Ministry of Health of Ukraine

DANYLO HALYTSKYI LVIV NATIONAL MEDICAL UNIVERSITY

Endocrinology Department

Methodical guidelines for practical classes on discipline of endocrinology
For 4th year students of medical faculty
(Magister level)

Lviv 2019

Methodological guidelines are compiled in accordance with the educational and qualification characteristics and educational professional programs of training specialists, experimental curriculum, developed on the principles of credit transfer system and approved At a meeting of the cyclic methodical Commission on therapeutic disciplines of Danylo Halytskyi Lviv National Medical University (Protocol No. 5 from 04.04.2019).

Authors:
A.M.Urbanovich, MD, Ph.D., Dr. Sc (Med), professor;
O.P.Kikhtyak, MD, Ph.D., Dr. Sc (Med), professor;
O.V.Safonova, PhD, associate professor;
Kh.A.Moskva, PhD, associate professor;

Editor-in-chief:
Deputy Rector of Studies, Prof. M. Gshegotskiy.

Reviewers:
Head of Department of Internal Medicine №2 at Danylo Halitsky Lviv National Medical University, MD, Prof. Radchenko O.M.
Head of Department of family medicine at Danylo Halitsky Lviv National Medical University, PhD, MD, Professor of medicine O.N. Nadashkevych.

Introduction

Although every organ system secretes and responds to hormones (including the brain, lungs, heart, intestine, skin, and the kidney), the clinical specialty of endocrinology focuses primarily on the endocrine organs, meaning the organs whose primary function is hormone secretion. These organs include the pituitary, thyroid, adrenals, ovaries, testes, and pancreas. The medical specialty of endocrinology involves the diagnostic evaluation of a wide variety of symptoms and variations and the long-term management of disorders of deficiency or excess of one or more hormones.

The diagnosis and treatment of endocrine diseases are guided by laboratory tests to a greater extent than for most specialties. Many diseases are investigated through excitation/stimulation or inhibition/suppression testing. This might involve injection with a stimulating agent to test the function of an endocrine organ. Blood is then sampled to assess the changes of the relevant hormones or metabolites. An endocrinologist needs extensive knowledge of clinical chemistry and biochemistry to understand the uses and limitations of the investigations.

A second important aspect of the practice of endocrinology is distinguishing human variation from disease. Atypical patterns of physical development and abnormal test results must be assessed as indicative of disease or not. Diagnostic imaging of endocrine organs may reveal incidental findings called incidentalomas, which may or may not represent disease.

Endocrinology involves caring for the person biology as well as the nucleus the enzymes as well as the disease. Most endocrine disorders area chronic diseases that need life-long care. Some of the most common endocrine diseases include diabetes mellitus, hypothyroidism and others. Care of diabetes, obesity and other chronic diseases necessitates understanding the patient at the personal and social level as well as the molecular, and the physician–patient relationship can be an important therapeutic process.

Each practical lesson is organized in a certain way (table 1)

Table 1

Structure of the practical lesson

№	Main 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 Main stage				
4.	Formation of professional skills in the clinical setting (Lviv Regional Endocrinological Hospital)		Case reports, prescriptions of	

5	Management of a patient	• Practical training	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%

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

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. Professional motivation: Diabetes is well recognized as a major global health problem with numbers forecast to reach 380 million by 2025. It often results in substantial morbidity and mortality primarily in the form of cardiovascular, eye and kidney diseases and limb amputations. Not only is diabetes the fourth leading cause of death in most developed countries, there is also overwhelming evidence that it is epidemic in many developing and newly industrialized nations. Diabetes will surely be one of our most common and challenging health problems in the 21st century. The economic and health impacts of diabetes are enormous. Developing nations may be experiencing an even greater burden as many of these countries are faced with the dual problem of rapidly escalating rates of diabetes and complications in addition to widespread communicable diseases.
Heterogeneity in the presentation of patients with diabetes has been recognized for more than 2000 years. In its classic form, two common forms of diabetes are recognized: type 1 (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 encompasses almost 90 % of general disease incidence.
Type 1 diabetes has greater likelihood of ketoacidosis, and absolute dependence on insulin for survival.
Type 2 diabetes has a long asymptomatic pre-clinical phase which frequently goes undetected. At the time of diagnosis, over half have one or more diabetes complications.
Retinopathy rates at the time of diagnosis range from 20 % to 40 %. Since the development of retinopathy is related to duration of diabetes, it has been estimated that type 2 diabetes may have its onset up to 12 years before its clinical diagnosis. It is asserted that the prevalence of undiagnosed diabetes is 50 % of 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 on classification, treatment approach, and evaluation of metabolic control in diabetes mellitus.

4. Integration between disciplines (see Table 2).

Table 2

Integration between disciplines

Discipline	**To know**	**How to do**
I. Previous Normal anatomy Normal 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 diabetes mellitus, distinguishing features of type 1 and type 2 diabetes, differential diagnostics	To examine a patient, to prescribe appropriate laboratory, to invite required specialists to diagnose a case.
III. Integration among disciplines	Current evaluation of metabolic control in diabetes	To institute adequate invastigation

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?

F. Normal
G. Impaired glucose tolerance
H. Diabetes mellitus
I. Impaired fasting glucose
J. Potential abnormality of glucose tolerance

#3
What criterion does represent compensation stage in diabetes?

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 of syndromes characterized metabolically by hyperglycemia and altered glucose metabolism and associated pathologically with specific microvascular complications, macrovascular disease secondary to accelerated atherosclerosis, and various other complications, including neuropathy, complicated pregnancy, and an increased susceptibility to infection.

A committee of the American Diabetes Association (1997) has revised the classification with respect to the pathogenesis of diabetes (see Table 3).

Table 3

Classification of diabetes mellitus

Classification	Characteristics
I* Type 1A	Immune mediated
Type 1B	Insulin deficient not autoimmune
II* Type 2	Insulin resistance ± insulin secretory deficiency
III** Other Specific Types	Maturity onset diabetes of youth, lipoatrophic, type A insulin resistant, endocrinopathies, drug induced***
IV Gestational Diabetes	Glucose intolerance with first recognition or onset during pregnancy

*Classes II and I are suggested to be primary forms of diabetes mellitus.
**Class III performs secondary diabetes because of its association with other various disorders. Secondary diabetes mellitus may be caused by endocrine diseases such as Acromegaly, Cushing syndrome, Pheochromocytoma, Hyperthyroidism etc. and non-endocrine pancreatic diseases: Pancreatectomy, Pancreatitis acute and chronic etc. Pathogenesis of the certain secondary diabetes mellitus is related with its aetiology.
***Following drugs impair insulin secretion: α-adrenergic agents, thiazide diuretics, phenytoin, diazoxide, and somatostatin. Drugs that impair insulin action are the following: glucocorticoids, oral contraceptive agents, and diazoxide too.

DIABETES MELLITUS, TYPE 1

Aetiology. Genetic predisposition is associated with diabetogenic gene(s): alleles of insulin gene on the 11th chromosome and short arm of 6th chromosome either within or in the close proximity to the major histocompatibility complex region – the HLA region. A number of human viruses can infect and damage β cells: viruses of mumps, variants of Coxsackie B (often B_4), rubella, measles, varicella, and cytomegalovirus. Stress can initiate pathogenetic sequence in genetically predisposed individuals.

Pathogenesis. Pathogenetic mechanism involves selective destruction of β cells (other islet cells remain secretion) owing to autoimmunity, genetics, and environmental factors. Destruction of 80-90% of β cells causes absolute insulin deficiency. Insulin deficiency results in hyperglycaemia and ketoacidosis. Within 1-3 months after diagnosis remission phase ("honeymoon" phase) may occur. Phenomenon of remission phase is due to a temporary recovery of β cell function and can last from weeks to less then 2 years. The extent of insulin insufficiency tends to increase with time.

Capillary basement-membrane thickening is responsible for the major vascular complications: premature atherosclerosis, intercapillary glomerulosclerosis, retinopathy, neuropathy, ulceration and gangrene of the extremities. Accumulation of sorbitol and resultant osmotic swelling are significant in the nerve lesions and cataracts.

Diagnostics. Inquiry of a patient (anamnesis of disease and life), physical examination (visual inspection), laboratory findings (OGTT, glucose in blood, HbA1c, glucose in urine, ketone bodies in urine).

Oral glucose tolerance testing is employed to establish impaired glucose tolerance if diagnose of diabetes mellitus is suspected. Dose is 75 g glucose in 250-300 ml water; for children 1.75 g glucose/kg body weight. Diagnosis of diabetes mellitus is showed in the table 4.

