy should be started before the verification by means of laboratory tests. Thyroid-stimulating hormone (TSH) levels are actually undetectable (<0.01 micro international units [mcIU]/L) with a concomitant increase of free T4 and T3. The high T3 is usualy more critical because of increased conversion of T4 to T3. Thus it is crucial to measure both T3 and free T4 levels when there is a possibility of thyroid storm. There are no differences in the results of TFT in patients with thyroid storm when compared to patients with symptomatic hyperthyroidism, and thyroid hormone levels cannot indicate which patients will experience decompensation from thyrotoxicosis to thyroid storm. Clinical record of acute organ dysfunction may help to make the distinction. Other typical laboratory abnormalities are hypercalcemia from osteoclast-mediated bone resorption, increased alkaline phosphatase caused by activated bone remodeling, and hyperglycemia secondary to enhanced glycogenolysis and increased circulation of catecholamines. Adrenal insufficiency, especially in patients with Grave's disease, is common and should be managed prior to the start of treatment.

TREATMENT

The treatment of thyroid storm encompasses 3 critical fundamental steps. First, supportive care should be provided to minimize the secondary effects of organ failure. This includes respiratory and hemodynamic support and treatment of hyperthermia. Second, revealing and treating the precipitating event is ensured to prevent progression of the disease. Third, and the most important, the production and effects of circulating thyroid hormone must be blocked. Suppression of the

peripheral conversion of T4 to T3 helps weaken the action of thyroid hormone. Propylthiouracil (PTU) blocks peripheral conversion of T4 to T3 and can be used in a 600- to 1000-mg loading dose, followed by 1200 mg/day divided into doses which are given every 4-6 hours. Methimazole may be an alternative medication, but it does not block peripheral T4 conversion. Both agents can be applied rectally if necessary. Peripheral thyroid hormone effect as well as tachycardia and hypertension can be minimized by beta-blockers; typically propranolol administered intravenously initially in 1-mg increments every 10-15 minutes until symptoms are controlled or esmolol used as a loading dose of 250-500 mcg/kg with later infusion of 50-100 mcg/kg/minute. It is possible to decrease thyroid hormone secretion with the help of lithium, iodinated contrast, and corticosteroids. Hydrocortisone 100 mg infused intravenously every 8 hours has proven to be efficient with the patients. Steroid therapy is also beneficial, given association with adrenal insufficiency. Iodine inhibits hormone secretion, but can only be used 1 hour after PTU administration. In refractory cases, plasmapheresis, plasma exchange, and peritoneal hemodialysis can be effective in removal of circulating thyroid hormone. With proper treatment, clinical and biochemical improvement are usually observed within 24 hours. Full recovery usually takes place within a week of treatment.
Thyroid storm requires diagnostic and therapeutic measures. The goal of treatment is to stop the thyrotoxic process at all levels. Early diagnosing and treatment is essential for successful management and is crucial in decreasing the high mortality caused by this disease.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
Patient R., 45 y.o, has an enlargement of the right lobe of the thyroid gland, in which a round soft and elastic growth can be palpated; the growth is neither fused with the surrounding tissues nor painful. Lymphatic nodes are not palpated. Clinical examinations and laboratory tests show no disruption of the thyroid function. What diagnosis can be suspected?
1. What is your diagnosis?
2. What are you going to do in this case?

Case 2.
D.G., a 26 y.o. school teacher, presented complaining of itchy skin and of being excessively nervous and jittery. Her symptoms started about two months ago. She was “short-tempered”, easily angered, and tremulous. She lost 5 kg despite a voracious appetite, perspired much more than normal, and preferred a cool room. She didn’t have diarrhea, polyuria, cough, headache, medication use, or change in menses.

1. What is the diagnosis?
2. What therapies are available to manage this problem?

Case 3.

A 23 y.o. lady was admitted with a short history of prolonged vomiting, diarrhoea, worsening palpitations, sweats and exhaustion. She had a past history of Grave's thyrotoxicosis for 6 years that was treated with suggestion of poor compliance contributing to this. She didn't take any medications for 2 weeks before this admission.

On admission, she was tremulous, pyrexial, in atrial fibrillation with a fast ventricular rate, tachypnoeic and hypoxic but without evidence of heart failure. She had a tender right hypochondrium without a palpable liver. A smooth moderate sized goitre was palpable without any bruit over it. She had exophthalmos but no chemosis. Initial investigations revealed grossly deranged liver biochemistry, coagulation failure and thrombocytopenia (see table). Her thyroid function tests confirmed severe hyperthyroidism (TSH <0.01(0.27-4.2 mU/L), fT4>100pmol/L (9-22pmol/L)).

1. What is the diagnosis?
2. How will your manage this problem?

Case 4.

Patient M., 33 y. o., after a stressful incident, presented with weakness, a 10 kg weight loss despite good appetite, feeling of inner tension, irritability, emotional lability, sweating, tachycardia, tremor, menstrual irregularity, diarrhea. Objective review: pulse 110 per min. BP 130/65, cardiac tones normal, skin is moist, warm, thyroid gland enlarged, with a firm and homogenous mass.

3. What is this patient's suspected diagnosis?
4. Choose the way of treatment of this patient.

2.4 Arterial hypertension in patients with endocrine pathology. Acute adrenal crisis.

Year of study: 6.
Faculty: medical.
Working place: classroom, hospital wards.
Number of study hours: 6.

1 Professional motivation: Despite the increasing awareness of the pathophysiology of hypertension, management of the disease is often difficult and far from optimal. Idiopathic (primary or essential) hypertension accounts for about 85 % of the diagnosed cases. It is estimated that nearly 15 % of patients with hypertension have identifiable conditions that result in raised blood pressure (secondary hypertension) such as primary renal disease, use of oral contraceptive, sleep apnea syndrome, inborn or acquired cardiovascular diseases (i.e. coarctation of the aorta) and excessive hormonal secretion.
Endocrine hypertension constitutes approximately 3% of the secondary forms of hypertension and is a term referred to the condition in which hormonal derangements induce clinically significant hypertension. The most frequent causes of endocrine hypertension are excessive production of mineralocorticoids (i.e. primary hyperaldosteronism), catecholamines (pheochromocytoma), thyroid hormone, and glucocorticoids (Cushing's syndrome). One important issue is when to check for secondary causes. The clinician should carefully screen for other cardinal signs and symptoms of Cushing's syndrome, hyper- or hypothyroidism, acromegaly, or pheochromocytoma. Hypertension in young patients and refractory hypertension (characterized by poorly controlled blood pressure on > 3 antihypertensive drugs) should induce the doctor to check for secondary causes. The importance of endocrine-mediated hypertension is the fact that in majority of cases, the cause is evident and can be traced to the influence of a hormone, often produced in excess amounts by a tumor such as an aldosteronoma in a patient with hypertension because of primary aldosteronism. More important, when the diagnosis is made, antihypertensive therapy aimed at specific disease can be implemented, and in some cases, surgical intervention may result in complete cure, obviating the demand in life-long antihypertensive treatment.
Acute adrenal crisis is a life-threatening state occuring when there is lack of cortisol. Causes of acute adrenal insufficiency are principally Waterhouse-Friderichsen syndrome, sudden withdrawal of long-term corticosteroid treatment and stress in patients with underlying chronic adrenal insufficiency. The latter is also called critical disease-related corticosteroid insufficiency.
In the absence of bilateral adrenal bleeding, the survival rate of patients with acute adrenal crisis that is diagnosed early and treated appropriately approaches that of

patients without acute adrenal crisis with similar course and severity of the illness. Patients, who developed bilateral massive adrenal hemorrhage before the hormonal testing or computed tomography scanning became available, rarely survived.

2 Study aim of this lesson.

To acquaint students with modern therapy of arterial hypertension in patients with endocrine pathology. Acute adrenal crisis (α=1)

In the study process students should know (α=2):

- classification of hypertension, diagnosis, surgery, medicamentous therapy; diagnosing and treatment of acute adrenal crisis.

In the study process student should be able to (α=3):

- carry out the examination of the patients with hypertension,
- differentiate variant of hypertension,
- prescribe appropriate treatment,
- treat and manage adrenal crisis,
- prevent adrenal crisis.

3. Educational aim of this lesson

To focus attention on differential variants of hypertension, treatment approach due to its origin, early recognition; first aid to adrenal crisis.

4. Interdisciplinary integration (see Table 6).

Table 6

Interdisciplinary integration

Discipline	To know	How to do
I. Previous General anatomy General physiology Histology Pathological physiology Pathological anatomy Biochemistry	Endocrine gland (morphology of the pituitary, hypothalamus, and other glands of endocrine secretion, capillaries, veins, nerve endings) Mechanism of interaction between hormones. Carbohydrate, lipid and protein metabolism in the human body	
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology Ophthalmology Nephrology	Clinical symptoms of endocrine hypertension	To examine a patient, to prescribe appropriate laboratory, to invite required specialists to diagnose a case.

Discipline	To know	How to do
III. Interdisciplinary integration	Blood pressure control	To institute adequate invastigation

5. Contents of the lesson.

- Criteria to define hypertension (international guidelines).
- Classification of hypertension.
- Differences between essential and secondary forms of hypertension.
- Variants of secondary hypertension.
- Types of endocrine hypertension.
- The most common causes of endocrine hypertension.
- Management and treatment of endocrine forms of hypertension.

6. Plan and organization structure of this lesson.
(See preface)

7. Recourses for systematic support of this lesson.

7.1. Recourses for preliminary stage of the lesson

Multiple choice questions (α=2)*
Choose the correct answer/statement. One answer/statement is correct.

#1
Patient R., 32y/o, was delivered with complaints of fatigue, reduced appetite, intensive pigmentation in the open areas of the body, palms of the hands, cyanosis, weight lose, nausea and vomiting. The symptoms began to aggravate within 1-2 weeks after acute poisoning. Objectively: arterial pressure – 60/30 mm column of mercury, pulse – 140 beats/minute, skin turgor is lowered, the colour is dark with intense pigmentation of the elbows, scars, skin folds on the palms; clear hyponatremia, hypochloremia and hyperkalemia; glycemia – 4.3 mmol/l. What is your diagnosis and treatment?

A) Intramuscular injection of 25mg hydrocortisone hemi-succinate
B) Injecting 500ml 5% glucose solution
C) Injecting 4% sodium carbonate 2.5 ml/kg
D) Injecting 5% ascorbic acid
E) Introducing 500 ml 0.9% sodium chloride

#2
Patient R., 32 y/o, was delivered with complaints of fatigue, decrease in appetite, intensification of pigmentation in the open areas of the body, palms of the hands, cyanosis, weight lose, nausea and vomiting. The symptoms began to aggravate within 1-2 weeks after acute poisoning. Objectively: arterial pressure – 60/30 mm column of mercury, pulse – 140 beats/minute, skin turgor is lowered, the colour is dark with intense pigmentation of the elbows, scars, skin folds on the palms; clearly low levels of sodium and chlorine, high levels of potassium in the blood; glycemia – 4.3 mmol/l. What is your diagnosis?

A) Addisonian crisis
B) Uremic coma
C) Brain coma
D) Acute cardio-vascular insufficiency
E) Hypoglycemic coma

#3
Which medications can be used for functional tests with suppression of adrenocorticotrophic hormone in diagnosing of the pathology of adrenal glands?

A) Prednisolone
B) Dexamethasonum
C) Hydrocortisone
D) Deoxycorticosterone acetate
E) Triamcinolone

#4
While ingesting glucocorticoids twice daily, how is the daily dose divided between the ingestions?

A) Half in the morning, half in the evening
B) Two thirds in the morning, one third in the evening
C) One third in the morning, two thirds in the evening
D) Half in the morning, half in the afternoon
E) One third in the afternoon, two thirds in the evening

7.2. Recourses for the main stage of the lesson.

The first step of examination of a patient with suspected endocrine-related hypertension is to exclude other causes of secondary hypertension, especially renal disorders. A thorough medical history and evaluation of systems should be taken into consideration. It is necessary to determine the onset of hypertension and the reaction to previous anti-hypertensive treatment. Following prescribed

antihypertensive regimen should be studied (poor compliance). A history of target organ damage (i.e. retinopathy, nephropathy, claudication, heart disease, abdominal or carotid artery disease) and general cardiovascular risk status should also be thoroughly considered.

The prevalence of constant hypertension is high: 53% of patients in NHANES had blood pressure < 140/90 mm Hg vs. 48% in the Framingham Heart Study. In NHANES individuals with chronic kidney disease, 37% had BP < 130/80 mm Hg. In ALLHAT, 34% of patients remained uncontrolled after 5 year monitoring on at least 2 antihypertensive medications.

As it is in all cases of hypertension, the doctor should question the patient about eating habits (salt intake etc.), weight fluctuations, use of non-prescription medications and health supplements including teas and herbal preparations, recreational drugs, and oral contraceptives. A detailed family history may also be extremely helpful in providing insights into family forms of endocrine hypertension.

The evaluation of systems requires disease-specific questions. Most patients with a pheochromocytoma have such symptoms as headaches, palpitations, anxiety-like attacks and profuse perspiration, similar to symptoms of hyperthyroidism. The headache, palpitations, and sweating in a hypertensive patient were found to have a sensitivity of 91% and specificity of 94% for pheochromocytoma. If these symptoms are absent, it is difficult to diagnose pheochromocytoma, though cases of normotensive and/or asymptomatic pheochromocytomas have been observed in approximately 15% of patients.

Patients with Cushing's syndrome often suffer from insomnia, overweight, depression, easy bruising and fatigue. Acne and hirsutism (in women) can also be present. The patients with evolving Cushing's syndrome have to be recognized among many obese and often poorly controlled diabetic individuals. A recent Endocrine Society Clinical Practice Guideline can be helpful in this task. Primary hyperaldosteronism is manifested by mild to severe hypertension. There may be hypokalemia, but it is not a universal feature and there is normokalemic primary aldosteronism. Polyuria, myopathy and cardiac dysrhythmias may occur in cases of severe hypokalemia. A close physical examination with attention to indicators of target organ injury and signs of secondary hypertension is required.