Table 4

Oral glucose tolerance testing

Diabetes mellitus (manifest)	Plasma (mmol/l)
fasting 2 hours after glucose ingestion	> 7.0 mmol/l > 11.0 mmol/l

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

Level of glycosylated haemoglobin shows an average blood concentration during the previous 2-3 months (red cells life-span is 120 days). Normal value <6.1 or <6.5 (%). Pursuant to recommendations of American Diabetes Association an A1c level of approximately 5% indicates the absence of diabetes, and according to the revised evidence-based guidelines, an A1c score of 5.7% to 6.4% indicates prediabetes, and an A1c level of 6.5% or higher indicates the presence of diabetes.

Urine ketones should be measured in order to recognise development of ketoacidosis.

Clinical picture. Type 1 diabetes usually has its onset in childhood or adolescence. Most

patients have normal or below normal weight. The serum insulin level is zero or low. Patients have pronounced tendency to ketosis and also to hypoglycaemic episodes. The raised glucose level in blood has wide fluctuations. The remission stage or in another words "honeymoon" phase may occur. Microangiopathy is usually reflected in ophthalmopathy, neuropathy and nephropathy.

DIABETES MELLITUS, TYPE 2

Aetiology. There is inherited predisposition to develop type 2 diabetes mellitus. A defect in the conversion of proinsulin into insulin, mutant insulin molecules or abnormal insulin receptors may be present in a few patients. Nongenetic environmental factors influence the development of overt clinical disease: obesity, diet, physical activity, stress, advancing age.

Pathogenesis. Insulin resistance + hyperinsulinemia, glucose desensitisation of β cells precedes insulin secretion failure. Endogenous hyperinsulinemia (at the first stages of the disease) is sufficient to maintain normal or only mildly impaired glucose tolerance. Insulin resistance and hyperinsulinemia are associated with hypertriglyceridemia, decreased high-density lipoprotein cholesterol, hypertension and increased risk of atherosclerosis. Macroangiopathy (atherosclerosis) is often presented in forms of angina pectoris, myocardial infarction, cerebral vascular disease, peripheral vascular disease with intermittent claudication, ulceration and gangrene in advanced states.

Diagnostics. Serum insulin level is often elevated. Raised glucose level in blood is relatively constant (See also type 1 diabetes mellitus).

Clinical picture. Type 2 diabetes usually has its onset in middle age or later life, usually after 36^{th} year. There is strong hereditary penetrance. Most patients are overweight. Serum insulin level is often elevated. Patients have little tendency to ketosis and hypoglycaemia. Raised glucose level in blood is relatively constant. Macroangiopathy is often presented in atherosclerosis in forms of angina pectoris, myocardial infarction, cerebral vascular disease, peripheral vascular disease with intermittent claudication, ulceration and gangrene in advanced states.

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

Case 1.

27 years old patient M. has attended to a hospital. After recovering from the flu, he complains of thirst, frequent urination, and weight loss. His blood glucose 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 are necessary to order?

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 began 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.

Theme 2:
Type 1 Diabetes Mellitus. Modern treatment approach.

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. Professional motivation: Type 1 diabetes mellitus is characterized by an insulin deficiency secondary to β-cell destruction. The typical pancreatic lesion of type 1A diabetes is a selective loss of almost all β-cells, whereas other islet cell types (A, D, and PP cells) are intact. In the absence of insulin therapy, the resulting metabolic abnormalities eventually lead to death. In the preinsulin era, patients were treated with the Allen starvation diet and sometimes lived without insulin therapy for 5 or more years after diagnosis.
Type 1 diabetes usually occurs before the age of 35.
Modern treatment of type 1 Diabetes Mellitus includes prophylaxis or elimination of ketoacids, hyperglycemia, glucose in urea, attaining and maintaining ideal weight, elimination of lipid and protein impairment and finally preventing as much as possible the development of diabetic microangiopathy, atherosclerosis, and neuropathy.
Insulin is the mainstay of therapy for all patients with type 1 diabetes. Subcutaneous insulin therapy attempts to mimic normal physiologic insulin secretion and regulation of fuel metabolism.

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 insulins 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 a stage of compensation,

- calculate daily dose of insulin,
- use food-exchange concept in a clinical practice,
- prescribe insulins,
- discern hypoglycaemia from other side effects of insulin treatment,
- diagnose and to prevent posthypoglycaemic hyperglycaemia.

3. Educational aim of this lesson

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

4. Integration between disciplines (see Table 5).

Table 5

Integration between disciplines

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 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. Integration among disciplines		
	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 regarding to 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, posthypoglycaemic 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 attended to a hospital. After recovering from the flu, doctor discovered high glucose level and the diagnosis of type 1 diabetes was established. His fasting glucose is 15,3 mmol/l, glucose in urine – 3%, acetone in urine ++. What is you 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 tolerant test
E. 4 IU per 1 mmol of glucose in blood

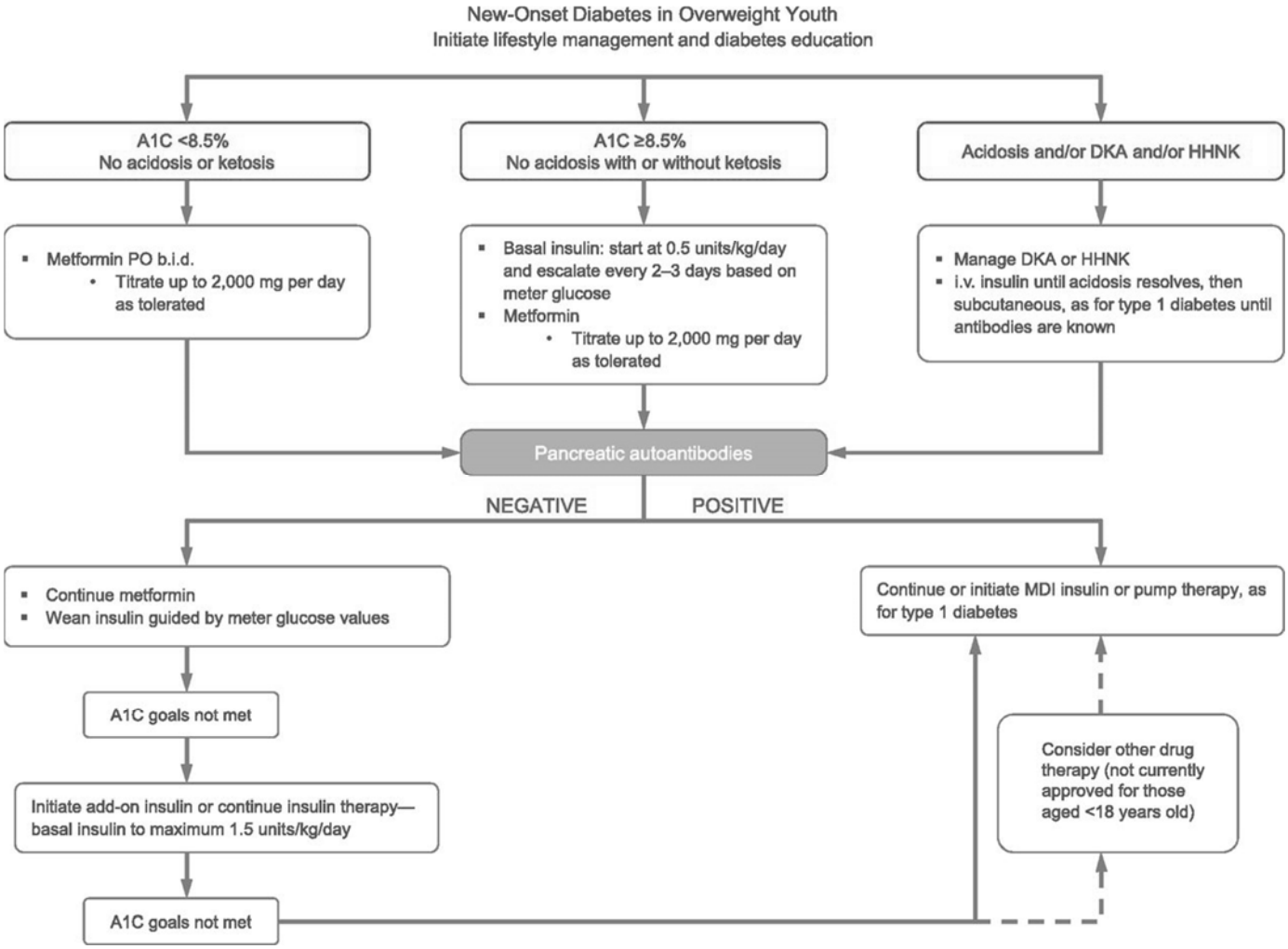
#4

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.

The main principle of type 1 diabetes mellitus therapy is replacement treatment with insulin preparations.



Management of new-onset diabetes in overweight youth (2). A1C 8.5% = 69 mmol/mol. DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; MDI, multiple daily injections.
American Diabetes Association. Diabetes Care 2019 Jan; 42(Supplement 1): S148-S164. https://doi.org/10.2337/dc19-S013

Insulin is available in cartridges (pen device), and in vials usually coloured. Red colour means that in every 1 ml there are 40 IUs of insulin, orange one – that 1 ml contains 100 IUs of insulin. Other concentration is also available. For instance regular insulin is available in a U500 strength for use in patients with high requirements (>200 U per day). Various pumps for continuous subcutaneous insulin infusion are also available. Insulin should be given 30 min. before meals, usually in subcutaneous tissues. In emergency insulin may be

injected intramuscularly or IV with glucose solution or saline. Sites of insulin administration may be different and rotation is obligatory, because of lipoatrophy threatening. Usual sites of insulin injection are the following: abdomen, buttock, anterior thigh, and dorsal arm. Abdominal subcutaneous absorption is much quicker in comparison with limbs.

There are three types of insulin regarding to their origin: beef, porcine and human. Beef is the most immunogenic; therefore its production is almost discontinued.

Insulins are divided into four generations. First generation means moiety from beef and pork pancreas with varies amounts of contaminants like proinsulin, glucagon, somatostatin, pancreatic polypeptide etc. Second generation includes mono-peak (MP) insulin that is usually contaminated by 0,5%. Third generation embraces monocomponent (MC) insulin carefully purified, fourth generation – biosynthetic human insulin obtained from Escherichia coli or Saccharomyces cerevisiae with the smallest contamination level.

Initial dose of insulin for children up to 1 year is 0.1 IUs/kg/day. Mean daily dose is 0.15 IUs/kg in the age from 1 to 3 years, and 0.2-0.5 IUs/kg after 3 years. Usual daily insulin demand for young diabetics is within 0.6-0.8 IUs/kg. Requirement in 1.0 IU/kg/day may be beneficial at the beginning of treatment. Teenagers may even need 1.5 IUs/kg/day during rapid growth and development. Remission phase is characterised by dose that often may be less than 0.3 IUs/kg/day. Dose ratio of short-acting insulin may be 2:2:1 or 2:3:1 according to the nutrient intake. Insulin amount ratio of short acting and intermediate acting is 25% and 75% respectively. Two thirds of the total dose of intermediate-acting insulin should be given before breakfast and one third – before supper. Sometimes treatment of type 1 diabetes is best begun by giving intermediate-acting insulin twice a day before breakfast as well as at bedtime or before supper at a dosage of 0,2 to 0.3 U/kg per day. This dose is increased gradually with or without the use of short-acting insulin given before breakfast and supper while the blood glucose profile is observed.

Insulin may be recognised 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**	**Mean 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. Intermediate-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)

*Every manufactured insulin has its own specific action profile. Besides this site and route of injection, outer and body temperature, concurrent diseases, complications, and a lot of different circumstances may affect pharmacokinetic properties of any insulin.

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

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

Indications of insulin therapy includes the following: patients with type 1 diabetes, patients with gestational diabetes, who have a fasting glucose level of > 120 mg/l (6,6 mmol/l regarding conversion factor 0,055), patients with type 2 diabetes who fail to respond to an adequate trial of diet and oral hypoglycaemic agents. Insulin therapy is advised during the perioperative period as well as during acute illnesses.

During pregnancy insulin requirements may drop slightly in the first trimester, and then gradually increase in the second trimester, and finally peak in the third trimester. Immediately after delivery, requirements drop precipitously and return to prepregnancy levels.

At the time of remission phase insulin administration slows autoimmune process, otherwise discontinuation will potentiate insulin allergy. Insulin therapy unloads β cells from the strained work directed to maintain euglycemia and prevents prompt insulin depletion. Insulin injections delay diabetic complications and facilitate course of diabetes mellitus.

Adverse effects of insulin therapy includes the following: hypoglycaemia, posthypoglycaemic hyperglycaemia (Somogyi phenomenon), insulin edema, lipoatrophy, lipohypertrophy, postural hypotension, insulin allergy

Causes of hypoglycaemia are the following: shortage of nutrient intake (missing meals, eating too late or too little), deterioration of insulin absorption (changes in blood flow in the site of injection as a result of heat, massage), concurrent diseases (renal failure, hypothyroidism, Addison disease, hypopituitarism), excessive physical activity (sports, heavy work), insulin overdose (taking too much insulin or hypoglycaemic tablets, sometimes suicidal gesture), altered glucose metabolism (consuming too much alcohol, taking salicylates, tetracyclines, β-adrenergic blockers), behaviour errors (mistakes in doses, forgetfulness, carelessness).

Under the term of “posthypoglycaemic hyperglycaemia or in other words “Somogyi phenomenon” chronic overinsulinisation is implied. “Rebound” hyperglycaemia may last two days and even precipitate frank diabetic ketoacidosis. Hypoglycaemia in the middle of night (3 a.m.) is an important sign of possible subsequent hyperglycaemia and for diagnosing Somogyi and dawn phenomenon. Reduction of insulin dose (usually in the second half of a day) may correct fasting hyperglycaemia.

Uncontrolled diabetes is accompanied by fluid loss and natriuresis, while treatment with insulin is associated with fluid and sodium retention. This may be the basis of insulin edema. It is assumed that glucagon has natriuretic effect, and insulin on the contrary retains sodium. Fluid retention goes along with weight gain, and may disappoint patient. Diuretics may be the best choice in such cases.

Lipoatrophy has pronounced relation to unpurified insulins. Presence of immunoglobulins that are able to release cytokines produces loss of fat at the site of injection.

On the contrary use of highly purified insulins may precipitate local hypertrophy of subcutaneous fat. Lipoatrophic areas should be treated with purified insulins. Rotation of injection site is obligatory for prophylaxis of insulin lipoatrophy or lipohypertrophy.

It is suspected that autonomic neuropathy produces opposite effect of insulin: vasodilatation instead of vasoconstriction. Vasodilation causes hypotension. Orthostatic hypotension sometimes is confused with hypoglycaemia because of sweating and tremor.

Nowadays problems with insulin allergy are reduced because of less contaminant. Allergic reactions may be local and systemic. Desensitisation should be performed, following special schedule. Treatment approach may include also antihistamines, oxygen, epinephrine, and corticosteroids.

There are several commonly used insulin regimens like 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 demands intensive monitoring of blood glucose, careful attention to diet, an insulin regimen that mimics the normal diurnal and postprandial insulin excursions, and frequent adjustment of the insulin dosage to match 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 order?

Case N 2.
Patient A., 36 years old. Type 1 diabetes lasts for 26 years. Patient regularly receives insulin (daily dose – 60 IU). In the last three years patient was not examined by endocrinologist. Foots are chilly, 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 suffers from type 2 diabetes 9 years. Anthropometric data: weight 120 kg, height 160 cm. Patient takes insulin preparations in daily dose 105 IU. Patients fasting blood glucose is 17 mmol/l, glucose in blood at 3 o'clock in the morning 2,7 mmol/l.
1. What complication does this patient going to have?
2. What approach do you need in order to eliminate these complications?

Theme 3:

Type 2 Diabetes Mellitus. Modern treatment approach.

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. Professional motivation: Type 2 diabetes mellitus is by far the most prevalent endocrine disease. It is estimated to affect almost 300 million people in the world. Development of type 2 diabetes is strongly influenced by genetic factors and environmental factors, including obesity, decreased physical activity, overeating. The major risk factor influencing the incidence of type 2 diabetes is the degree of obesity. Large studies show that the risk of the illness rises exponentially with increasing body mass index. In addition, a pattern of central distributed body fat (also called visceral adiposity) appears to increase the risk of type 2 diabetes more than does a similar degree of excess that is more uniformly distributed.
Type 2 diabetes usually occurs after the age of 35.
In type 2 diabetes, β-cell mass is relatively well preserved, but insulin secretion in response to specific secretagogues such as glucose is reduced, and clear evidence exists for resistance to insulin action in the peripheral tissues.
Type 2 diabetes is truly a chronic disease, one in which the complications of the kidney, eyes, and heart develop over many years, sometimes decades, after the onset of hyperglycemia. At the same time the diagnosis of type 2 diabetes is usually established after 10-12 years after the onset of disease. This occurs because patients do not have any complaints till serious complications develop.
Initially, sulfonylureas were the only class of oral agent available in the world. Subsequently, biguanides, α-glucosidase inhibitors, meglitinides, thiazolidinediones, DPP-4 inhibitors, and GLP-1 agonists have become available. The choice among these groups in order to treat patient 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,
- about 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),
- about side effects of oral hypoglycemic drugs,
- principles of oral agents treatment: initiation, combined use of drugs, and combination with insulin preparations,
- AACE/ACE and ADA/EASD consensuses with regard to treatment type 2 diabetes mellitus.