PRIMARY ALDOSTERONISM

Elevated plasma aldosterone concentrations within the physiologic range predisposed individuals to the development of hypertension in a community-based study (Framingham Offspring) involving 1688 nonhypertensive participants. Earlier research indicated a prevalence of primary aldosteronism (PA) of 1-2 %. Newer data show a general prevalence of approximately 6% among the hypertensive population. In patients with mild to moderate hypertension without hypokalemia, the incidence of PA has been defined to be 3%. In individuals with persistent hypertension the

prevalence ranges between 17 and 23 %. In a study involving 1616 patients with resistant hypertension, 21% (338 pts) had an Aldosterone/Renin Ratio of > 65 with plasma aldosterone concentrations of > 416 pmol/L (15 ng). After tests on salt suppression, only 11% (182 pts) of these patients had primary aldosteronism. The incidence of aldosteronism was low at 2% in patients with adrenal incidentaloma and hypertension. Many patients with PA (up to 60%) may not have hypokalemia but are rather normokalemic. Low renin hypertension may commonly be mistaken for PA. In a recent study, 56% of 553 patients with primary aldosteronism had hypokalemia and 16% had cardio-and cerebrovascular comorbidities. In addition to the patient group with resistant hypertension, monitoring for primary aldosteronism is advisable for those patients with diuretic-induced or spontaneous hypokalemia, those with hypertension and a family history of early-onset hypertension or cerebrovascular accident at young age, and those with hypertension and an adrenal incidentaloma.

PA can be a sporadic or familial condition. Sporadic PA is usually caused by an aldosterone-producing adrenal adenoma. However, bilateral zona glomerulosa hyperplasia is much more likely in sporadic primary hyperaldosteronism than was previously considered and is a crucial differential diagnosis, as it is treated medically with aldosterone antagonists, rather than by adrenalectomy. Selective administration of adrenal venous sampling is efficient in this case. In only few incidences, PA can be caused by an adrenal carcinoma, or unilateral adrenal cortex hyperplasia (also termed primary adrenal hyperplasia).

Familial aldosteronism is considered to affect 2% of all individuals suffering from primary hyperaldosteronism and is classified as type 1 and 2. Recently, there was found another form of familial aldosteronism, probably a type 3, as these patients produce amounts of 18-OHF and 18-oxoF 10-1,000 times higher than patients with FH type 1 (approx. 20 times normal) or patients with FH type 2 or sporadic aldosteronism. Moreover, in patients suffering from “FH type 3” there is a paradoxical increase in aldosterone after dexamethasone, atrophy of the zona glomerulosa, diffuse hyperplasia of the zona fasciculata, and severe hypertension in early childhood (around age 7 years) that is resistant to drug therapy but curable by bilateral adrenalectomy.

In familial hyperaldosteronism type 1, an autosomal dominantly inherited chimeric gene defect in CYP11B1/CYPB2 (coding for 11beta-hydroxylase/aldosterone synthase) leads to ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin. There has been a hybrid gene found on chromosome 8. Under normal conditions, aldosterone secretion is mainly stimulated by hyperkalemia and angiotensin II. An increase of serum potassium of 0.1 mmol/L increases aldosterone by 35%. In familial hyperaldosteronism type 1 or glucocorticoid-remediable aldosteronism, urinary hybrid steroids 18-oxocortisol and 18-hydroxycortisol are

approx. 20 times higher than in sporadic aldosteronomas. Intracranial aneurysms and hemorrhagic stroke are clinical features often connected with familial hyperaldosteronism type 1. The desease is diagnosed by documenting dexamethasone suppression of serum aldosterone using the Liddle's Test (dexamethasone 0.5 mg q 6h for 48h should reduce plasma aldosterone to nearly undetectable levels (below 4 ng/dl) or by genetic testing (Southern Blot or PCR). In contrast, familial hyperaldosteronism type 2 is not glucocorticoid-remediable. The gene responsible for this condition has been connected to chromosome 7p22 but has not yet been identified.

Primary aldosteronism is screened for by measuring plasma aldosterone (PA) and plasma renin activity (PRA) or concentration of direct renin. Measuring aldosterone is not an easy task. Measuring PRA is complex and includes generating angiotensin from endogenous angiotensinogen. Calculation of renin conversion of angiotensinogen to angiotensin is carried out by using radioimmunoassays for PRA which are not standardized among laboratories. Measurement of plasma renin molecules directly with the help of an automated chemiluminescence immnoassay as direct renin concentration is possible in Europe but is not approved by the FDA in the United States. A PA/PRA-ratio > 30 with a concomitant PA > 20 ng/dl has a sensitivity of 90% and specificity of 91% for primary aldosteronism. As it is difficult to differenciate low renin hypertension from PA, an upright plasma aldosterone not less than 15 ng/dl can be efficient.

Since hypokalemia can cause decrease in secretion of aldosterone, it should be treated prior to further diagnostic measures. Primary aldosteronism is also likely, if a patient with hypertension treated with an ACE inhibitor or ARB, calcium channel blocker, and a diuretic (all of which should increase PRA, thereby lower the PA/PRA-ratio or ARR), still has a suppressed renin and 2-digit plasma aldosterone level. Due to the effect of medicine, it is generally recommended to discontinue betablockers, ACE inhibitors, ARBs (angiotensin receptor blockers), renin inhibitors, dihydropyridine calcium channel blockers, and central alpha2-agonists approximately 2 weeks before PA/PRA-ratio or ARR test, and to continue spironolactone, eplerenone, amiloride, and triamterene, and loop diuretics approximately 4 weeks before ARR testing. However, this often is not possible in real clinical circumstances. The Endocrine Society Practice Guideline advises using an ARR > 30 for screening.

Confirmatory testing can be carried out using various techniques.

To distinguish hyperplasia from unilateral adenoma, computed tomography and magnetic resonance imaging are important, but adrenal venous sampling (AVS) with cosyntropin (ACTH) infusion is often required if the patient chooses surgery in case of a unilateral adenoma: cut-off for unilateral adenoma > 4 "cortisol-corrected" aldosterone ratio (adenoma side aldosterone/cortisol: normal adrenal gland

aldosterone/cortisol); cutoff for bilateral hyperplasia < 3 "cortisol-corrected" aldosterone ratio (high-side aldosterone/cortisol: low-side aldosterone/cortisol). If a patient does not choose surgery/adrenalectomy in case of a unilateral aldosteronoma/hyperplasia, medical treatment should be commenced. AVS and CT/MRI of the adrenal glands show a unilateral abnormality in 60.5% and 56%, respectively, but were congruent on the involved side in the same individual in only 37% in a late systematic review. If a patient is older than 40, the risk for an adrenal incidentaloma is higher. Unilateral adrenalectomy can be effective in some patients with primary aldosteronism and bilateral adrenal hyperplasia.

Adrenal adenomas producing aldosterone should be removed. Almost all patients with such endocrine hypertension have improvement in blood pressure control and approximately 60% are cured (normotensive without antihypertensive therapy) from hypertension. This is due to such factors as age, hypertension duration, accompanying renal insufficiency, use of more than 2 antihypertensive drugs before surgery, family history of hypertension, and others. Spironolactone, epleronone, and/or amiloride are administered in the treatment of bilateral adrenal hyperplasia. Aldosterone synthase inhibitors are being tested at present which may not have any nongenomic/non-mineralocorticoid receptor-mediated side effects. It is also possible to regulate blood pressure by means of brain mineralocorticoid receptors. In cases of familial hyperaldosteronism type 1, dexamethasone is also efficient due to suppressing ACTH and eventually aldosterone overproduction. Treatment of PA can restore parameters of insulin sensitivity to norm. A recent cross-sectional study including 460 patients with primary aldosteronism and 1363 in control group with essential hypertension didn't feel a considerable difference between pre- and postoperative levels of fasting plasma glucose and serum lipids. However, a recent review shows that aldosterone excess has adverse metabolic effects.

PHEOCHROMOCYTOMA

These rare neuroendocrine tumors are composed of chromaffin tissue containing neurosecretory granules. Most pheochromocytomas are sporadic but some are hereditary. Recent studies have revealed that approximately 24% of pheochromocytomas are hereditary. Patients suffering from numerous endocrine neoplasia type 1 or type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and with germline mutations in the SDHB/C/D genes can experience hereditary pheochromocytomas. There are doubts about when genetic testing should be done in patients with pheochromocytoma, especially considering cost effectiveness. Erlic and co-workers used six predictors to develop a screening algorithm in order to detect which patients should be genetically tested for germline mutations. The patient requires testing if any of these 6 indicators is present.

The biochemical profile of pheochromocytomas related to the aforementioned hereditary syndromes is variable. Clinically "silent" pheochromocytomas may be

experienced by patients with MEN 2 and VHL syndrome. Normotensive patients may also suffer from sporadic pheochromocytomas, which appears in approximately 15% of patients with pheochromocytoma who are normotensive. Blood pressure level is not caused by circulating catecholamines in individuals with pheochromocytoma. On the other hand, renal norepinephrine spillover from both kidneys in patients with hypertension, caused by increased activity of renin, can take place. Hypertension in these patients may be ameliorated with radiofrequency ablation of renal arteries and renal nerves which carry efferent sympathetic and afferent sensory fibers. Hypertension is paroxysmal in nearly 50% of patients suffering from pheochromocytoma. Free plasma or fractionated urinary metanephrines and normetanephrines are measured in order to make the diagnosis. If it is impossible to measure plasma free metanephrines by HPLC with electrochemical detection or high-throughput automated liquid–chromatography-tandem mass spectrometry (LC-MS/MS), measuring plasma free metanephrines by RIA or measuring plasma chromogranin A may have good markers for pheochromocytoma. The results of plasma chromogranin A together with urinary catecholamines may give an almost 100% sensitivity for diagnosis of pheochromocytoma. In rare cases, large amounts of dopamine are produced by pheochromocytomas. Plasma concentrations of free metanephrines can be increased twofold in patients with renal failure.

About 35% of extra-adrenal pheochromocytomas are malignant (metastasizing) in contrast to around 10% of those appearing in the adrenal gland. The chance of malignancy is higher when the tumor size is over 5 cm and when there is a germline mutation in the SDHB gene. Therefore, for such tumors, open adrenalectomy is advised for tumor removal rather than laparoscopic or retroperitoneoscopic minimally invasive tumor removal (Koch, unpublished observation in a patient with MEN2-related bilateral pheochromocytomas and unilateral tumor recurrence 11 years after bilateral adrenalectomy).

CT or MR imaging can help localize the tumor in around 95 % of cases. For malignant pheochromocytomas, 18F-Fluorodopamine PET proves to be more efficient than 123I-MIBG or 131I-MIBG scintigraphy. Actually, MIBG scintigraphy can only been used in certain patients. Many medications can interfere with 123I-MIBG or 131I-MIBG uptake (for instance, calcium channel blockers, antipsychotics) and should be discontinued prior to the scan/imaging. For patients with head and neck paragangliomas, 111In-octreotide has a very good sensitivity. Around half of patients with malignant pheochromocytomas react to 131I-MIBG therapy by partial remission or at least stable condition. Chemotherapy is commonly ordered according to the so-called Averbuch protocol adopted in 1988. To the new ways of treatment belongs administration of tyrosine kinase inhibitors in some patients.

Although in older textbooks the term Sipple syndrome refers to multiple endocrine neoplasia type 2, it now appears that the original description of classic MEN-2 was made by Felix Fraenkel in 1886.

CONGENITAL ADRENAL HYPERPLASIA: 11BETA-HYDROXYLASE DEFICIENCY

The major cause of congenital adrenal hyperplasia (CAH) is defficiency of 21-hydroxylase. Hypertension itself has not been considered a component of this syndrome. Recent data have shown that hypertension may occur more often in this patient population than it was previously thought.

Around 5% of all CAH care cases were caused by 11beta-hydroxylase deficiency. 11beta-hydroxylase is responsible for the conversion of deoxycorticosterone (DOC) to corticosterone (precursor of aldosterone) and 11-deoxycortisol to cortisol. In approximately 2/3 of individuals suffering from lack of this enzyme, monogenic low renin hypertension with low aldosterone levels ensues caused by accumulation of 11-deoxycortisol and DOC. The inheritance mode is autosomal recessive. The responsible gene CYP11B1 is located on chromosome 8 and mutated. Since corticotropin (ACTH) is chronically increased and precursors such as 17-OH progesterone and androstendione accumulate, androgen production grows and may result in prenatal virilization with following pseudohermaphroditism in females and pseudoprecocious puberty in males. Usually, glucocorticoid replacement eases hypertension in these individuals. In selected patients, bilateral adrenalectomy may be safe and efficient in regulating blood pressure.

CONGENITAL ADRENAL HYPERPLASIA: 17ALPHA-HYDROXYLASE DEFICIENCY

This enzyme deficiency is rare and causes decreased production of cortisol and sex steroids. Chronic elevation of ACTH leads to excessive production of DOC and corticosterone with following hypertension, hypokalemia, low aldosterone concentrations with suppressed renin as well as pseudohermaphroditism in XY males, and sexual infantilism and primary amenorrhea in females. It may be difficult to make diagnosis until puberty. The levels of plasma adrenal androgen are decreased as are cortisol, aldosterone, plasma renin activity, and 17alpha-hydroxyprogesterone. DOC, corticosterone, and 18-hydroxycorticosterone are increased. Glucocorticoid replacement helps to reduce blood pressure. The gene responsible for cytochrome P450C17 is located on chromosome 10q24.