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

- establish a 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. Integration between disciplines (see Table 7).

Table 7

Integration between disciplines

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 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. Integration among disciplines		

	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, SGLT2 inhibitors).
- Characteristics of oral hypoglycemic agents (indications, contraindications, doses, frequency of administration, side effects).
- Insulin therapy in type 2 diabetes mellitus.
- AACE/ACE and ADA/EASD 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 synthesise insulin
C. Inhibiting beta cell to secrete insulin
D. Beyond pancreatic activity
E. Stimulation 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 of carbohydrate absorption
D. Inhibition of gluconeogenesis
E. Stimulation of insulin synthesis

7.2. Recourses for the main stage of the lesson.

Treatment of type 2 diabetes mellitus involves the following: diet, phytotheraspy, exercises, and oral hypoglycaemic agents.
Main principle in diet is to limit the intake of simple carbohydrates. Refined or simple carbohydrates can be found in food like sugar, certain drinks (e.g. Coca-Cola, lemonade etc.), jam, cakes, honey, sweets, chocolate etc. This food should be avoided because it immediately raises glucose level in blood. At the same time unrefined carbohydrates are advised. Food like bread, cereals, rice, potatoes, and pasta include unrefined or complex carbohydrates. These products are digested much slower, therefore damp glucose elevation. Diet should form balance with oral hypoglycaemic drugs.
Various herbs can decrease glucose level in blood, mostly by extrapancreatic way. These are: Galega officinalis, Phaseolus vulgaris, Vaccinium myrtillus, Cichorium intybus, Taraxacum officinale, Artemisia vulgaris, Aralia mandshurica etc. Phytotherapy alone may be beneficial only at the early stages of type 2 diabetes mellitus. In advanced stages of type 2 diabetes it can be considered as supportive and accessory approach.

Class	**Compound(s)**	**Dosage strength/product (if applicable)**	**Maximum approved daily dose**[a]
Biguanides	• Metformin	500 mg (IR)	2,000 mg
		850 mg (IR)	2,550 mg
		1,000 mg (IR)	2,000 mg
		500 mg (ER)	2,000 mg
		750 mg (ER)	1,500 mg

Class	Compound(s)	Dosage strength/product (if applicable)	Maximum approved daily dose*
		1,000 mg (ER)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	8 mg
	• Glipizide	10 mg (IR)	40 mg (IR)
		10 mg (XL)	20 mg (XL)
	• Glyburide	6 mg (micronized)	12 mg (micronized)
		5 mg	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	45 mg
	• Rosiglitazone	4 mg	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	300 mg
	• Miglitol	100 mg	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	360 mg
	• Repaglinide	2 mg	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	25 mg
	• Saxagliptin	5 mg	5 mg
	• Linagliptin	5 mg	5 mg
	• Sitagliptin	100 mg	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	15 mg
	• Dapagliflozin	10 mg	10 mg
	• Canagliflozin	300 mg	300 mg
	• Empagliflozin	25 mg	25 mg
GLP-1 receptor agonists	• Exenatide (extended release)	2 mg powder for suspension or pen	2 mg**

Class	Compound(s)	Dosage strength/product (if applicable)	Maximum approved daily dose*
	• Exenatide	10 µg pen	20 µg
	• Dulaglutide	1.5/0.5 mL pen	1.5 mg**
	• Semaglutide	1 mg pen	1 mg**
	• Liraglutide	18 mg/3 mL pen	1.8 mg
Bile acid sequestrants	• Colesevelam	625 mg tabs	3.75 g
		3.75 g suspension	3.75 g
Dopamine-2 agonists	• Bromocriptine	0.8 mg	4.8 mg
Amylin mimetics	• Pramlintide	120 µg pen	120 µg/injection†††

- AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1, glucagon-like peptide 1; IR, immediate release; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2.
- ↲† Calculated for 30-day supply (AWP [44] or NADAC [45] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price.
- ↲* Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially.
- ↲** Administered once weekly.
- ↲††† AWP and NADAC calculated based on 120 µg three times daily.

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Oral hypoglycemic agents include the following groups: carbohydrase inhibitors, thiazolidinediones (in other words 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 considered as euglycemic or antihyperglycemic drugs, because they have no any evident hypoglycaemic effect in non-diabetic individuals except of special conditions (simultaneous consumption of alcohol etc.)

First of all oral agents should be prescribed according to pathogenetic stage of disease. Sulfonylureas and meglitinides as secretagogues may be useful when insulin level is normal or decreased to some extent whereas PPAR-γ agonists will be reasonable when hyperinsulinemia occurs. In the case when relative insulin deficiency changes to absolute one replacement treatment with insulin is mandatory.

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

The group of agents known as carbohydrase inhibitors includes acarbose, miglitol. The mechanism of action both drugs is inhibition of the α-glucosidases in the intestinal brush border, leading to a delay in carbohydrate absorption. For both agents, the therapeutic dose is between 50 and 100 mg; higher doses lead to abdominal distention, flatulence, malabsorption, and diarrhoea. The use of these agents has generally been associated with only modest improvements in glycated haemoglobin measurements. Contraindications to use carbohydrate inhibitors are the following: gastrointestinal diseases with impaired digestion and absorption (peptic ulcer, ulcerative colitis, Crohn's disease) and blockage or obstruction in intestines

Nowadays biguanides include only one metformin. Metformin reduces absorption of glucose from the gastrointestinal tract, probably due to inhibition of glucose uptake at the mucosal surface. Metformin also inhibits hepatic glucose production and increases insulin-stimulated glucose uptake at the periphery by stimulating the GLUT 4 glucose transporter. Unlike therapy with insulin or sulfonylureas, therapy with metformin does not lead to weight gain and may be associated with modest weight loss because of slight anorectic effect of the drug.

When metformin is used appropriately the incidence of lactic acidosis is rare. For this reason metformin is contraindicated in patients with impaired renal function. Starting dosages of metformin range from 1.0 to 2.0 per day in divided doses of 500 mg or 850 mg. The maximum dosage is 3 g, usually given in three divided doses. Obese patients with type 2 diabetes usually start their treatment on biguanides.Contraindications to metformin therapy include impaired creatinine clearance, liver disease, heart failure, chronic obstructive lung disease, ad alcohol abuse. Side effects are mainly gastrointestinal; abdominal discomfort, diarrhoea, and nausea and vomiting have been reported.

Thiazolidinediones act to enhance insulin sensitivity. Two drugs in this category are currently marketed in the United States: rosiglitazone and pioglitazone. Rosiglitazone has been recalled from most European markets in 2011 because of its cardiac side effects and hepatic toxicity.

All of the thiazolidinediones are associated with a statistically increased incidence of edema and weight gain when compared with placebo. When edema occurs it tends to be mild or moderate. The thiazolidinediones should not be used in patients with congestive heart failure. The drugs are associated with an increase of plasma fluid volume and may result in mild, dilutional-related decreases in haemoglobin, hematocrit, and white cell count. Also weight gain is known occurrence in many studies of patients with type 2 diabetes in general. Liver enzymes should be monitored before and during therapy (every 2 months). Rosiglitazone should not be used with insulin while pioglitazone is approved to be used in combination with insulin preparations.

Meglitinides are considered as postprandial hypoglycaemic agents. Meglitinides include two groups with one drug in each group. Phenylalanine derivates presents nateglinide, and benzoic acid derivates – repaglinide. Recommended dosage to repaglinide is from 0.5 to 4 mg taken with meals 2 to 4 times daily with a maximum dosage of 16 mg per day. Nateglinide is available in tablets of 60 and 120 mg. Each dose should be prescribed 1-30 min. before meals 2-4 times a day. Drugs should be taken with a full glass of water. If patients skip a meal they need to miss the dose for this meal. Taking additional meal demands one more tablet. The main contraindication to meglitinides is liver diseases.

Nateglinide or repaglinide may also be used in combination with metformin. Meglitinides should not be used with sulfonylureas. Alcoholic beverages enhance hypoglycaemic threatening. Therapeutic effect of nonsteroidal anti-inflammatory drugs, diuretics, salicylates, and beta-blockers may be altered with meglitinides following concurrent use.

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

There are primary and secondary failures of sulfonylureas. The primary failure refers to inadequate diet. The secondary one is related to β cell's inability to produce insulin.

Sulfonylureas close K^+ channel, producing alteration of membrane charge. This process leads opening of Ca^+ channels. Calcium enters a cell and pushes insulin out of the cell into the blood circulation.

The priority should be given to once daily sulfonilureas. Once daily regimen allows to increase compliance of patients and to improve glicemic control. Gliclazide MR and glimepiride may be prescribed for this reason. Other SU usually taken twice or three times daily. Each dose should be taken with a full glass of water. Contraindications for use are the following: hepatic insufficiency, renal insufficiency (except gliclazide MR, gliquidone, glipizide).

Alcohol lowers blood sugar and may 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.

The name of combined hypoglycaemic drugs is usually related to the composition of two pharmacological agents (various sulfonylureas and biguanides, i.e. metformin). For instance: (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) sometimes are called incretins. Such drugs are able to decrease glucose level in physiologic manner following two different mechanisms. GLP-1 analogs and agonists as the group for replacement treatment approach increases the level of glucagon-like peptide in the body helping to prepare β-cells to produce insulin after glucose stimulation. But dipeptidyl

peptidase-4 inhibitors (DPP-4) diminish the intrinsic amount of dipeptidyl peptidase which destroys GLP-1.
Exenatide is the first GLP-1 agonist approved for the treatment of type 2 diabetes. Exenatide is not an analogue of GLP, but rather a GLP agonist. Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life. Typical reductions in A1C values are 0.5–1.0%. Liraglutide is a once daily human analogue (97% homology). Both of these drugs should be prescribed subcutaneously.
DPP-4 inhibitors involve saxagliptin and sitagliptin that available in tablets.
Exenatide is presented on the market 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 prescribed twice a day before meal, while liraglutide – once a day without relationship to meals.
Saxagliptin may 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 market.

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

Case 1.
Patient N. 46 years old, complains of an itch about 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. Foots are chilly, 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 complication.
2. Choose the proper therapeutic approach.

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

Theme 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.

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. **Professional motivation**: The diabetic acidoses and comas remain a significant cause of mortality and morbidity, much of it unnecessary. Infection is by far the most common of the precipitating factors for diabetic acidosis. Infection causes a marked increase in secretion of cortisol and glucagon. Other precipitating factors include omission of insulin doses, cerebrovascular accidents, acute myocardial infarction, and trauma.

Hyperosmolar hyperglycemic nonketotic coma occurs at approximately a tenth of the frequency of classic diabetic ketoacidosis; however, it carries a much higher mortality. It usually occurs in patients with type 2 diabetes mellitus and often is the first indication that the patient has diabetes. The precipitating factors for hyperosmolar hyperglycemic nonketotic coma are the following: infection, cardiovascular emergencies (such as a cerebrovascular accident and myocardial infarction), and cerebrovascular accident. These clinical cases may be associated with an inability to drink, and hyperosmolality can ensue.

Hypersecretion of counterregulatory hormones may occur as well, causing metabolic disturbance.

The risks of late complications vary markedly in individuals but generally increase with increasing duration of diabetes mellitus. Hyperglycemia causes the initial metabolic alterations in the kidney, peripheral nervous and retina in diabetics, but evidence suggests that once these structural alterations reach a given stage, factors other than hyperglycemia determine the subsequent cause. The signs and symptoms of late complications of diabetes mellitus mimic those of pathologically similar or indistinguishable disease in the same organ or system in nondiabetics. For example coronary artery disease (manifested by angina pectoris and / or myocardial infarction) and peripheral vascular disease (manifested by intermittent claudication and gangrene) that are more common in diabetics than in nondiabetics. The manifestations may be present at diagnosis in those 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 subset will ultimately 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 (bony abnormalities,

callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation, and poor glycemic control.

Before the advent of insulin, few young diabetic women lived to childbearing age. Before 1922, fewer 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 counseling diabetic women to avoid pregnancy. As the pathophysiology of pregnancy complicated by diabetes has been elucidated and as management programs have achieved and maintained normoglycemia throughout pregnancy, perinatal mortality rates have decreased to levels seen in the general population.

The literal meaning of gestational diabetes mellitus is pregnancy-related diabetes, which usually refers to diabetes that occurs during pregnancy and disappears after the pregnancy is over. Usually gestational diabetes occurs during the second half of pregnancy in those who are overweight, or aging, and who have a family history of diabetes. Most women revert to normal glucose tolerance post-partum but have a substantial risk (30 to 60%) of developing diabetes mellitus later in life.

Diabetes is associated with increased requirement for surgical procedures and increased postoperative morbidity and mortality. Patients with diabetes undergo surgical procedures at a higher rate than do nondiabetic people. The stress of major surgery can significantly influence glucose homeostasis in the diabetic individuals. Major surgical operations require a period of fasting during which oral antidiabetic medications cannot be used. Patients can develop severe hyperglycemia and ketosis during and following surgery regardless of whether they are receiving prior drug therapy. The stress response itself may precipitate diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome during surgery or postoperatively, with negative prognostic consequences. Hyperglycemic hyperosmolar syndrome is a well known postoperative complication following certain procedures, including cardiac bypass surgery, where it is associated with 42% mortality. Furthermore, gastrointestinal instability provoked 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, thereby increasing the risk for ischemic events and acute renal failure. Subtle to gross deficits in key electrolytes (principally potassium, but also magnesium) may pose an arrhythmogenic risk, which often is superimposed on a milieu of endemic coronary artery disease in middle-aged or older people with diabetes.Thus any diabetic patient undergoing surgery should be in the best nutritional, metabolic, and general condition possible.

2. Study aim of this lesson

is to acquaint students with therapy of emergency states in diabetes, management of diabetic complications, treatment of the pregnant diabetic woman and treatment 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 states 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 woman,
- general treatment strategy of diabetic patient that undergo surgery.

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

- discern hypoglycaemia from other acute complications,
- differentiate macrovascular and microvascular events,
- treat patient with chronic diabetic complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic foot, macrovascular complications),
- manage patients with emergency states,
- know diagnostic criteria for gestational diabetes,
- treatment approach of labor and delivery in diabetic woman,
- prescribe insulin to patients going to undergo surgery.

3. Educational aim of this lesson

Is to focus attention on treatment of emergency states, late diabetic complications, labor and delivery as well as patients going to be undergone to surgery

4. Integration between disciplines (see Table 8).

Table 8

Integration between disciplines

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 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 diagnosis.

III. Integration among disciplines	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 like 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 states.
- Treatment strategies of diabetic patients that undergo surgery.

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. Developing of foot gangrene
E. Paresthesia

7.2. Recourses for the main stage of the lesson.

Diabetic ketoacidosis results from absolute or relative insulin deficiency which leads to hyperglycemia and a resulting osmotic dieresis, dehydration and electrolyte depletion. The insulin deficiency activates glycogenolysis (glycogen breakdown to glucose) and gluconeogenesis (protein breakdown that leads to nitrogen loss and production of amino acids that serve as precursors in forming new glucose). In addition, lipolysis results in production of free fatty acids as well as glycerol, which further helps fuel new glucose production. Contributing further to the hyperglycemia are the decreased peripheral glucose utilization (secondary to both insulin lack and resistance) and the volume depletion (secondary to osmotic diuresis) that decrease renal blood flow and therefore the amount of glucose filtered and excreted by the kidney. Free fatty acids are delivered to the liver where ketone bodies are produced (ketogenesis) with resultant ketonemia, which is intensified by decreased peripheral utilization. This leads to ketonuria, which futher depletes electrolytes by an associated obligatory loss of cations. Acidosis occurs as body bases are exhausted in the process of buffering the ketone bodies that are being produced in an uncontrollable fashion (Fig. 1).