APPARENT MINERALOCORTICOID EXCESS

Low-renin hypertension (undetectable aldosterone, hypokalemia) can manifest itself in various forms, one of them is apparent mineralocorticoid excess (AME), an autosomal recessive disorder caused by lack of the 11beta-hydroxysteroid

dehydrogenase type 2 (11beta-HSD2) enzyme. This enzyme converts cortisol to the inactive cortisone in renal tubular cells.
In 1977, New et al. first described this syndrome and in 1995 Wilson et al. first reported mutations in the 11beta-HSD2 gene located on chromosome 16q22 cause AME. The 11beta-HSD2 enzyme is co-expressed with the mineralocorticoid receptor in renal tubular cells and causes conversion of cortisol to cortisone. Cortisone is not bound to the mineralocorticoid receptor. Cortisol and aldosterone bind with equal affinity to the mineralocorticoid receptor but normal circulating concentrations of cortisol are 100 to 1000 fold higher than those of aldosterone. If 11beta-HSD2 is oversaturated or defective, there is more cortisol available to bind to the mineralocorticoid receptor. Decreased 11beta-HSD2 activity may be hereditary or acquired. Acquired lack of this enzyme may be caused by inhibition by glycyrrhhetinic acid which may occur with use of licorice, chewing tobacco, and carbenoloxone. In children, AME often causes growth retardation/short stature, hypertension, hypokalemia, diabetes insipidus renalis, and nephrocalcinosis. Diminished 11beta-HSD2 activity may take part in the pathogenesis of preeclampsia. In order to diagnose AME measuring free unconjugated steroids in urine (free cortisol/free cortisone ratio), and/or steroid metabolites (tetrahydrocortisol + allotetrahydrocortisol/tetrahydrocortisone) may be used. Affected patients have decreased levels of renin and aldosterone, normal plasma cortisol levels, and hypokalemia. Treatment of AME includes spironolactone, eplerenone, triamterene, or amiloride. Renal transplant is an option for patients with advanced renal deficiency.

CONSTITUTIVE ACTIVATION OF THE MINERALOCORTICOID RECEPTOR (GELLER SYNDROME)

The MC receptor can mutate resulting in hypertension before the age of 20. In vitro experiments show that progesterone and spironolactone, usually antagonists of the mineralocorticoid receptor, become agonists in Geller syndrome, suggesting "gain of function" mutations in the MC gene on chromosome 4q31. The inheritance pattern is autosomal-dominant.

LIDDLE SYNDROME

In 1963, Liddle described patients with severe hypertension, hypokalemia, and metabolic alkalosis, who had decreased plasma aldosterone levels and plasma renin activity. The hypertension improved after salt restriction and triamterene therapy. Spironolactone is not efficient in this autosomal-dominant inherited syndrome. So-called "gain of function" mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located at chromosome 16p13, cause constitutive activation of renal sodium resorption and following volume expansion. The 24-h urine cortisone/cortisol ratio is normal.

PSEUDOHYPALDOSTERONISM TYPE 2

Pseudohypoaldosteronism type 2 or Gordon's syndrome is a rare Mendelian disorder, transmitted in an autosomal dominant fashion, which can lead to low renin hypertension. Its prevalence is unknown, since many patients remain undiagnosed. Recorded families with this condition (hypertension, hyperkalemia, metabolic acidosis, normal renal function, low/normal aldosterone levels) are mostly from Australia (Gordon et al.) or the United States (Lifton et al.). Hypertension in these patients may develop as a result of high renal salt reabsorption, and hyperkalemia ensues as a result of reduced renal K excretion despite normal glomerular filtration and aldosterone secretion. The low renal secretion of potassium makes this condition resemble an aldosterone-deficient state, thus the term "pseudohypoaldosteronism". These features are chloride-dependent. Injecting sodium chloride instead of sodium bicarbonate corrects the abnormalities as does the administration of thiazide diuretics which inhibit salt reabsorption in the distal nephron. Gordon and coworkers revealed that it is possible to reverse all disease features by very strict restriction of salt intake. Gordon syndrome is an autosomal dominantly inherited disorder with genes mapping to chromosomes 1, 12, and 17. Mutations have been found in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively. Disorders such as activating mutations in the amiloride-sensitive sodium channel of the distal renal tubule cause the clinical phenotype. Severe limiting of salt intake, antihypertensives with advisable administration of thiazide diuretics are able to control the hypertension in this syndrome. Interestingly, common variants in WNK1 contribute to blood pressure variation in the general population.

INSULIN RESISTANCE

The metabolic syndrome is characterized by hypertension, abdominal/visceral obesity, dyslipidemia, and insulin resistance. At least 24% of adult population in the United States meet the criteria for the diagnosis of metabolic syndrome, and this number may even be higher for individuals over the age of 50 years. Insulin resistance is strongly connected with hypertension in Hispanics and can lead to vascular dysfunction. Individuals with essential hypertension often turn out to be insulin resistant. Interestingly, not all insulin resistant patients are overweight. Obesity, however, is responsible for as much as 70% of the risk for essential hypertension and also increases the risk for end stage renal disease. In insulin-sensitive tissues, insulin can directly stimulate the calcium pump causing calcium loss from the cell. In an adipocyte, increased cytosolic calcium concentrations can trigger insulin resistance. In a cell resistant to insulin, the insulin-induced calcium loss from cells would be decreased. With the following increase in intracellular calcium, vascular smooth muscle cells respond better to vasoconstrictors and thus lead to elevated blood pressure. Other mechanisms possibly explaining the

connection of insulin resistance and hypertension are increased sodium retention and increased activity of the adrenergic nervous system. In case of obesity, the excessive production of most adipokines (bioactive peptides secreted by adipose tissue) influence various functions including insulin sensitivity, blood pressure, lipid metabolism, and others.

HYPERPARATHYROIDISM

The levels of parathyroid hormone in patients with hypertension usually are in the normal range and appropriate for the serum calcium concentration. However, patients with essential hypertension have increased calcium excretion compared to normotensive people, indicating an enhanced parathyroid gland function. When infused, PTH is a vasodilator, although chronic administration of PTH raises blood pressure in healthy individuals. High-calcium intake may decrease blood pressure. However, hypercalcemia is connected with high occurrence of hypertension. Patients with primary hyperparathyroidism suffer from hypertension in approximately 40% of cases. The mechanisms of these observations/associations are unclear. Hypertension is usually not cured or better controlled after parathyroidectomy. In patients with asymptomatic primary hyperparathyroidism, surgery/parathyroidectomy was not successful regarding blood pressure or quality of life when compared to medical management. On the other hand, severe hypertension may improve in individuals with primary HPT who are subject to parathyroidectomy. Arterial stiffness measured in the radial artery is usually elevated in patients with mild primary hyperparathyroidism. Individuals suffering from primary hyperparathryoidism have carotid vascular abnormalities. Another factor that contributes to hypertension in patients with primary HPT may be endothelial dysfunction. In MEN syndromes, hypertension in patients with hyperparathyroidism may be caused by underlying pheochromocytoma or primary aldosteronism. Criteria for parathyroidectomy have recently been revisited at the Third International Workshop on the management of asymptomatic primary hyperparathyroidism.

CUSHING'S SYNDROME

Hypercortisolemia is connected with hypertension in around 80% of adult cases and half of children. In patients suffering from Cushing's disease, night-time blood pressure decline is much lower than that in patients with essential hypertension. Upon recovering after Cushing's syndrome, approximately 30% of patients have persistent hypertension. In children and adolescents, blood pressure normalization commonly takes place within a year and seems to depend on the degree and duration of presurgical hypercortisolemia. In individuals with Cushing's disease, renin and DOC levels are usually normal, whereas in case of ectopic corticotropin syndrome, hypokalemia is usual and associated with high mineralocorticoid activity with suppressed renin and elevated DOC levels.

In case of Cushing's syndrome there are several mechanisms responsible for blood pressure elevation: increased hepatic production of angiotensinogen and cardiac output by glucocorticoids, low production of prostaglandins via inhibition of phospholipase A, high insulin resistance, and oversaturation of 11beta-HSD activity with increased mineralocorticoid effect through stimulation of the mineralocorticoid receptor. Screening studies for Cushing's syndrome encompass measuring 24-h urinary free cortisol excretion on at least 2 occasions, carrying out a 1 mg dexamethasone suppression test, checking a midnight salivary cortisol and diurnal rhythm of cortisol secretion, and others listed in the recent Endocrine Society Clinical Practice Guidelines. Treatment should be aimed at removing glucocorticoid excess. Mineralocorticoid receptor antagonists such as spironolactone or eplerenone may be administered for treatment of hypokalemia (especially in patients with ectopic ACTH production). Use of thiazide diuretics may also be effective.
Since there has been much improvement in imaging and laboratory (assays etc.) techniques/modalities, there can be expected an increasing number of incidentally discovered tumors and nodules in various organs including the adrenal glands. The future concern will be the time and extent to which individuals should be tested for disease conditions. For patients with adrenal incidentalomas but clear insufficiency of clinical features of Cushing's syndrome, subclinical hypercortisolism may be detected biochemically depending upon which cutoff values and assays will be used. For the latter population, the American Association of Clinical Endocrinologists advise using a cutoff for (8 AM) serum cortisol of 5 mcg/dl after 1 mg overnight (11 PM) dexamethasone which reveals approx. 58% sensitivity at a 100% specificity. A lower cutoff for serum cortisol suppression, i.e. 1.8 mcg/dl, may cause adrenalectomy. A prospective, randomized study including 45 patients with subclinical hypercortisolism and adrenal incidentalomas was divided into 23 pts who were subject to adrenalectomy and 22 pts under surveillance. Monitoring encompassed glycemic control, blood pressure, lipid profile, obesity, and bone mineral density. In the surgical group, diabetes mellitus improved in 62% and hypertension in 67% of pts, whereas there was deterioration of glycemic control, blood pressure and lipid profiles in the conservative group.

GLUCOCORTICOID RESISTANCE

This autosomal recessive or dominant inherited disorder is rare and induced by inactivating mutations of the glucocorticoid receptor gene. Cortisol and ACTH are increased but there are no clinical features of Cushing's syndrome. Continuous rise of ACTH can cause stimulation of adrenal compounds with mineralocorticoid activity (corticosterone, DOC), and elevation of cortisol may result in stimulation of the mineralocorticoid receptor, triggering hypertension. In women, hirsutism and oligomenorrhea may develop through stimulation of androgens (androstendione, DHEA, DHEAS). Clinically, children may have ambiguous genitalia and precocious

puberty. Men may be infertile and/or oligospermic. Women may suffer from acne, excessive hair, menstrual irregularities with oligo- and anovulation as well as infertility.
Mineralocorticoid receptor dependent hypertension is treated with blockage of the receptor, for example by a receptor antagonist such as spironolactone or suppression of ACTH secretion with dexamethasone (1-3 mg/day).

HYPERTHYROIDISM
Hyperthyroidism increases systolic blood pressure due to heart rate elevation, reducing systemic vascular resistance, and raising cardiac output. In thyrotoxicosis, patients commonly suffer from tachycardia and have high cardiac output with an elevated stroke volume and high systolic blood pressure. Around one third of patients with hyperthyroidism are diagnosed with hypertension which often resolves after achieving euthyroidism. Subclinical hyperthyroidism may cause to left ventricular hypertrophy and thus induce hypertension (168), although it has not yet been proven to be connected with hypertension.

HYPOTHYROIDISM
Individuals with hypothyroidism have impaired endothelial function, elevated systemic vascular resistance, extracellular volume expansion, and an increased diastolic blood pressure. Hypothyroid patients have higher mean 24-h systolic blood pressure and BP variability on 24-h ambulatory BP monitoring. In 32% of hypertensive hypothyroid patients, replacement therapy with thyroxine causes reduction in diastolic blood pressure to 90 mm Hg or less. There is a positive association between serum TSH and blood pressure within the normal serum TSH range, statistically significant for diastolic hypertension. There may or may not be connecton between subclinical hypothyroidism and hypertension.

ACROMEGALY
The occurence of hypertension in patients with excessive growth hormone is around 46% and more frequent than in the general population. Growth hormone has antinatriuretic actions and may cause sodium retention and volume expansion. Such manifestations of hyperkinetic syndrome as high systolic output and increased heart rate may lead to congestive heart failure. Blood pressure values are elevated in individuals with acromegaly associated with reduced glucose tolerance or diabetes compared to those with normal glucose tolerance. The RAAS system is implicated in the pathogenesis of hypertension in patients with excessive growth hormone. Comorbidities in acromegalics, such as hypertension, hyperlipidemia, diabetes mellitus, and cardiomyopathy, all may improve even with partial biochemical control of growth hormone excess.

DESCRIPTION AND INCIDENCE OF ACUTE ADRENAL CRISIS

Acute adrenal crisis is an extreme manifestation of adrenal insufficiency, which may be life-threatening. It takes place secondary to interruption of a normal or hyperfunctioning adrenal or pituitary gland or sudden interruption of adrenal replacement therapy. Adrenal insufficiency is a hormone deficiency syndrome that develops when there is severe loss of function of the adrenal gland. The prevalence of adrenal insufficiency varies and depends on the underlying disease and severity of the illness. The occurrence is also highly variable among populations of patients. For instance, among critically ill patients with septic shock, 76% of patients are diagnosed with absolute or relative adrenal insufficiency. There have been established no racial, gender, or age predilection.

There are 3 categories of adrenal insufficiency: chronic primary adrenal insufficiency (Addison disease), chronic secondary adrenal insufficiency, and adrenal crisis (acute adrenal insufficiency). Addison disease is caused by destruction of the adrenal cortex, and 80% of cases are the result of autoimmune disease. The remaining 20% are triggered by infections (tuberculosis, autoimmune deficiency virus, fungal diseases) and metastasis of a malignancy. Insufficient adrenocorticotropic hormone (ACTH) may cause chronic secondary adrenal insufficiency. It is usually the result of exogenous glucocorticoid therapy but can also be caused by pituitary tumors. Finally, adrenal crisis can occur acutely in individuals suffering from adrenal hemorrhage, pituitary apoplexy, or secondary to stress or abrupt withdrawal of chronic steroid use in patients with underlying chronic adrenal insufficiency. To the causes of adrenal crisis belong adrenal hemorrhage (induced by meningococcal or other kinds of sepsis) necrosis (coagulopathy, warfarin therapy), or thrombosis (antiphospholipid syndrome). Adrenal crisis may also result fron pituitary dysfunction from postpartum pituitary necrosis (Sheehan syndrome), a pituitary macroadenoma, or primary central nervous system lesions.