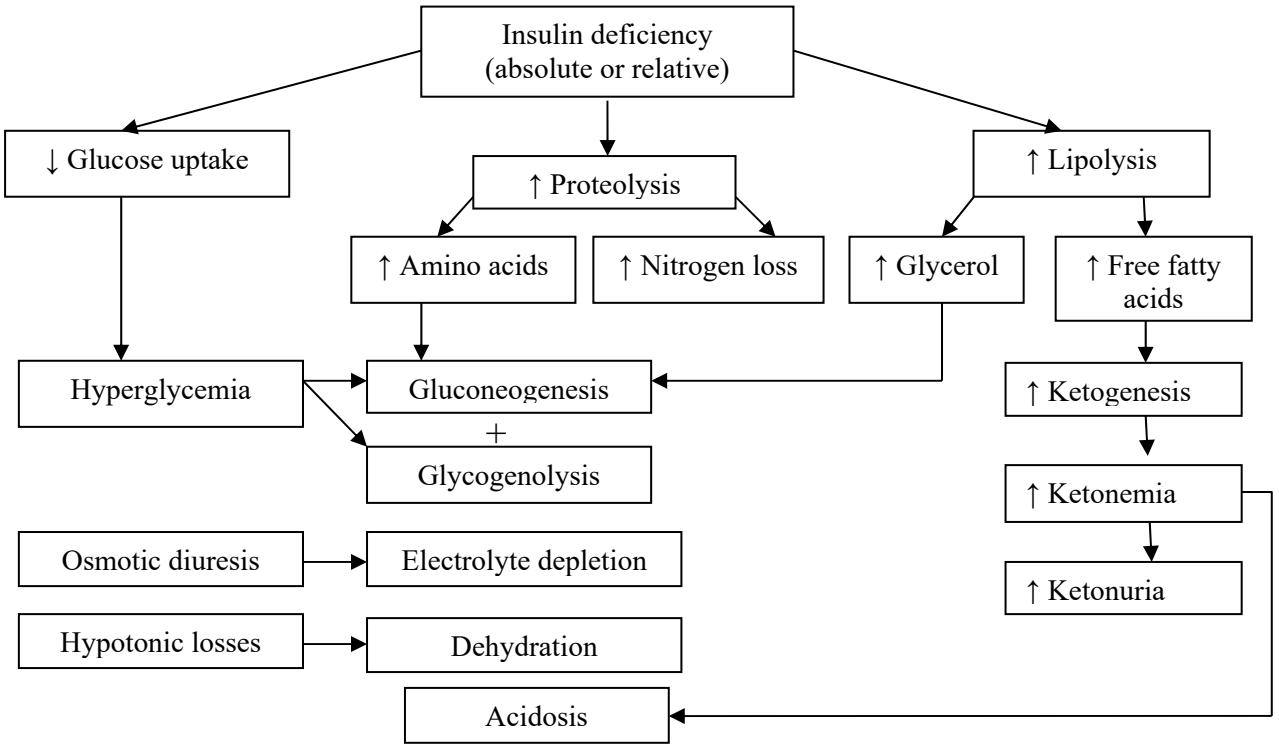


Figure 1. Pathophysiology of diabetic ketoacidosis.

The symptoms and physical signs of diabetic ketoacidosis are listed in the table 9 and usually develop over 24 hours. Diabetic ketoacidosis may be the initial symptom complex that leads to a diagnosis of type 1 diabetes mellitus, but more frequently it occurs in individuals with established diabetes. Signs of infection, which may precipitate diabetic ketoacidosis, should be sought on physical examination, even in the absence of fever. Tissue ischemia (heart, brain) can also be a precipitating factor.

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 respirations/respiratory distress
	Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
	Lethargy /obtundation/cerebral edema/possibly coma

Diabetic ketoacidosis may be defined as a state of uncontrolled diabetes mellitus in which there is hyperglycemia (usually >16.7 mmol/l) with a significant lowering of arterial blood pH (<7.3) and an elevation of total blood ketone body concentration (β-hydroxybutyrate plus acetoacetate >5 mmol/l). The cutoff between diabetic ketoacidosis and hyperosmolar

hyperglycemic nonketotic coma is somewhat arbitrary, although hyperglycemia tends to be much more severe in the latter, with ketone body levels lower.
Treatments of diabetic ketoacidosis are listed 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 events for diabetic ketoacidosis are the following: inadequate insulin administration, infection (pneumonia/ urinary tract infection /gastroenteritis/sepsis), infarction (cerebral, coronary, mesenteric, and peripheral), drugs (cocaine), pregnancy.
The prototypical patient with hyperosmolar hyperglycemic nonketotic coma is an elderly individual with type 2 diabetes mellitus, with a several week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma. The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of diabetic

ketoacidosis. Hyperosmolar hyperglycemic nonketotic coma is often precipitated by a serious, concurrent illness such as myocardial infarction or stroke. Sepsis, pneumonia, and other serious infections are frequent precipitants and should be sought. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder.

Relative insulin deficiency and inadequate fluid intake are the underlying 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 discussion of diabetic ketoacidosis). Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in hyperosmolar hyperglycemic nonketotic coma is not completely understood. Presumably, the insulin deficiency is only relative and less severe than in diabetic ketoacidosis. Lower levels of counterregulatory hormones and free fatty acids have been found in hyperosmolar hyperglycemic nonketotic coma than in diabetic ketoacidosis in some studies. It is also possible 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 stores are usually depleted.

Volume depletion and hyperglycemia are prominent features of both hyperosmolar hyperglycemic nonketotic coma and diabetic ketoacidosis. Consequently, therapy of these disorders shares several elements. In both disorders, careful monitoring of the patient's fluid status, laboratory values, and insulin infusion rate is crucial. Underlying or precipitating

problems should be aggressively sought and treated. In hyperosmolar hyperglycemic nonketotic coma, fluid losses and dehydration are usually more pronounced than in diabetic ketoacidosis due to the longer duration of the illness. The patient with hyperosmolar hyperglycemic nonketotic coma is usually older, more likely to have mental status changes, and more likely to have a life-threatening precipitating event with accompanying comorbidities. Even with proper treatment, hyperosmolar hyperglycemic nonketotic coma has a substantially higher mortality than diabetic ketoacidosis (up to 15% in some clinical series).

Lactic acidosis occurs when the metabolism of pyruvate and lactate is blocked. It is a condition in which 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 sharply since its association with phenformin (and buformin) usage became well known. Metformin is now the only biguanides that is widely available; the incidence of lactic acidosis associated with its use is five to ten per 100,000 patient-years, only marginally above the rate in non-metformin users.

Patients with lactic acidosis probably will be hypotensive, obviously ill, and hyperventilating. They are likely to be oliguric or anuric. There will be a history of metformin use or of cardiovascular disease, and there may be a recent cerebrovascular accident or myocardial infarction. Diagnosis is aided by the scheme shown in Table 14.

Treatment of lactic acidosis in unsatisfactory, with a mortality of 50% in biguanides-associated cases and 60% to 80% in others. The first priority is vascular support and reversal of hypotension. Any cause should be treated (e.g., stopping the administration of biguanides). Equally important is reversal of the academia. As long as pH remains below 7.0 the liver produces, rather than clears, lactate and is not able to generate hydroxyl ions through the oxidation of lactate. A vicious cycle then develops. Sodium bicarbonate should be given iv in large amounts, 250 mmol over 1 hour initially, with repeated similar doses until the pH is >7.1. In some patients, as much as 2500 mmol has been given with success. Almost inevitably, patients require hemodialysis or peritoneal dialysis. This also may help

remove the hydrogen ion load and any responsible drugs. It is obvious that the most effective treatment is prevention.
Bedside differential diagnosis of coma are 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