CLINICAL MANIFESTATION AND DIAGNOSIS

Since adrenal crisis occurs secondary to mineralocorticoid deficiency, the clinical manifestations are usually hypotension or hypotensive shock. The clinical picture may be complicated by the underlying disease (sepsis, pituitary or adrenal hemorrhage, surgery, trauma). Adrenal crises should be suspected in patients with unexplained hypotension and fluid or catecholamine-resistant hypotension, especially if there have been detected symptoms of chronic adrenal insufficiency. There also may be nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, or coma. Abdominal or groin pain, peritoneal signs, vomiting, confusion, or hypotension should cause suspicion for acute adrenal hemorrhage.

The diagnostics of adrenal crisis differs from that for primary adrenal insufficiency. Basal cortisol levels can be obtained in primary adrenal insufficiency and then the

underlying cause studied. In adrenal crisis, immediate therapeutic intervention is essential before confirmation of the diagnosis. Patients with adrenal crisis often have hyponatremia and hyperkalemia. A baseline cortisol level should be obtained followed immediately by a cortrosyn (cosyntropin) stimulation test. Empiric steroid therapy should be carried out until laboratory results are received. To perform cortrosyn stimulation test first a baseline cortisol level is obtained, 250 mcg of cortrosyn (synthetic ACTH) is administered, and then cortisol level is measured at 30 and 60 minutes postinfusion. This is an effective diagnostic test for patients suspected of having chronic adrenal insufficiency. It enables to directly measure adrenal function and also provides an indirect measure of the hypothalamic and pituitary function because the adrenal glands depend on endogenous ACTH for their tropic effect. In studies of patients with septic shock, a baseline cortisol level under 10 g/dL or a cortrosyn-stimulated total cortisol increment under 9 g/dL was the best indicator of adrenal insufficiency. On the other hand, the combination cortrosyn-stimulated cortisol level of 44 g/dL or more and an increment in total cortisol of 16.8 g/dL or more excluded the diagnosis of adrenal insufficiency.

TREATMENT

After initial diagnostic laboratory results have been received, immediate treatment of adrenal crisis should start involving intravenous fluids, steroid replacement, and reversal of electrolyte abnormalities. Normal saline is the intravenous fluid of choice. Hypotonic saline should be avoided as it can worsen the hyponatremia. If adrenal insufficiency has been diagnosed or is highly likely, stress-dose steroid replacement should be administered. Hydrocortisone may be used as a 100-mg intravenous push followed by continuous infusion of 150-300 mg/day for 2 to 3 days. In order to avoid interference with testing of cortisol levels, dexamethasone as a 4-mg intravenous bolus may be administered instead of hydrocortisone. A mineralocorticoid, namely fludrocortisone acetate, should also be administered at 0.1 mg daily. One study suggested that hydrocortisone 50 mg every 6 hours in addition to fludrocortisone 50 mg daily reduced 28-day death rate in patients with septic shock. In addition, hydrocortisone (by enhancing vascular responsiveness to catecholamines) made vasopressor therapy last less. There is no proof that lower doses of hydrocortisone in acute crisis would generate equivalent or better survival, thus most institutions begin with hydrocortisone at approximately 200-300 mg/day. Steroid therapy can be tapered over 1 to 3 days and then converted to an oral maintenance dose. Most patients suffering from adrenal crisis have primary adrenal insufficiency and therefore need lifelong glucocorticoid and mineralocorticoid therapy. The usual oral replacement dosages are dexamethasone 0.5-2.5 mg or prednisone 5-7.5 mg once daily.

Adrenal crisis needs immediate recognition and treatment since it endangeres the life of a patient. A simple strategy of diagnostic screening and early intervention

with sodium chloride-containing fluids and hydrocortisone should be widely implemented to improve the results.

7.3. Recourses for concluding stage of the lesson: test situation tasks (cases).

Case 1.
Patient R., 32 y/o, was delivered with complaints of fatigue, decrease of appetite, intensification of pigmentation in the open areas of the body, palms of the hands, cyanosis, losing weight, nausea and vomiting. The symptoms began to aggravate during 1-2 weeks after acute poisoning. Objectively: arterial pressure – 60/30 mm column of mercury, pulse – 140 beats/minute, skin turgor is lowered, the colour is dark with intense pigmentation of the elbows, scars, skin folds on the palms; clearly low levels of sodium and chlorine, high levels of potassium in the blood; glycemia – 4.3 mmol/l.
1. What is your diagnosis?
2. What are you going to do in this case?

Case 2.
Patient M., 42 y/o, was taken in with complaints of heavy fatigue, anorexia, severe nausea and vomiting, which does not bring relief of the patient's condition, dizziness. The symptoms began to increase during 1-2 days after stopping the use of cortisone. Objectively: arterial pressure – 65/20 mm column of mercury, pulse – 148 beats/minute, weak, skin turgor is lowered, the colour is pale, the patient is suffering from shortness of breath, and his respiration is shallow. Hb of blood – 166g/l, clear hyponatremia, hypochloremia and hyperkalemia. Urine: proteinuria, leucocyturia and microhematuria.
1. What is your diagnosis?
2. What are you going to do in this case?

Case 3.
J.B., a 40-year-old carpenter, complained of fatigue and weakness. His fatigue began about 6 months earlier. He attributed the tiredness to heat and working 10 to 11 hours each day while framing houses during the midsummer. During the fall, however, the work load was lighter, yet he could just barely make it to the end of the day. He often felt nauseated but never vomited. He found himself adding salt to almost every food, something he had never done before. BP while standing was 95/60 with a pulse of 84/min without any symptoms. He was a pleasant, dark-complected white male. The melanosis was accentuated over the sun-exposed areas, the scrotum and perineum, nipple areola, and in the skin creases. Several small hyperpigmented areas over the gingival and buccal mucosa were found.

1. What is your working diagnosis, and what other possibilities are less likely?
2. How would you manage this patient?

Case 4.
Patient C., 56 y/o, complains of weakness, muscle ache, loss of appetite, nausea, vomiting, aching bones, deterioration of memory and cramps. Anamnesis contains a record of the ulcerous disease of stomach, frequent pathological bone fractures. Objectively: the consciousness is clouded, the skin is dry of ashy gray color, present deformity of the vertebrae bodies, "goose-stepping" gait, X-ray shows systemic osteoporosis. Heart sounds are dull, rhythmical, arterial pressure – 160/100, pulse – 56beats/minute. The level of calcium in the blood – 3.9mmol/l; hypophosphatemia, hyperphophaturia; glycemia – 4.8mmol/l. What is your diagnosis?
1. What is your diagnosis?
2. What are you going to do in this case?

Final modular test. List of tests for the final modular assessment

#1
The major action of insulin is
A) Conversion of glucose to glycogen
B) Proteolysis
C) Conversion of fatty acids to glucose
D) Glycogenolysis
E) Gluconeogenesis

#2
Insulin inhibits this catabolic process
A) Conversion of protein to aminoacids
B) Conversion of aminoacids to proteins
C) Conversion of glucose to fatty acids
D) Glycogenesis
E) Conversion of fatty acids to triglycerides

#3
One of the main causes of hypoglycaemia is
A) Unaccustomed exercise
B) Stress
C) Weight loss
D) Weight gain
E) Diarrhoea

#4
Beta-blockers in the presence of hypoglycaemia may interact as follows
A) Mask tachycardia
B) Mask bradycardia
C) Increase sweating
D) Upset pulmonary circulation
E) Formation of antibodies and immune complexes

#5
Mechanism of sulphonylureas' action includes
A) Stimulation beta cells to secrete insulin
B) Stimulating beta cells to synthesise insulin
C) Inhibiting beta cell to secrete insulin
D) Beyond pancreatic activity

E) Inhibiting insulin resistance

#6
Duration of intermediate-acting insulin is
A) 12-18 hours
B) 6-18 hours
C) 12-24 hours
D) 24-36 hours

#7
Duration of long-acting insulin is
A) 18-30 hours
B) 6-18 hours
C) 24-36 hours
D) 36-72 hours

#8
Which assertion is true for long acting insulin?
A) Acts 24-30 hours
B) Peak of action on 24 hour
C) Include Sol. Insulin Actrapid
D) Is not recommended for short-term treatment
E) Begins its action in 30 min.

#9
Choose insulin without peak of action
A) Glargine
B) Actrapid
C) Novorapid
D) Protaphane
E) Insulin NPH

#10
Which insulin allows for once-daily dosing?
A) Glargine
B) Actrapid
C) Novorapid
D) Protaphane
E) Insulin NPH

#11
Insulin is obligatory in the following states, except:
A) Light course of type 2 diabetes mellitus
B) Pregnancy in patients with type 2 diabetes mellitus
C) Lactation in patients with type 2 diabetes mellitus
D) Ketoacidosis in patients with type 2 diabetes mellitus
E) Surgery in patients with type 2 diabetes mellitus

#12
Which of the following is not correct for oral hypoglycaemic drugs?
A) Stimulation of insulin synthesis
B) Reduction of carbohydrate absorption
C) Inhibition of gluconeogenesis
D) Stimulation of insulin release
E) Anorexigenic effect

#13
Which drug is considered first-generation sulfonylureas?
A) Chlorpropamide
B) Glyburide
C) Glipizide
D) Glimepiride
E) Gliquidone

#14
Choose appropriate caloric needs (kcal/kg) regarding light physical activity
A) 30
B) 35
C) 40
D) 45
E) 50

#15
Interpret GTT. Fasting glucose level is 6.3 mmol/l; 2 hours after glucose ingestion 15.7 mmol/l in plasma.
A) Diabetes mellitus
B) Impairment of carbohydrate tolerance
C) Normal
D) Necessary to repeat test
E) Additional laboratory investigations are indicated

#16
Interpret GTT. Glycemia: I trial – 5,3 mMol/l, II trial – 8,2 mMol/l, III trial – 4,8 mMol/l
A) Normal
B) Impairment of carbohydrate tolerance
C) Diabetes mellitus
D) Necessary to repeat test
E) Necessary to order additional laboratory tests.

#17
Which of the statement given below is correct relatively to GTT?
A) Correlates with determination of potential abnormalities of glucose tolerance
B) Helpful to choose the most appropriate treatment
C) Used to differentiate type of diabetes
D) Indicate stage of diabetes
E) Useful in the seeking of early diabetic complications

#18
Development of type 2 DM is characterised by
A) Overwhelming secretion of β-cells in Langerhans islets
B) Overwhelming secretion of α-cells in Langerhans islets
C) Increased insulin sensitivity
D) Decreased glucose level in plasma
E) Hypercortisolism
#19
What is the most dangerous adverse effect following use of biguanides?
A) Lactic acidosis
B) Hypoglycaemia
C) Diabetic ketoacidosis
D) Hyperosmolality
E) Hyperglycaemia

#20
Which of the following drugs may precipitate cardiovascular complications?
A) Glyburide
B) Gliclazide
C) Glimepiride
D) Acarbose
E) Nateglinide

#21
Macroangiopathy, as a symptom of diabetes mellitus, most often destroy vessels of:
A) Brain
B) Lung
C) Retina
D) Kidneys
E) Liver

#22
Criterion for light stage of type 2 diabetes mellitus:
A) Reaching compensation by diet and phytotherapy
B) Glomerulosclerosis
C) Glucose in blood – 3.3-5.5 mmol/l
D) Nonproliferative retinopathy
E) Reaching compensation by oral drug therapy

#23
Criterion for severe course of type 1 diabetes mellitus
A) Proliferative diabetic retinopathy
B) Ketoacidosis
C) Diarrhoea
D) Daily insulin dose within 60-70 U
E) Acanthosis nigricans

#24
Renal complications in patients with diabetes mellitus present with symptoms of:
A) Frequent urinary infection
B) Increased frequency of renal cancer
C) Nephrolithiasis
D) Nephrocystosis
E) Nephrocele

#25
Which assertion is not correct as regards to angiopathy of lower extremities?
A) Paresthesia
B) Pain in legs when walking
C) Decrease of foot temperature
D) Developing of foot gangrene
E) Step by step trophic disturbance beginning with fingers

#26
Clinical feature of lung impairment due to diabetes mellitus include all, except:
A) Cancer
B) Recurrent pneumonia
C) Tuberculosis with dump cavern
D) Disseminated tuberculosis
E) Effusion forms of tuberculosis

#27
We can suspect hypoglycaemia after use of:
A) Sulfonamides
B) Coffeinum
C) Cardiac glycosides
D) Penicillin
E) Levothyroxine

#28
Skin impairment which takes place in patients with diabetes mellitus is:
A) Disposition to skin infection
B) Hyperpigmentation
C) Depigmentation
D) Dermatofibrosis
E) Dermatomyoma

#29
Gastrointestinal complications of diabetes include all, except:
A) Gastrorrhagia
B) Diarrhoea
C) Gastroparesis
D) Decreasing of gastric secretion
E) Anorexia

#30
Choose false statement relatively to the nervous system impairment in patients with diabetes mellitus
A) Incidence is rare
B) Often manifest with reduction of tendon reflexes
C) Usually presented as encephalopathy
D) Associated with sensitive lesions on lower extremities
E) Charcot Joint" spares motor function

#31
Which of the features given below is correct with regard to bone lesion due to diabetes mellitus?
A) Dupuytren contracture
B) Aseptic necrosis of bone
C) Skeletal hyperostosis
D) Articular cartilage calcification
E) Seronegative polyarthritis

#32
Patient K., suffering from diabetes mellitus during the past 8 years, is in coma. The skin is dry, Kussmaul's respiration, acetone breath is evidenced. What type of coma is it?
A) Ketoacidosis
B) Lactic acidosis
C) Hyperosmolar state
D) Hypoglycaemic coma
E) Brain coma

#33
Thyroid secretes all of the following hormones, except:
A) Thyrotropin
B) Calcitonin
C) Thyroxine
D) Diiodotyrosine
E) Triiodothyronine

#34
Biological role of thyroid hormones embrace all of the following, except
A) Sexual development
B) Growth regulation
C) Tissue differentiation
D) Regulation of metabolic processes
E) Calorigenesis

#35
To estimate thyroid function you should order:
A) Determination of T_3 and T_4 levels in blood

B) Film of sella turcica
C) Determination of ^{131}I uptake
D) Ultrasonography of thyroid gland
E) Biopsy

#36
Which assertions regarding thyroid synthesis are correct?
A) Disturbed following iodine deficiency
B) Stimulated by corticotropin
C) Depressed by hyperglycaemia
D) T_4 is derived from T_3 on periphery
E) Thyroid synthesis 80% of T_3 and 20% of T_4

#37
Symptoms of hyperthyroidism are, except
A) Weight gain
B) Increased metabolism
C) Tachycardia
D) Exophthalmia
E) Increased heat production

#38
Choose correct statement relatively to the detrimental action of increased thyroid hormone production
A) T_3 sensitises the myocardium to the effects of catecholamines
B) T_3 and T_4 cause hyperprolactinemia
C) Weight gain is related with thyroid overproduction
D) T_4 directly induce tachycardia
E) Excessive level of thyroid hormones predisposes to constipation

#39
Choose agent, which inhibits synthesis of thyroid hormones
A) Thiamazole
B) Potassium perchlorate
C) Potassium iodide
D) Iopanoic acid
E) Dexamethasone

#40
Choose agent, which decreases thyroid hormone release
A) Potassium iodide

B) Potassium perchlorate
C) Thiamazole
D) Propylthiouracil
E) Dexamethasone

#41
Choose agent, which diminishes sympathetic reactions in the treatment of Graves' disease
A) Propranolol
B) Potassium perchlorate
C) Thiamazole
D) Propylthiouracil
E) Potassium iodide

#42
Mean duration of symptomatic treatment of thyrotoxicosis is
A) 2-4 weeks
B) 1-2 weeks
C) 1 week
D) 10-12 days
E) 1-2 months

#43
Choose agent, which inhibits iodide trapping
A) Potassium perchlorate
B) Propranolol
C) Thiamazole
D) Propylthiouracil
E) Potassium iodide

#44
What potential adverse effects may be expected following long-term use of ^{131}I for the treatment of hyperthyroidism?
A) Hypothyroidism
B) Suppurative thyroiditis
C) Thyroid storm
D) Toxic multinodular goiter
E) Autoimmune thyroiditis

#45
The treatment of Grave's disease first of al usually include

A) Thionamides
B) Antidepressants
C) Narcotic analgesics
D) Diuretics
E) Sulfonamides

#46
Which states are contraindications for surgical treatment of goiter?
A) Diffuse toxic goiter in decompensation
B) Nodular goiter
C) Toxic goiter in pregnancy
D) Adenoma of thyroid gland
E) Diffuse toxic goiter in compensation

#47
In the moderate stage of thyrotoxicosis which of the following statements is not typical:
A) Retinopathy
B) Tachycardia 100-120/min.
C) ^{131}I uptake after 4 hours within 30-40%
D) 10-20% of weight loss
E) Low level of TSH

#48
Severe course of thyrotoxicosis may be established, if there is
A) Tachycardia over 120/min.
B) III stage of thyroid enlargement
C) ^{131}I uptake after 4 hours within 30-40%
D) "Hot" zones on radioisotope scanning
E) High level of TSH

#49
In the pathogenesis of hypothyroidism which of the following is not correct?
A) Low levels of antithyroid antibodies
B) Autoimmune process in thyroid gland
C) Decrease in thyroid hormone synthesis
D) Inadequate secretion of thyrotropin
E) Peripheral resistance to effect of thyroid hormones

#50
Clinical picture of hypothyroidism includes all the following symptoms except

A) Hyperdefecation
B) Drowsiness
C) Slow speech
D) Weight gain
E) Pernicious anaemia

#51
In hypothyroidism the cardiac system presents as follows:
A) Decrease of ECG voltage
B) Increase of ECG voltage
C) High, sharp T wave
D) Persistent tachycardia
E) Relation to the early development of atherosclerosis is absent

#52
Which symptom is common for hypothyroidism?
A) Dry skin
B) Face plethora in the evening
C) Swelling of legs in the morning
D) Paresthesia of hands after light home work
E) Ulcer on crura

#53
Features of hypothyroidism in children include all, except:
A) Wet skin
B) Retardation of sexual development
C) Retardation of physical and intellectual development
D) Retarded bone age
E) Constipation

#54
Appropriate treatment of hypothyroidism includes
A) Using sodium levothyroxine
B) Using triiodothyronine
C) Complex preparations with thyroxine and triiodothyronine
D) Potassium iodide
E) Vitamin D

#55
State adverse effects of thyroid hormone replacement, except
A) Oedema

B) Weight loss
C) Tachycardia
D) Cardiac arrhythmias
E) Restlessness

#56
Primary hypothyroidism develops as a result of
A) Thyroid pathology
B) Pathologies of pituitary gland
C) Hypothalamus disorders
D) Peripheral resistance to effect of thyroid hormones
E) Loss of thyroid hormones during nephritis

#57
Secondary hypothyroidism develops as a result of
A) Pathologies of pituitary gland
B) Thyroid pathology
C) Hypothalamus disorders
D) Peripheral resistance to effect of thyroid hormones
E) Loss of thyroid hormones during nephritis

#58
Laboratory findings show elevation of TSH concentration and increment in T_3 and T_4 level. State the most appropriate type of hypothyroidism
A) Peripheral hypothyroidism
B) Secondary hypothyroidism
C) Primary hypothyroidism
D) Tertiary hypothyroidism
E) Resultant hypothyroidism following autoimmune thyroiditis

#59
Lack of thyroid hormones in children produces
A) Cretinism
B) Myxedema
C) Hashimoto disease
D) Graves' disease
E) Autoimmune thyroiditis

#60
What is the dose range of sodium levothyroxine in the treatment of hypothyroidism?
A) 25-200 μg once a day in the morning

B) 25-200 μg once a day in the evening
C) 100-200 μg once a day in the morning
D) 25-100 μg once a day in the evening
E) 25-50 μg once a day in the morning

#61
What points, concerning myxedema coma are correct ?
A) Hypothermia is common
B) Feeling warm may provoke myxedema coma
C) Cause is – increase sensitivity to T_3 and T_4 receptors.
D) Hyperfunction of adrenal glands is present
E) Thyroid cancer

#62
All clinical signs are typical for acute thyroiditis except:
A) Vomiting
B) Increasing of body temperature
C) Neck pain
D) Enlargement of regional lymphatic nodules
E) Painful of thyroid gland during palpation

#63
Manifestation of acute thyroiditis upon thyroid palpation include:
A) Pain upon palpation
B) Solid as stone appearance
C) Doughy consistency
D) Palpation of separate nodules
E) Connecting with skin

#64
Treatment of subacute thyroiditis includes:
A) Acetylsalicylic acid
B) Surgery
C) Lugol's solution
D) β-Adrenergic blockers
E) Radioactive iodine (^{131}I)

#65
Which group of drugs is the most suitable in the treatment approach of acute thyroiditis?
A) Antibiotics

B) Acetylsalicylic acid
C) Physiotherapy
D) Corticosteroids
E) β-Adrenergic blockers

#66
Which statement is not correct relatively to Hashimoto thyroiditis?
A) Abscess of thyroid
B) Often occurs in young persons
C) Lymphoid infiltration in thyroid
D) Lymphocytosis
E) Plasmatic infiltration in thyroid

#67
Calcitonin has the following biological effects, except:
A) Inhibition of vitamin D activity
B) Decreased Ca level in blood
C) Decreased phosphorus levels in blood
D) Inhibition of gastrin secretion
E) Inhibits bone resorption

#68
To remove onset of tetany you will order
A) Calcium chloride
B) Prednisolone
C) Benzylpenicillin
D) Potassium citrate
E) Magnesium sulfate

#69
Obesity is not typical for
A) Hyperparathyroidism
B) Hypogonadism
C) Hypothyroidism
D) Lipomatosis
E) Hypercortisolism

#70
Name criterion, which is not indicate hypoparathyroidism
A) Hypercalcemia
B) Hypocalcemia

C) Hyperphosphatemia
D) Law level of parathyroid hormone in blood
E) Hypocalceuria

#71
You determine bone pain in patient with recidivation of nephrolithiasis. What should you suspect?
A) Hyperparathyroidism
B) Hypoparathyroidism
C) Paget disease
D) Myeloma
E) Anaemia

#72
In hyperparathyroidism it is not common to find
A) Persistent hypotension
B) Muscle weakness
C) Neuropathy
D) Recidivation of nephrolithiasis
E) Pain in bone

#73
Biological activity of vitamin D includes all of the following, except
A) Increase of Ca^{2+} excretion in kidneys
B) Intensification of Ca^{2+} absorption in guts
C) Stimulation of synthesis of bone matrix
D) Stimulation of calcification matrix in bone
E) Stimulation of metabolism in muscles

#74
The anterior part of the hypophysis secretes the following hormones, except
A) Vasopressin
B) Somatotropin
C) Corticotropin
D) Thyrotropin
E) Prolactin

#75
Developing of gigantism is conditioned by:
A) Overwhelming secretion of GH in adolescence
B) Overwhelming secretion of GH in old age

C) Overwhelming secretion of GH in adults
D) Overwhelming secretion of somatostatin in adults
E) Inborn sensitivity lack in tissues to GH

#76
Physiological influence of vasopressin is evidenced by:
A) Increased water reabsorption in distal tubules
B) Increased diuresis
C) Intensification of Na excretion
D) Spasm of uterus
E) Increased glucose reabsorption

#77
What is the main cause of Cushing disease?
A) Hypersecretion of corticotropin
B) Tuberculosis
C) Adrenocortical carcinoma
D) Autoimmune adrenalitis
E) Hypersecretion of catecholamines

#78
Next statement is not common in clinic of hypopituitarism:
A) Hirsutism
B) Hypogonadism
C) Hypothyroidism
D) Hypocorticism
E) Lose flesh

#79
In the treatment of diabetes insipidus it is necessary to prescribe
A) Chlorpropamide
B) ACTH
C) Sulphonamides
D) Furosemide
E) Penicillin

#80
Concerning acromegaly the following is not correct:
A) Hypotension is common

B) Hypersecretion of somatotropin
C) Increased cranial pneumatization
D) Impaired glucose tolerance
E) Thickened cranial bone on film

#81
Examination of the patient with acromegaly reveals all signs given bellow, except:
A) Lagging physical and sexual development
B) Pituitary adenoma
C) Osteoporosis
D) Cardiomegaly
E) Splanchomegaly

#82
What specific sign you may notice in the urine analyses in the patient with diabetes insipidus?
A) Low level of specific gravity
B) High proteinuria
C) Macroscopic hematuria
D) Microscopic hematuria
E) Leukocyturia

#83
Which state, given below, is not allied with short stature?
A) Rheumatoid arthritis
B) Hypothyroidism in children
C) Pituitary nanism
D) Osteochondroplasias
E) Mauriac syndrome

#84
What bone changes are not common in patients with acromegaly?
A) Osteochondrosis
B) Bony disfigurement
C) Osteoporosis
D) Polyostotic fibrous dysplasia
E) Arthropathy

#85
The following hormone is not synthesised by the adrenal cortex:
A) Testosterone

B) Cortisol
C) Aldosterone
D) Dehydroepiandrosterone
E) Androstenedione

#86
Choose factors, which can cause Addison's disease
A) Tuberculosis
B) Tumour acting on hormone of adrenals
C) Pneumonia
D) Autoimmune thyroiditis
E) Diabetes mellitus

#87
Main clinical signs of acute adrenal failure are:
A) Vomiting, diarrhoea
B) Loud breathing, bradycardia
C) Acetone breath, aggressiveness
D) Polydipsia, polyuria
E) Neck pain, hypertension

#88
The following clinical features of Addison's disease are all correct, except
A) Diffuse lipomatosis
B) Weight loss
C) Hyperpigmentation
D) Hypotension
E) Dyspepsia

#89
Gastrointestinal affects in patients with Addison's disease are associated with:
A) Hyposecretion of gastric fluids
B) Constipation
C) Bulimia
D) Hypersecretion of gastric fluids
E) Intestinal colic

#90
Affects on the cardiovascular system in patients with Addison's disease include all, except:
A) Cardiomegaly

B) Hypotension
C) Bradycardia
D) Decreasing ECG voltage
E) Reduction in the dimensions of heart

#91
Which statement is correct according to low Liddle's test?
A) In the diagnostic approach to determine hypercortisolism
B) To differentiate Cushing's syndrome from Cushing's disease
C) Total 4 mg of dexamethasone per day
D) Total 6 mg of dexamethasone per day
E) 0.5 mg of dexamethasone once a day

#92
Prominent effect of the cardiovascular system in patient with hypercortisolism is:
A) Hypertension
B) Bacterial endocarditis
C) Bundle-branch block
D) Sinus bradycardia
E) Respiratory arrhythmia

#93
Overproduction of androgens is evidenced by
A) Hirsutism
B) Low level of 17-KS in urine
C) Gigantism
D) Cretinism
E) Mental retardation

#94
Temporary lack of physical pubertal development due to the following conditions, except:
A) Isolated gonadotropin deficiency
B) Malnutrition
C) Emotional stress
D) Excessive physical stress
E) Untreated endocrinopathies

#95
Permanent hypothalamic or pituitary gonadotropin deficiency due to the following conditions, except:

A) Untreated endocrinopathies
B) Isolated gonadotropin deficiency
C) Multiple pituitary hormone deficiency
D) Prader-Willi syndrome
E) Kallmann syndrome

#96
Differential diagnosis of ambiguous genitalia includes the following measures, except;
A) Bone age x ray
B) Physical examination
C) Contrast urography
D) Chromosomal evaluation
E) Stimulation or suppression tests

#97
Contraindications to estrogen therapy in menopause embrace the following, except:
A) Osteoporosis
B) Estrogen-dependent tumors
C) Acute liver disease
D) Thromboembolic disease
E) Severe hypertension

#98
Indications to estrogen therapy does not include:
A) Thromboembolic disease
B) Osteoporosis
C) Disable hot flushes
D) Severe mucosal atrophy of the GU tract
E) Certain psychiatric symptoms

#99
Choose the drug, which will not cause gynecomastia
A) Metformin
B) Cimetidine
C) Estrogens
D) Isoniazid
E) Digitalis preparations