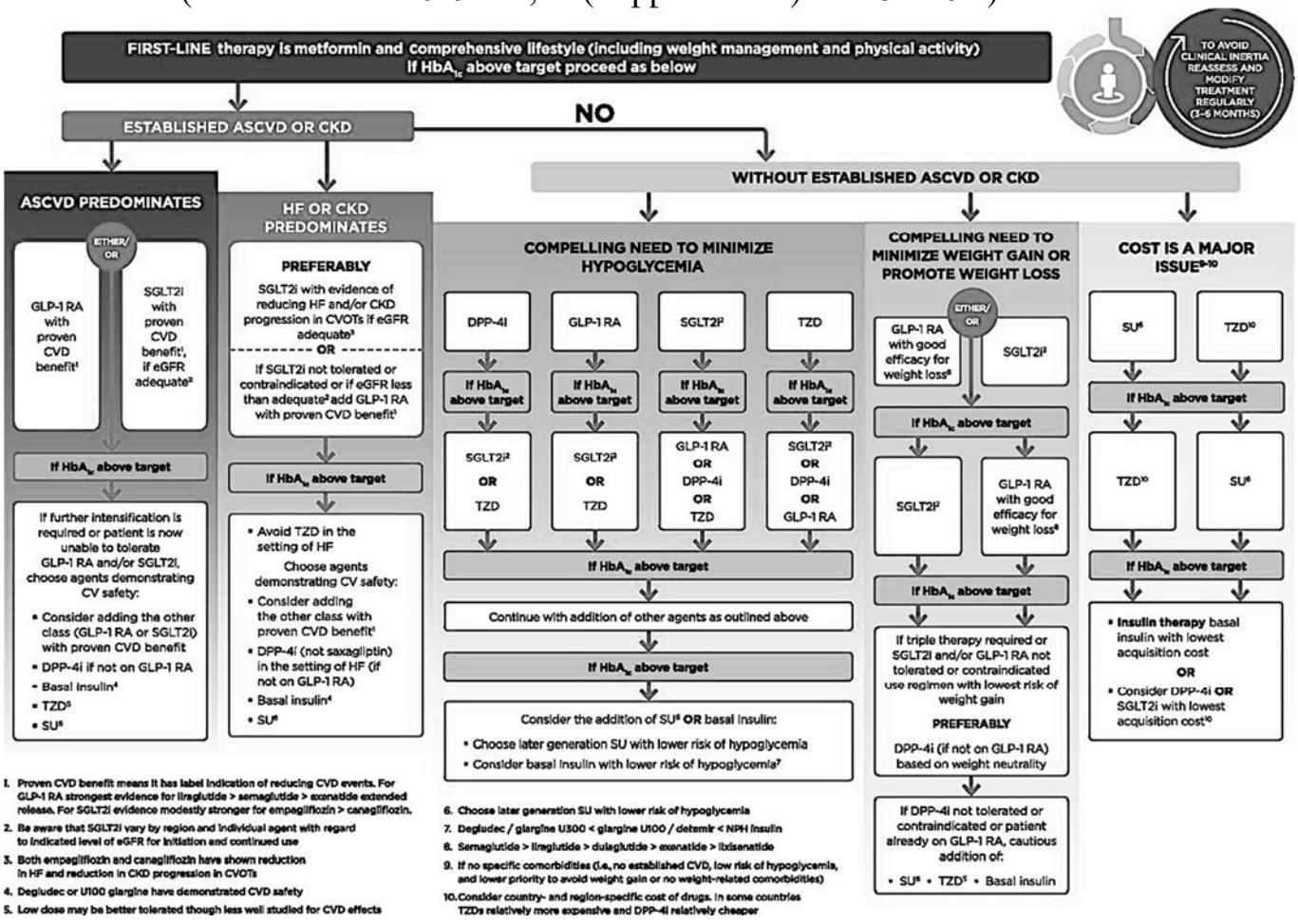
Notes: + - mild, ++ - moderate, +++ - severe, * - using test strips.

The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications (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 disease is increased in individuals with type 1 or type 2 diabetes mellitus. Type 2 diabetes patients without a prior myocardial infarction have a similar risk for coronary artery related events as nondiabetic individuals who have had a prior myocardial infarction. The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures. Coronary artery disease is more likely to involve multiple vessels in individuals with diabetes mellitus. Here you can see the scheme for choosing hypoglycemic therapy, taking into account the cardiovascular risks recommended by American Diabetes Association (Diabetes Care 2019 Jan; 42(Supplement 1): S148-S164.)



Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, an elevation of serum creatinine, and abnormal platelet function. Insulin resistance, as reflected by elevated serum insulin levels, is associated with an increased risk of cardiovascular complications in individuals with and without diabetes mellitus.

Proof that improved glycemic control reduces cardiovascular complications in diabetes mellitus is lacking; in fact, it is possible that macrovascular complications may be unaffected or even worsened by such therapy. Concerns about the atherogenic potential of insulin remain, since in nondiabetic individuals, higher serum insulin levels (indicative of insulin resistance) are associated with a greater risk of cardiovascular morbidity and mortality.

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

Hypertension can accelerate other complications of diabetes mellitus, particularly cardiovascular disease and nephropathy. Hypertension therapy should first emphasize life-style modifications such as weight loss, exercise, stress management, and sodium restriction. Antihypertensive agents should be selected based on the advantages and disadvantages of the therapeutic agent in the context of an individual patient's risk factor profile. Diabetes mellitus-related considerations include the following:

- ACE inhibitors are either glucose- and lipid-neutral or glucose- and lipid-beneficial and thus positively impact the cardiovascular risk profile. For example, α-adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile, whereas beta blockers and thiazide diuretics can increase insulin resistance and negatively impact the lipid profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid- and glucose-neutral.
- Beta blockers may slightly increase the risk of developing type 2 diabetes mellitus. Although often questioned because of the potential masking of hypoglycemic symptoms, beta blockers are safe in most patients with diabetes and reduce cardiovascular events.
- Sympathetic inhibitors and α-adrenergic blockers may worsen orthostatic hypotension in the diabetic individual with autonomic neuropathy.
- Equivalent reduction in blood pressure by different classes of agents may not translate into equivalent protection from cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs positively impact cardiovascular endpoints (MI or stroke). The cardiovascular protective effect of calcium channel blockers, central adrenergic antagonists, and α-adrenergic blockers is either controversial or not known. ACE inhibitors and ARBs slow the progression of diabetic renal disease; the effect of other classes of agents on diabetic nephropathy is not known.
- Non-dihydropyridine calcium channel blockers (verapamil and diltiazem), rather than dihydropyridine agents (amlodipine and nifedipine), are preferred in diabetics.

Diabetes mellitus is the leading cause of blindness between the ages of 20 and 74. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular edema. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots. Mild nonproliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages.

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development or slow the progression of retinopathy. Paradoxically, during the first 6 to 12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy. Individuals with known retinopathy are candidates for prophylactic photocoagulation when initiating intensive therapy. Laser photocoagulation is very successful in preserving vision.

Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation.

Proteinuria in individuals with diabetic nephropathy is associated with markedly reduced survival and increased risk of cardiovascular disease. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and cause an increase of the glomerular filtration rate (GFR). After 5 to 10 years of type 1 DM, ~40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30 to 300 mg/d in a 24-h collection or 30 to 300 μg/mg creatinine in a spot collection (preferred method). The appearance of microalbuminuria (incipient nephropathy) in type 1 DM is an important predictor of progression to overt proteinuria (>300 mg/d) or overt nephropathy. Blood pressure may rise slightly at this point but usually remains in the normal range. Once overt proteinuria is present, there is a steady decline in GFR, and ~50% of individuals reach end-stage renal disease in 7 to 10 years.

The optimal therapy for diabetic nephropathy is prevention. Interventions effective in slowing progression from microalbuminuria to overt nephropathy include: (1) near normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors or ARBs, and (4) treatment of dyslipidemia.

Diabetic neuropathy occurs in approximately 50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control; both myelinated and unmyelinated nerve fibers are lost.

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss. Hyperesthesia, paresthesia, and dysesthesia also occur. Symptoms include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night.

Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be pursued and will improve nerve conduction velocity, but the symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoidance of neurotoxins (alcohol), supplementation with vitamins for possible deficiencies (B_{12}, B_6, folate) and symptomatic treatment are the mainstays of therapy. Aldose reductase inhibitors do not offer significant symptomatic relief. Chronic, painful diabetic neuropathy is difficult to treat but may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, nonsteroidal anti-inflammatory agents (avoid in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream).

Regarding diabetic foot, diabetes mellitus is the leading cause of nontraumatic lower extremity amputation in the world. The reasons for the increased incidence of diabetic foot involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, peripheral arterial disease, and poor wound healing. The peripheral sensory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered proprioception causes abnormal weight bearing while walking and subsequent

formation of callus or ulceration. Motor and sensory neuropathy lead to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint).

A recent consensus statement from the American Diabetes Association identified six interventions with demonstrated efficacy in diabetic foot wounds: (1) off-loading, (2) debridement, (3) wound dressings, (4) appropriate use of antibiotics, (5) revascularization, and (6) limited amputation. Mild or non-limb-threatening infections can be treated with oral antibiotics (cephalosporin, clindamycin, amoxicillin/clavulanate, and fluoroquinolones), surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection. More severe ulcers may require intravenous antibiotics as well as bed rest and local wound care. Intravenous antibiotics should provide broad-spectrum coverage directed toward Staphylococcus aureus, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial regimens include cefotetan, ampicillin/sulbactam, or the combination of clindamycin and a fluoroquinolone.