#100
What statement is not correct relatively to the polycystic ovary syndrome?
A) Alopecia is common

B) Polycystic ovary syndrome presents with elevated androgen levels
C) Patients with polycystic ovary syndrome have amenorrhea
D) Hirsutism is common
E) Obesity is often found

#101
All of the following medications are types of insulin, except:
A) Aspart (Novolog)
B) Glargine (Lantus)
C) Lispro (Humalog)
D) Glulisin (Apidra)
E) Exenatide (Byetta)

#102
Insulin therapy has all of the following effects, except:
A) Increases concentration of free fatty acids in blood plasma
B) Stimulates glucose uptake by tissues
C) Inhibits lipolysis
D) Activates protein synthesis

#103
Insulin preparations can have the following durations of action:
A) Fast and long
B) Fast, medium and long
C) Polar, non-polar, neutral
D) Very fast, fast, medium and long
E) Subpolar, polar, non-polar

#104
The insulin that does not have a peak of action is:
A) Glulisin (Apidra)
B) Glargine (Lantus)
C) Isophane (Protaphane)
D) Biphasic Insulin N 70/30
E) Aspart (Novolog)

#105
Insulin formulation that has a very fast onset of action is:
A) Glargine (Lantus)
B) Soluble human (Humodar)

C) Lispro (Humalog)
D) Human Isophane (Фармасулін HNP)
E) Detemir (Levemir)

#106
Oral hypoglycemic agents include all of the following, except:
A) Sulfonylureas
B) Biguanides
C) Phosphodiesterase inhibitors
D) Thiazolidinediones
E) Alpha-glucosidase inhibitors

#107
Which of the following medications is not one of the sulfonylurea derivatives?
A) Gliclazide
B) Glimepiride
C) Gliquidone
D) Glibenclamide
E) Avandia

108
Which of the following medications belongs to the sulfonylurea derivatives:
A) Nateglinide
B) Pioglitazone
C) Glimepiride
D) Repaglinide
E) Metformin

#109
Please, choose an appropriate therapy for treatment of patients with type II diabetes and obesity:
A) Actrapid and protaphane
B) Metformin and glimepiride
C) Glibenclamide and protaphane
D) Glibenclamide and glibomet
E) Gliclazide and actrapid

#110
Please, choose the best therapy for treatment of diabetes in a patient with coexisting coronary artery disease:
A) Glimepiride

B) Acarbose
C) Rosiglitazone
D) Glibenclamide
E) Metformin

#111
Which side effects are not commonly seen with sulfonylureas?
A) Hypoglycemia
B) Headache
C) Dizziness
D) Diaphoresis
E) Gastrointestinal disturbances

#112
Sulfonylureas are contraindicated in all of the following patients, except:
A) Patients with type I diabetes mellitus
B) Patients with renal insufficiency
C) Patients with liver disease
D) Pregnant patients
E) Patients with arterial hypertension

#113
Metformin is contraindicated in all of the following situations, except:
A) Increased BMI
B) Tendency to develop lactic acidosis
C) Diarrhea and other gastrointestinal disturbances
D) Pregnancy
E) Breast feeding

#114
All of the following are indications for acarbose use, except:
A) Monotherapy for type II diabetes
B) Monotherapy for type I diabetes
C) Combination therapy with insulin for type I diabetes
D) Combination therapy with glimepiride for type II diabetes
E) Combination therapy with insulin for type II diabetes

#115
AAll of the following qualities apply to nateglinide, except:
A) Short half-life
B) Minimal risk for developing hypoglycemia

C) Metabolized by liver
D) Restores early insulin secretion
E) Excreted by kidneys

#116
One of the indications for prescribing nateglinide is:
A) Depletion of pancreatic beta-cells
B) Significant postprandial hyperglycemia
C) Tendency to develop lactic acidosis
D) Resistance to sulfonylureas
E) Insulin resistance

#117
All of the following are true with respect to thiazolidinediones, except:
A) They influence insulin resistance
B) They result in frequent episodes of hypoglycemia
C) They slow down progression of renal disease and development of hypertension.
D) They decrease blood level of free fatty acids
E) They improve metabolism

#118
All of the following are true with respect to alpha-glucosidase inhibitor, except:
A) It inhibits intestinal alpha-glucosidase
B) It decreases enzymatic conversion of oligo- to monosaccharides
C) It lowers postprandial glucose
D) It causes gastrointestinal disturbances.
E) It may cause development of hypertension.

#119
Alpha-glucosidase inhibitors are contraindicated in all of the following cases, except:
A) Diabetic ketoacidosis
B) Liver cirrhosis
C) Hypertension
D) Large abdominal hernias
E) Ulcerative colitis

#120
Activity of alpha-glucosidase inhibitors is decreased by all of the following medications, except:
A) Enzymes

B) Adrenergic blockers
C) Oral contraceptive agents
D) Thiazide diuretics
E) Isoniazid

#121
All of the following medications augment activity of sulfonylureas, except:
A) Anabolic steroids
B) ACE inhibitors
C) Salicylates
D) Loop diuretics
E) Tetracyclines

#122
All of the following augment activity of biguanides, except:
A) MAO inhibitors
B) ACE inhibitors
C) Beta blockers
D) Delayed calcium channel blockers
E) Tetracyclines

#123
What is typically seen with biguanide use?
A) Increased glucose uptake by muscle tissue
B) Decreased basal insulin level
C) Decreased intestinal glucose absorption
D) Gastrointestinal disturbances
E) Decreased lactate level

#124
Which of the following medications does not have hypoglycemic effects (does not augment insulin activity)?
A) Loop diuretics
B) Somatostatin analogues
C) MAO inhibitors
D) ACE inhibitors
E) Beta- blockers
#125
Which of the following medications does not have hypoglycemic effects (does not augment insulin activity)?
A) Glicised (Glicinum)

B) Salicylates
C) Sulfanilamide
D) Ethanol
E) Fluoxetine

#126
Which of the following medications does not have hyperglycemic effects (does not decrease insulin actions)?
A) Calcium channel blockers
B) Beta 2 agonists
C) Pentoxifylline
D) H2 histamine receptor blockers
E) Isoniazid

#127
Which of the following medications does not have hyperglycemic effects (does not decrease insulin action)?
A) Calcitonin
B) Morphine sulfate
C) Nicotine
D) Betadin
E) Thyroid hormones

#128
Insulin should be prescribed under all of the following circumstances, except:
A) Status post pancreatectomy
B) Type 2 diabetes with diabetic foot syndrome
C) Type 1 diabetes
D) Gestational diabetes
E) Type 2 diabetes

#129
All of the following are possible side effects of insulin use, except:
A) Hypoglycemic coma
B) Insulin resistance
C) Weight loss
D) Weight gain
E) Lipodystrophy at injection sites

#130
What insulin dose is used for coma secondary to diabetic ketoacidosis?
A) 0,1 U/кg/hr

B) 1 U/кg/hr
C) 80-100 U/24 hours
D) 40-60 U/24 hours
E) 100-200 U/24 hours

#131
Thyroid hormones have all of the following qualities, except:
A) They activate synthesis of RNA and amino acids
B) They increase basal metabolism
C) They inhibit erythropoesis
D) They increase heat production
E) They stimulate insulin breakdown

#132
Thyroid hormones have all of the following qualities, except:
A) They stimulate gluconeogenesis
B) They acrivate central respiratory center
C) They inhibit pituitary TSH (thyroid stimulating hormone) synthesis
D) They inhibit gluconeogenesis
E) They increase basal metabolism

#133
All of the following are side effects associated with thyroid hormone use, except:
A) Heat intolerance
B) Weight gain
C) Hyperhydrosis
D) Irritability
E) Insomnia

#134
All of the following are side effects associated with thyroid hormone use, except:
A) Weight loss
B) Tachycardia
C) Decreased tendon reflexes
D) Diarrhea
E) Tachyarrythmia

#135
Thyroid medications are contraindicated in all of the following circumstances, except:
A) Chronic heart failure

B) Untreated hyperthyroidism
C) Untreated adrenal insufficiency
D) Acute coronary syndrome
E) Decompensated tachyarrhythmia

#136
Thyroid hormone doses should be increased when used concurrently with:
A) Estrogens
B) Clofibrate
C) 5 methylfluorouracil
D) Androgens
E) Tamoxifen

#137
All of the following are true about anti-thyroid medications, except:
A) They inhibit iodine transport into a follicle
B) They alter thyroid hormone synthesis
C) They inhibit release of thyroid hormones
D) They activate synthesis of thyroid peroxidase
E) They destroy thyroid gland follicles

#138
All of the following are side effects associated with thionamide use, except:
A) Arterial hypertension
B) Agranulocytosis
C) Nausea
D) Arthralgia
E) Toxic hepatitis

#139
Activity of thionamide is potentiated by all of the following, except:
A) Anticoagulants
B) Beta blockers
C) Sulfasalazine
D) ACE inhibitors
E) Theophylline

#140
Which of the following endocrine side effects is not typically seen with glucocorticoid use?
A) Development of Cushing syndrome

B) Increased virility in male patients
C) Delayed growth and development of pediatric patients
D) Decreased carbohydrate tolerance
E) Disturbances in ovulatory/menstrual cycles

#141
Which of the following electrolyte/fluid regulation abnormalities is not seen with glucocorticoid use?
A) Sodium retention
B) Fluid retention
C) Arterial hypertension
D) Heart failure
E) Potassium retention

#142
Which of the gastrointestinal side effects is not usually seen with glucocorticoid use?
A) Peptic ulcer disease
B) Gastrointestinal bleeding
C) Hemorrhoids
D) Pancreatitis
E) Abdominal bloating

#143
Which of the musculoskeletal side effects is not usually seen with glucocorticoid use?
A) Muscle weakness
B) Increase in muscle mass
C) Osteoporosis
D) Pathologic fractures of long bones
E) Spine compression fractures

#144
Which of the following is not true with respect to glucocorticoid use?
A) They augment actions of anticoagulants
B) They augment actions of antiplatelet agents
C) They augment actions of hypoglycemic agents
D) They decrease efficacy of hypoglycemic agents
E) They increase side effects associated with anabolic steroids use.

#145

All of the following doses of iodine containing agents are used to prevent iodine deficiency in the following patients, except:
A) Breastfeeding mothers 200 mcg/24 hours
B) Pregnant women 200 mcg/24 hours
C) Teenagers and adults 100-200 mcg/24 hours
D) Children 50-100 mcg/24 hours
E) People with intellectual work 300 mcg/24 hours

#146
When glucocorticoids are prescribed using "twice a day" dosing, the doses should be divided in the following manner:
A) Half in the morning and half in the evening
B) Two thirds in the morning and one third in the afternoon
C) One third in the morning and two thirds in the evening
D) Half in the morning and half in the afternoon
E) One third in the afternoon and two thirds in the evening

#147
You have just diagnosed lactic acidosis and associated coma. What is the first medication that should be administered in this situation?
A) 8.5% Sodium Bicarbonate drip
B) 20-25 U of short-acting insulin IV (intravenous)
C) 40-60 U of short-acting insulin SQ (subcutaneous)
D) 50-10 cc of 40% glucose
E) 400-500 cc of 5% glucose

#148
Which of the following medications has the longest duration of action?
A) Glibenclamide
B) Gliquidone
C) Repaglinide
D) Metformin
E) Gliclazide MR

#149
Which of the anti-hypertensive agents listed below is the agent of choice for treatment of diabetic kidney disease?
A) Rezerpin
B) Adelphane
C) Crystepin
D) Haemiton

E) Lisinopril

#150
Patient developed thyrotoxic crisis. Which of the following medications should be used in this case?
A) Methimazole 50-60 mg may be prescribed through a nasogastric tube (should be crushed first)
B) 40-60 U of short-acting insulin SQ
C) 40-60 cc if 40% glucose solution
D) 8.5% Sodium Bicarbonate drip
E) 400 cc of 0.9% of sodium chloride

#151
Which of the following medications should be used in the case of hypoglycemic coma?
A) 20 U of insulin SQ
B) 40-80-100 cc of 40% glucose solution
C) 20 U of insulin IV
D) 500 cc of 5% glucose solution IV
E) 500 cc of 0.9% of sodium chloride IV

#152
Which of the following medications are used in the treatment of pheochromocytoma?
A) Ganglion blockers
B) Slow calcium channel blockers
C) Alpha blockers
D) Beat blockers
E) Chloditanum

#153
In what trimester should pregnant women with adrenal insufficiency take higher doses of glucocorticoids?
A) First
B) Second
C) Third
D) First and second
E) First and third

#154
Which of the following medications is contraindicated in Addison's disease?
A) Prednisolone

B) Dexamethasone
C) Fludrocortisone Acetate
D) Adrenocorticotropic hormone
E) Hydrocortisone

#155
Patient developed rhinitis and conjunctivitis while undergoing treatment for diffuse toxic goiter. Which of the following medications could have caused these side effects?
A) Reserpin
B) Propranolol
C) Mercazolilum
D) Lugol's solution
E) Prednisolone

#156
Which of the following medications should be used in a patient with autoimmune thyroiditis who has a large goiter and high titer of anti-thyroid antibodies?
A) Thyroxin
B) Prednisolone
C) Suprastin
D) Verapamil
E) Propranolol

#157
Which of the following side effects can be associated with anti-diuretic hormone (ADH) analogues?
A) Depression
B) Increased irritability
C) Decreased vision
D) Seizures
E) Headache

#158
What is a 24 hour requirement of insulin in an adult person?
A) 10-20 U
B) 20-30 U
C) 30-40 U
D) 40-60 U
E) 100-120 U

#159

Which medication is an agent of choice for treatment of diffuse toxic goiter?
A) Lithium carbonate
B) Lithium gluconate
C) Thiamazole
D) Glucocorticoids
E) Propranolol

#160
Which of the following medications should be prescribed for a patient with type II diabetes and co-existing chronic pyelonephritis?
A) Glibenclamide
B) Metformin
C) Gliquidone
D) Gliclazide
E) Rosiglitazone

#161
Indications for prescribing sulfonylurea for diabetes include:
A) Type 1 diabetes
B) Type 2 diabetes with normal body weight
C) Type 2 diabetes with increased body weight
D) Type 2 diabetes with weight loss
E) Diabetic nephropathy

#162
They following class of medications is the treatment of choice for diabetic nephropathy:
A) Angioprotectors
B) ACE inhibitors
C) Non-selective beta blockers
D) Selective beta blockers
E) Alpha blockers

#163
Patient has chronic adrenal insufficiency. Which medication should be prescribed first?
A) 25 mg of hydrocortisone IM (intramuscularly)
B) 500 cc of 5% glucose solution
C) 4% of sodium bicarbonate 2.5 cc/kg
D) 5% ascorbic acid solution
E) 500 cc of 0.9& sodium chloride solution

#164
Which of the following treatments is appropriate for a patient with diffuse toxic goiter during the third trimester of pregnancy?
A) Subtotal thyroid gland resection
B) Treatment with radioactive iodine
C) Lugol's solution
D) Propylthiouracil
E) Prednisolone

#165
Thyroid hormone analogue overdose can be associated with:
A) Tremors
B) Increased irritability
C) Nightsweats
D) Weight loss
E) All of the above

#166
Patient with toxic multinodular goiter developed hyperthermia and sore throat while undergoing medical therapy. Which medication could have caused these side effects?
A) Potassium and magnesium aspartate
B) Propranolol
C) Mercazolilum
D) Prednisolone
E) Dimedrolum

#167
Which of the following medications should be used to stabilize arterial blood pressure in a patient with diabetes and lactic acidosis coma?
A) Phenylephrine
B) Adrenalin
C) Glucagon
D) Hydrocortisone
E) Cordiaminum

#168
Which of the following medications is most efficient at increasing glucose uptake by peripheral tissues?
A) Pentoxifylline
B) Chlorpropamide

C) Nicotinic acid
D) Metformin
E) Solcoseryl

#169
Overdose by thyroid hormones during childhood leads to:
A) Delayed sexual development
B) Early sexual maturation
C) Heart rhythm abnormalities
D) Acceleration of growth and bone differentiation
E) Deceleration of growth and bone differentiation

#170
Overdose by thyroid hormones in elderly patients most commonly leads to:
A) Increased irritability
B) Atrial fibrilation
C) Aggression
D) Psychosis
E) Psychomotor excitation

#171
Which of the following medications is most appropriate for treatment of arterial hypertension in patients with benign prostatic hypertrophy?
A) Amlodipine
B) Atenolol
C) Diltiazem
D) Doxazosin
E) Losartan

#172
Which of the following combinations should not be used for treatment of hypertension in patients with erectile dysfunction?
A) Dosartan + torasemide
B) Lisinopril + furosemide
C) Doxazosin + tadanafil
D) Nimodipine + sildenafil
E) Metoprolol + spironolactone
#173
Which of the testosterone formulations has the longest duration of action?
A) Testosterone proprionate
B) Testosterone enantat
C) Testosterone cypionate

D) Testosterone undecanoat
E) Testosterone phenylproprionat

#174
Which of the following combinations should be used in the setting of hypogonadism with decreased testicular size?
A) Fludrocortisone + testosterone proprionate
B) Chorionic gonadotropin + testosterone undecanoat
C) Doxazosin + sildenafil
D) Metoprolol + sildenafil
E) Chorionic gonadotropin + spironolactone

#175
Which of the following medications is the treatment of choice for hyperprolactinemia?
A) Chloditanum
B) Cabergoline
C) Bromocriptine
D) Clomiphen
E) Mesterolone

#176
Which of the following medications does not have anti-androgen properties?
A) Spironolactone
B) Cabergoline
C) Cimetedine
D) Cyproterone
E) Ketoconazole

#177
Which of the following medications is used most frequently for stimulation of ovulation?
A) Cabergoline
B) Fludrocortisone
C) Cyproterone
D) Clomiphen
E) Dydrogesterone

#178
Which of the oral contraceptives listed below has anti-androgen properties?
A) Mersolon
B) Novinet

C) Lindynet
D) Logest
E) Diane 35

#179
Which of the following side effects is not usually seen with overdose of calcitriol (vitamin D3) during treatment of hypoparathyroidism?
A) Hypercalcemia
B) Arterial hypertension
C) Metallic taste
D) Hypocalciuria
E) Myalgia

#180
All of the following are contraindications for prescribing calcium supplements and vitamin D3, except:
A) Hypercalcemia
B) Arterial hypertension
C) Hypercalciuria
D) Sarcoidosis
E) Chronic kidney disease.

#181
Patient C., 32 y/o, was delivered unconscious to the intensive care department. The patient has a medical history of diabetes. Insulin was not found. The breathing is noisy, of Kussmaul's type; acetone breath, the skin is dry, turgor is lowered, the facial features are sharp, periosteal reflexes are absent, eye ball tone is lowered. Blood contains 1.2 mmol/l of lactic acid (norm - 0.62-1.3 mmol/l), glycemia - 29 mmol/l. What kind of coma can be suspected?
A) Ketoacidotic
B) Brain coma
C) Hyperosmolar
D) Hypochloremic
E) Lactacidemic

#182
Patient T., 26 y/o, is in the intensive care unit with a ketoacidotic coma. Her consciousness is clouded, eye ball tone is lowered, arterial pressure - 90/60, pulse - 130 beats/minute, glycemia - 35 mmol/l, PH - 7.1. The content of ketone bodies is 18 mg %. How would you manage this patients?

A) Introducing 10-20 units of insulin at first by stream infusion and then by drip infusion during 1 our by 0.05-0.1 units/kg/hour till the termination of ketoacidosis
B) Introducing 500ml 5% glucose solution
C) Introducing 4% sodium carbonate 2.5 ml/kg
D) Introducing 40 – 60 units of insulin hourly
E) Introducing 500 ml 0.9% sodium chloride

#183
Patient M., 36 y/o, was found in the street unconscious. The patient has a medical history of diabetes. There is a smell of alcohol from the mouth. The skin is moist, warm, arterial pressure - 145/90 mm column of mercury, convulsive twitching of muscles. Breathing is shallow, eye ball tone is retained, pupils are dilated, hyperflexion. How would you treat this patients?
A) Intravenous introduction of 40-80-100 ml 40% glucose solution
B) Injecting 20 units of insulin subcutaneously
C) Injecting 20 units of insulin intravenously
D) Injecting 500 ml 5% glucose solution intravenously
E) Injecting 500 ml 0.9% sodium chloride intravenously

#184
Patient B., 18 y/o, is at a pharmacy store, and complains of intensive sweating, trembling hands, numbing of the tip of the tongue, palpitation. It is known that the patient has type 1 diabetes mellitus. His consciousness is clouded; he is disorientated in space and time, aggressive, refuses sweet food. Objectively: tendon and periosteal reflexes are sharply enhanced, positive Babinski's symptom; the skin is moist and warm. Glycemia level on the glucometer is 2.3 mmol/l. There is no odor of acetone from the mouth. What are you going to do in this case?
A) Injecting 20-40 ml (not more than 80 ml) of 40% glucose solution intravenously
B) Injecting 20 units of insulin subcutaneously
C) Injecting 20 units of insulin intravenously
D) Injecting 500 ml 0.9% sodium chloride intravenously
E) Injecting 500 ml 5% glucose solution intravenously

#185
Patient T., 66 y/o, complains of stomach ache, nausea, vomiting and muscle ache. Objectively: evident symptoms of dehydration, Kussmaul's breathing, arterial pressure – 90/50 mm column of mercury, anuria, temperature – 35.9 ºC, glycemia – 12.9 mmol/l, no acetonuria, blood PH – 6.8, lactic acid content -1.7 mmol/l (norm - 0.62 -1.3 mmol/l). What is your diagnosis?
A) Hyperlactacidemic coma
B) Uremic coma

C) Ketoacidotic coma
D) Brain coma
E) Hyperosmolar coma

#186
Patient M., 57 y/o, complains of nausea, vomiting and muscle ache. Objectively: evident symptoms of dehydration, Kussmaul's respiration, arterial pressure - 90/50 mm column of mercury, anuria, temperature – 35.9 ºC, glycemia – 12.9 mmol/l, no acetonuria, blood PH – 6.8, lactic acid content -1.7mmol/l (norm - 0.62 -1.3 mmol/l). Hyperlactacidemic coma has been diagnosed. What therapeutic measures should be taken first of all?
A) Injecting 8.5% solution of sodium bicarbonate, and 1% solution of methylene blue
B) Injecting 20-25 units of short-acting insulin intravenously by stream infusion
C) Injecting 40-60 units of short-acting insulin subcutaneously
D) Injecting 50-100 ml 40% glucose solution
E) Injecting 400 -500 ml 5% glucose solution

#187
Patient M., 72 y/o, is in the intensive care unit with the symptoms of dehydration, oliguria, hypothermia and hypoxia. In anamnesis there is a record of type 2 diabetes mellitus, the patient was treated with biguanides. Her condition began to deteriorate after she had a myocardial infarction one month ago. Objectively: the skin is dry; turgor is lowered, arterial pressure – 80/40 mm column of mercury, pulse – 136beats/minute. The breathing is shallow, eye ball tone is lowered. What is your diagnosis?
A) Hyperlactacidemic coma
B) Uremic coma
C) Ketoacidotic coma
D) Brain coma
E) Hyperosmolar coma

#188
A 14-year-old girl was taken to the department of surgery complaining of acute abdominal pain, nausea and vomiting. The patient has been ill for two weeks after she had an acute respiratory viral disease followed by increasing thirst, mouth dryness and poliuria. Objectively: her consciousness is clouded; eye ball tone is lowered, the breathing is deep and noisy, arterial pressure – 100/55, pulse – 136 beats/minute. The abdominal muscles are tense. Glycemia – 21 mmol/l, acetonuria, plasma osmolarity – 200 mosm/l. What is your diagnosis?
A) Ketoacidotic coma with pseudoperitoneal developments

B) Renal form of ketoacidotic coma
C) Encephalopathic form of ketoacidotic coma
D) Hyperosmolar coma
E) Acute diffuse peritonitis

#189
A girl, 13 y/o, was taken to the department of surgery with complaints of acute abdominal pain, nausea and vomiting. The patient has been ill for two weeks after she had an acute respiratory viral disease followed by increasing thirst, mouth dryness and poliuria. Objectively: her consciousness is clouded; eye ball tone is lowered, the breathing is deep and noisy, arterial pressure – 100/55, pulse – 136 beats/minute. The abdominal muscles are tense. Glycemia – 21 mmol/l, acetonuria, plasma osmolarity – 200mosm/l. How would you treat this patient?
A) Introducing 10-20 units of insulin at first by stream infusion and then by drip infusion during 1 hour by 0.05-0.1 units/kg/hour till the termination of ketoacidosis
B) Introducing 500ml 5% glucose solution
C) Introducing 4% sodium carbonate 2.5 ml/kg
D) Introducing 40 – 60 units of insulin hourly
E) Introducing 500 ml 0.9% sodium chloride

#190
Patient Ch., 29 y/o, was taken to the cardiology department. Objectively: he has cold cyanotic extremities, infrequent and noisy respiration, of Kussmaul's type, alternating with shallow breathing, weak pulse, and arterial pressure – 60/35 mm column of mercury. There are clear signs of vascular collapse – flattened veins, especially in the neck. ECG shows ciliary arrhythmia. Glycemia - 23mmol/l, PH – 7.1. The content of ketone bodies is 23mg%. What is your diagnosis?
A) Cardiovascular form of ketoacidotic coma
B) Renal form of ketoacidotic coma
C) Uremic coma
D) Myocardial infarction
E) Hyperlactacidemic coma

#191
A 68-year-old patient was delivered to the intensive care unit with the suspicion of hyperlactacidemic coma and complaints of severe muscle ache, vomiting drowsiness alternating with stupor, pain in the heart region. Objectively: eye ball tone is lowered, arterial pressure – 100/55, pulse - 136beats/minute, glycemia - 14mmol/l, acidosis, blood PH – 7.0, level of lactic acid – 1.9mmol/l. What are you going to do in this case?
A) Injecting 1% solution of methylene blue

B) Injecting 500ml 5% glucose solution
C) Injecting 0.1% adrenaline solution
D) Introducing 100 mg prednisolone
E) Introducing 500 ml 0.9% sodium chloride

#192
Patient R., 32 y/o, was delivered with complaints of fatigue, decrease of appetite, intensification of pigmentation in the open areas of the body, palms of the hands, cyanosis, losing weight, nausea and vomiting. The symptoms began to aggravate during 1-2 weeks after acute poisoning. Objectively: arterial pressure – 60/30 mm column of mercury, pulse – 140 beats/minute, skin turgor is lowered, the colour is dark with intense pigmentation of the elbows, scars, skin folds on the palms; clearly low levels of sodium and chlorine, high levels of potassium in the blood; glycemia – 4.3 mmol/l. What is your diagnosis?
A) Addisonian crisis
B) Uremic coma
C) Brain coma
D) Acute cardio-vascular insufficiency
E) Hypoglycemic coma

#193
13. Patient R., 32y/o, was delivered with complaints of fatigue, reduced appetite, intensive pigmentation in the open areas of the body, palms of the hands, cyanosis, losing weight, nausea and vomiting. The symptoms began to aggravate during 1-2 weeks after acute poisoning. Objectively: arterial pressure – 60/30 mm column of mercury, pulse – 140 beats/minute, skin turgor is lowered, the colour is dark with intense pigmentation of the elbows, scars, skin folds on the palms; clear hyponatremia, hypochloremia and hyperkalemia; glycemia – 4.3 mmol/l. What is your diagnosis?
A) Intramuscular injection of 25mg hydrocortisone hemi-succinate
B) Injecting 500ml 5% glucose solution
C) Injecting 4% sodium carbonate 2.5 ml/kg
D) Injecting 5% ascorbic acid
E) Introducing 500 ml 0.9% sodium chloride

#194
Patient M., 42 y/o, was taken in with complaints of heavy fatigue, anorexia, severe nausea and vomiting, which does not bring relief of the patient's condition, dizziness. The symptoms began to increase during 1-2 days after stopping the use of cortisone. Objectively: arterial pressure – 65/20 mm column of mercury, pulse –

148 beats/minute, weak, skin turgor is lowered, the colour is pale, the patient is suffering from shortness of breath, and his respiration is shallow. Hb of blood – 166g/l, clear hyponatremia, hypochloremia and hyperkalemia. Urine: proteinuria, leucocyturia and microhematuria. What is your diagnosis?
A) Acute renal failure
B) Uremic coma
C) Brain coma
D) Acute cardio-vascular insufficiency
E) Hypoglycemic coma

#195
Patient B., 56 y/o, is complaining of weakness, muscle ache, paresthesia in the facial zone, lower extremities, tonic-clonic seizures, breathing difficulty. Anamnesis contains a record of previous subtotal resection of thyroid gland. Objectively: her consciousness is clouded, the skin is dry, cyanotic, "main d'accoucheur"(obstetrician's hand) convulsions in the upper extremities swallowing function is disturbed, shortness of breath. Heart sounds are dull, rhythmical, arterial pressure – 115/55, pulse – 56 beats/minute. Positive Chvostek's and Trusso's symptoms. The level of calcium in the blood – 1.3mmol/l; hyperphosphatemia, hypocalciuria; glycemia – 5.6mmol/l. What is your diagnosis?
A) Hypocalcemic crisis
B) Hypothyroid coma
C) Kidney failure
D) Hyperthyroid coma
E) Brain coma

#196
Patient B., 56 y/o, complains of weakness, muscle ache, paresthesia in the facial zone, lower extremities, tonic-clonic seizures, breathing difficulty. Anamnesis contains a record of previous subtotal resection of thyroid gland. Objectively: her consciousness is clouded, the skin is dry, cyanotic, "main d'accoucheur"(obstetrician's hand) convulsions in the upper extremities swallowing function is disturbed, shortness of breath. Heart sounds are dull, rhythmical, arterial pressure – 115/55, pulse – 56 beats/minute. Positive Chvostek's and Trusso's symptoms. The level of calcium in blood – 1.3mmol/l; hyperphosphatemia, hypocalciuria; glycemia – 5.6mmol/l. How would you manage this patient?
A) Injecting 10-20ml 10% solution of calcium chloride
B) Injecting 10-15ml 4.5% solution of potassium chloride
C) Introducing 100 mg prednisolone
D) Introducing 1-2ml 0.5% solution of strophanthin

E) Injecting 40-60ml 40% glucose solution

#197
Patient C., 56 y/o, complains of weakness, muscle ache, loss of appetite, nausea, vomiting, aching bones, deterioration of memory and cramps. Anamnesis contains a record of the ulcerous disease of stomach, frequent pathological bone fractures. Objectively: the consciousness is clouded, the skin is dry of ashy gray color, present deformity of the vertebrae bodies, "goose-stepping" gait, X-ray shows systemic osteoporosis. Heart sounds are dull, rhythmical, arterial pressure – 160/100, pulse – 56beats/minute. The level of calcium in the blood – 3.9mmol/l; hypophosphatemia, hyperphophaturia; glycemia – 4.8mmol/l. What is your diagnosis?
A) Acute hyperparathyroidism
B) Hypothyroid coma
C) Acute hypoparathyroidism
D) Climacteric osteoporosis
E) Hyperlactacidemic coma

#198
Patient K., 58 y/o, complains of weakness, muscle ache, loss of appetite, nausea, vomiting, aching bones, deterioration of memory and cramps. In anamnesis there is a record of the ulcerous disease of stomach, frequent pathological bone fractures. Objectively: the consciousness is clouded, the skin is dry of ashy gray colour, present deformity of the vertebrae bodies, "goose-stepping" gait, X-ray shows systemic osteoporosis. Heart sounds are dull, rhythmical, arterial pressure – 160/100, pulse – 56beats/minute. The level of calcium in the blood – 3.9mmol/l; hypophosphatemia, hyperphophaturia; glycemia – 4.8mmol/l. What are you going to do with this patient?
A) Introducing 2-3 l of 0.9 % solution of sodium chloride and the potassium phosphate and sodium
B) Introducing 150ml of 4.5 % solution of sodium chloride, 100mg prednisolone
C) Introducing 100mg prednisolone, 40g furosemide
D) Introducing 1-2ml 0.5% solution of strophanthin, 100mg prednisolone
E) Introducing 40-60ml of 40% glucose solution, 80g furosemide

#199
A 46-year-old patient was taken to the intensive care unit with the symptoms of dehydration. Anamnesis has a record of type 1 diabetes mellitus and obesity. The patient is known to have taken diuretics for the purpose of loosing weight, which

caused increasing thirst, mouth dryness and polyuria. Objectively: her consciousness is clouded, eye ball tone is lowered, respiration is deep and noisy, arterial pressure – 110/60, pulse - 140beats/minute, glycemia - 45mmol/l, hyperchloremia, hypernatremia, azotemia, absence of ketonemia and acetonuria, plasma osmolarity – 400 mOsm/l. What is your diagnosis?
A) Hyperosmolar coma
B) Ketoacidotic coma
C) Brain coma
D) Uremic coma
E) Hyperlactacidemic coma

#200
Patient P., 46y/o, was taken to the intensive care unit with the symptoms of dehydration. Anamnesis has a record of type 1 diabetes mellitus and obesity. The patient is known to have taken diuretics for the purpose of loosing weight, which caused increasing thirst, mouth dryness and polyuria. Objectively: her consciousness is clouded, eye ball tone is lowered, respiration is deep and noisy, arterial pressure – 110/60, pulse - 140beats/minute, glycemia - 45mmol/l, hyperchloremia, hypernatremia, azotemia, absence of ketonemia and acetonuria, plasma osmolarity – 400 mOsm/l. What is the treatment for this condition?
A) Introducing 4-6 l 0.45 % solution of sodium chloride, insulin in proportion 0.05-0.1 units/kg/hour
B) Injecting 500ml 5% glucose solution, 40-60 units
C) Injecting 4% sodium carbonate 2.5 ml/kg, 20-30 units of insulin
D) Introducing 40 – 60 units of insulin hourly, 500ml of 5%glucose solution
E) Introducing 500 ml 0.9% sodium chloride, 40-60 units of insulin

#201
Patient M., 36 y/o, was found unconscious in the street. The patient has a medical history of diabetes mellitus. His breath smells of alcohol, his skin is moist and warm, arterial pressure – 145/90 mm column of mercury, convulsive twitching of muscles, some tonic-clonic seizures. Breathing is shallow, eye ball tone is retained, pupils are dilated, hyperflexion. What is your diagnosis?
A) Hypoglycemic coma
B) Ketoacidotic coma
C) Alcoholic coma
D) Brain coma
E) Hyperlactacidemic coma

#202
Patient C., 32 y/o, complains of excessive weight, shortness of breath, defective memory, performance decrement, feeling cold, emotional retardation. It is known

from the case history that the patient is suffering from primary hypothyroidism. Objectively: the skin is dry, waxlike, swollen, periosteal reflexes are lowered, body mass index: 33.5 kg/cubic meter, TSH (thyroid-stimulating hormone) – 25 μU/dL (norm 0.5 -5.0). Obesity is homogenous. Arterial pressure: 150/100 mm column ob mercury. What type of obesity can be suspected?
A) Endocrine hypothyroid
B) Endocrine accompanying dysfunctions of hypothalamopituitary system
C) Alimentary constitutional
D) Hypothalamic
E) Androidal with the developed symptoms of metabolic syndrome

#203
Patient T., 26 y/o, complains of excessive body weight, shortness of breath, disruption of the ovarian menstrual cycle, she has been ill since childhood. Family anamnesis is burdened by obesity on the mother's side. Objectively: BMI – 35.8 kg/cubic meter, dysplastic obesity prevailing in the abdominal area, hypertrichosis. In the abdominal and groin areas there are multiple stretch marks from pearl to burgundy colour. Arterial pressure – 160/100, pulse – 96 beats/minute. What tests should be done to exclude hypercorticism?
A) Small dexamethasone test
B) Large dexamethasone test
C) Test with clonidine/clophelinum
D) Test with cerucal
E) Test with insulin

#204
Patient K., 34 y/o, complains of excessive body weight, shortness of breath, disruption of the ovarian menstrual cycle, she has been ill since childhood. Family anamnesis is burdened by obesity on the mother's side. Objectively: BMI – 35.8 kg/cubic meter, dysplastic obesity prevailing in the abdominal area, hypertrichosis. In the abdominal and groin areas there are multiple stretch marks from pearl to burgundy colour. Arterial pressure – 160/100, pulse – 96 beats/minute. What is the treatment for this condition?
A) Dietotherapy, sibutramine (influencing the center of hunger and satiation), xenical (blocking GI lipases)
B) Dietotherapy
C) Dietotherapy, thyroxine (thyroid medicines)
D) Dietotherapy, furosemide (diuretic medicines)
E) Dietotherapy, vitamin therapy

#205

25. Patient a., 28 y/o, has been diagnosed with Ishchenko-Cushing's disease. Which methods of treatment of Ishchenko-Cushing's disease listed below can be referred to etiological?
A) Unilateral adrenalectomy
B) Bilateral adrenalectomy
C) Gamma ray teletherapy of the pituitary gland area
D) All the above mentioned

#206
Patient P., 45 y/o, has an enlargement of the right lobe of the thyroid gland, in which a round soft and elastic growth can be palpated; the growth is neither fused with the surrounding tissues nor painful. Lymphatic nods are not palpated. Cyst is suspected. What is the specific of the ultrasound picture of the thyroid cyst?
A) Exogenic density is increased
B) Exogenic density is decreased
C) Exogenic density is without change
D) Exogenic density is nonhomogenous

#207
Patient R., 45 y/o, has an enlargement of the right lobe of the thyroid gland , in which a round soft and elastic growth can be palpated; the growth is neither fused with the surrounding tissues nor painful. Lymphatic nods are not palpated. Clinical examinations and laboratory tests show no disruption of the thyroid function. What diagnosis can be suspected?
A) Nodular thyroid gland
B) Toxic goiter (Grave's disease)
C) Autoimmune thyroiditis
D) Hypothyroidism

#208
Damage of what areas of the brain most often causes obesity?
A) Cerebellum
B) Cortex
C) Ventromedial nuclei of the hypothalamus
D) Pituitary gland
E) Subcortical structures

#209
What functional test is most informative in diagnosing diabetes insipidus?
A) With clophelinum
B) With hypothiazid

C) With dexamethasonum
D) By limiting liquid
E) By fast (abstinence from food)

#210
Which medications can be used for functional tests with suppression of adrenocorticotrophic hormone in diagnosing of the pathology of adrenal glands?
A) Prednisolone
B) Dexamethasonum
C) Hydrocortisone
D) Deoxycorticosterone acetate
E) Triamcinolone

#211
Which of the medications listed below should be used for pubertal gynecomastia?
A) Testosterone
B) Progestin
C) Glucocorticoids
D) Chorionic gonadotropin
E) Tamoxifen, clomiphene citrate

#212
Which of the listed medications should be prescribed to a diabetic patient for the normalization of the arterial pressure in lactacidemic coma?
A) Mesatonum
B) Adrenaline
C) Glucagon
D) Hydrocortisone
E) Anacardone/ Cordiamidum

#213
Patient M, 72 y/o, is in the intensive care unit with the symptoms of dehydration, oliguria, hypothermia, hypoxemia (hypoxia). In the anamnesis there is a record of type 2 diabetes mellitus treated with biguanides. Her condition began to deteriorate after she had a myocardial infarction one month ago. Objectively: the skin is dry; turgor is lowered, arterial pressure – 80/40 mm column of mercury, pulse – 136beats/minute. The breathing is shallow, eye ball tone is lowered. What is your diagnosis?
A) Hyperlactacidemic coma
B) Uremic coma
C) Ketoacidotic coma

D) Brain coma
E) Hyperosmolar coma

#214
Patient N., 70 y/o, is complaining of stomach ache, nausea, vomiting and muscle ache. Objectively: evident symptoms of dehydration, Kussmaul's breathing, arterial pressure – 95/60 mm column of mercury, anuria, temperature – 35.9 ºC, glycemia – 11.6 mmol/l, acetonuria is not present, blood PH – 6.7, content of lactic acid -1.9 mmol/l (norm - 0.62 -1.3 mmol/l). What is your diagnosis?
A) Hyperlactacidemic coma
B) Uremic coma
C) Ketoacidotic coma
D) Brain coma
E) Hyperosmolar coma

#215
A 5-year-old boy began to show symptoms of gynecomastia. What is your preliminary diagnosis?
A) Klinefelter syndrome
B) Corticosteroma
C) Liver disease
D) Reifenstein's syndrome
E) Turner's syndrome

#216
Which of the enumerated products of steroidogenesis are produced mainly in the ovaries?
A) Testosterone
B) Cortisol
C) Dehydroepiandrosterone sulfate
D) Dehydroepiandrosterone
E) Adrenocorticotrophic hormone

#217
Patient B., 18 y/o, is at a pharmacy store, and is complaining of intensive sweating, trembling hands, numbing of the tip of the tongue, palpitation. It is known that the patient has type 1 diabetes mellitus. His consciousness is clouded; he is disorientated in space and time, aggressive, refuses sweet food. Objectively: tendon and periosteal reflexes are sharply enhanced, positive Babinski's symptom; the skin is moist and warm. Glycemia level on the glucometer is 2.3 mmol/l. There is no odor of acetone from the mouth. What is your tactic?

A) Injecting 20-40 ml (not more than 80 ml) of 40% glucose solution intravenously
B) Injecting 20 units of insulin subcutaneously
C) Injecting 20 units of insulin intravenously
D) Injecting 500 ml 0.9% sodium chloride intravenously
E) Injecting 500 ml 5% glucose solution intravenously

#218
When ingesting glucocorticoids twice daily how is the daily dose divided between the ingestions?
A) Half in the morning, half in the evening
B) Two thirds in the morning, one third in the evening
C) One third in the morning, two thirds in the evening
D) Half in the morning, half in the afternoon
E) One third in the afternoon, two thirds in the evening

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