Diagnosis of gestational diabetes mellitus is shown 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 cause a stereotypical metabolic stress response that could overwhelm homeostatic mechanisms in patients with pre-existing abnormalities of glucose metabolism. The invariant features of the metabolic stress response include release of the catabolic hormones epinephrine, norepinephrine, cortisol, glucagons, and growth hormone and inhibition of insulin secretion and action.

In addition to insulin resistance induced by circulating stress hormones, surgical stress has a deleterious effect on pancreatic β-cell function. Plasma insulin levels fall, and insulin secretory responses to glucose become impaired during surgery.

People whose diabetes is well controlled by a regimen of dietary modification and physical activity may require no special preoperative intervention for diabetes. If surgery is minor (>1 h), no specific therapy is required. If surgery is major or if diabetes is poorly controlled (blood glucose >200 mg/dl), an intravenous infusion of insulin and dextrose should be considered, and hourly intraoperative glucose monitoring is recommended.

Second-generation sulfonylureas should be discontinued 1 day before surgery, with the exception of chlopropramide, which should be stopped 2–3 days before surgery. Other oral agents can be continued until the operative day. Although metformin has a short half-life of ∼6 h, it is prudent to temporarily withhold therapy 1–2 days before surgery, especially in sick patients and those undergoing procedures that increase the risks for renal hypoperfusion, tissue hypoxia, and lactate accumulation.

Patients treated with long-acting insulin (e.g., ultralente, glargine, protamine zinc insulin) should be switched to intermediate-acting forms 1–2 days before elective surgery.

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 became thinner, 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, glucoseurea is 2,0 %.

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

Case 2.

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.

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

Case 3.

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 %.

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

Theme 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: "Basics of diagnosis, management, and prophylaxis of main endocrine disorders" in the module 1: "The basis of internal medicine"

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. **Professional motivation**: Severe and moderate iodine deficiency is prevalent in many mountainous regions and in central Africa, central South America, and northern Asia. Mild deficiency is present in Europe. The World Health Organization (WHO) estimates that about 2 billion people are iodine-deficient, based on urinary excretion data. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. Cretinism is characterized by mental and growth retardation and occurs when children who live in iodine-deficient regions are not treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early life. These children are often born to mothers with iodine deficiency, and it is likely that maternal thyroid hormone deficiency worsens the condition. India is the most outstanding, with 100 million suffering from iodine deficiency (4 million from goiter, and 0.5 million from cretinism). Concomitant selenium deficiency may also contribute to the neurologic manifestations of cretinism. Iodine supplementation of salt, bread, and other food substances has markedly reduced the prevalence of cretinism. Unfortunately, however, iodine deficiency remains the most common cause of preventable mental deficiency, often because of societal resistance to food additives or the cost of supplementation. In addition to overt cretinism, mild iodine deficiency can lead to subtle reduction of IQ. Oversupply of iodine, through supplements or foods enriched in iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The recommended average daily intake of iodine is 150 μg/d for adults, 90–120 μg/d for children, and 200 μg/d for pregnant women. Urinary iodine is >10 μg/dL in iodine-sufficient populations.
Public health initiatives to lower the risk of cardiovascular disease have resulted in lower discretionary salt use at the table, and with a trend towards consuming 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 to make it, gives rise to high levels of thyroid stimulating hormone TSH, which stimulates the thyroid gland to increase many biochemical processes; the cellular growth and proliferation can result in the characteristic swelling or hyperplasia of the thyroid gland, or goiter.

Early hypothyroidism is often asymptomatic and can have very mild symptoms. Subclinical hypothyroidism is a state of normal thyroid hormone levels, thyroxine (T4) and triiodothyronine (T3), with mild elevation of thyrotropin, thyroid-stimulating hormone (TSH). With higher TSH levels and low free T4 levels, symptoms become more readily apparent in clinical (or overt) hypothyroidism. Hypothyroidism can be associated with female infertility.

Thyroiditis is a group of disorders that all cause thyroidal inflammation. There are many different symptoms for thyroiditis, none of which are exclusively limited to this disease. Many of the signs imitate symptoms of other diseases, so thyroiditis can sometimes be difficult to diagnose. Thyroiditis is generally caused by an attack on the thyroid, resulting in inflammation and damage to the thyroid cells. This disease is often considered a malfunction of the immune system. Antibodies that attack the thyroid are what causes most types of thyroiditis. It can also be caused by an infection, like a virus or bacteria, which works in the same way as antibodies to cause inflammation in the glands. Certain people make thyroid antibodies, and thyroiditis can be considered an autoimmune disease, because the body acts as if the thyroid gland is foreign tissue. Some drugs, such as interferon and amiodarone, can also cause thyroiditis because they have a tendency to damage thyroid cells. Hashimoto's thyroiditis was first discovered by Japanese physician Hashimoto in 1912. Hashimoto’s thyroiditis is also known as lymphocytic thyroiditis, and patients with this disease often complain about difficulty swallowing. This condition may be so mild at first that the disease goes unnoticed for years. The first symptom that shows signs of Hashimoto’s thyroiditis is a goitre on the front of the neck.

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

Thyroid nodules are of particular concern when they are found in those under the age of 20. The presentation of benign nodules at this age is less likely, and thus 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 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 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.

3. Educational aim of this lesson

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

4. Integration between disciplines (see Table 17).

Table 17

Integration between disciplines

Discipline	To know	How to do
I. Previous		
Normal anatomy and physiology, histology, pathology 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 Surgery Obstetrics & Gynecology Neurology	Main clinical signs of thyroid disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment, prophylactics.	To make clinical observation, to recommend proper diagnostic assays, consultation of associative specialists for verification diagnosis, to prescribe medication
III. Integration among disciplines	Contemporary methods of diagnosis and treatment	To prescribe 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 to 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 relatively to detrimental action of increased thyroid hormone production.

A. T_3 and T_4 cause hyperprolactinemia
B. T_3 sensitises myocardium to the effects of catecholamines
C. Weight gain is related with thyroid overproduction
D. T_4 induce tachycardia directly
E. Excessive level of thyroid hormones predisposes to 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.

Iodine is an essential trace element; the thyroid hormones thyroxine and triiodotyronine contain iodine. In areas where there is little iodine in the diet – typically remote inland areas where no marine foods are eaten – iodine deficiency gives rise to goiter (so-called endemic goiter), as well as cretinism, which results in developmental delays and other health problems. While noting recent progress, The Lancet noted, "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".
In some such areas, this is now combated by the addition of small amounts of iodine to table salt in form of sodium iodide, potassium iodide, and/or potassium iodate – this product is known as iodized salt. Iodine compounds have also been added to other foodstuffs, such as flour, water and milk in areas of deficiency. Seafood is also a well known source of iodine. Thus, iodine deficiency is more common in mountainous regions of the world where food is grown in soil poor in iodine.
Following is a list of potential risk factors that may lead to iodine deficiency:[29]

1. Low dietary iodine
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 tobacco
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 a goiter. There is no direct correlation between size and function- a person with a goiter can be euthyroid, hypo- or hyperthyroid.
Regarding morphology, goitres may be classified either as the growth pattern or as 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 toxic multinodular goitre
- Diffuse (struma diffuse), with the whole thyroid appearing to be enlarged.

Size

- Class I – palpation struma – in normal posture of the head, it cannot be seen; it 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.

Group of thyroiditis includes the following diseases: Hashimoto's thyroiditis, the most common cause of hypothyroidism, postpartum thyroiditis, subacute thyroiditis, silent thyroiditis, drug-induced thyroiditis, radiation-induced thyroiditis, and acute thyroiditis.
Each different type of this disease has its own causes, clinical features, diagnoses, durations, resolutions, conditions and risks.
Common hypothyroid symptoms manifest when thyroid cell damage is slow and chronic, and may include fatigue, weight gain, feeling “fuzzy headed”, depression, dry skin, and constipation. Other, rarer symptoms include swelling of the legs, vague aches and pains, decreased concentration and so on. When conditions become more severe, depending on the type of thyroiditis, one may start to see puffiness around the eyes, slowing of the heart rate, a drop in body temperature, or even future heart failure. On the other hand, if the thyroid cell damage is acute, the thyroid hormone within the gland leaks out into the bloodstream causing symptoms of thyrotoxicosis, which is similar to those of hyperthyroidism. These symptoms include weight loss, irritability, anxiety, insomnia, fast heart rate, and fatigue. Elevated levels of thyroid hormone in the bloodstream cause both conditions, but thyrotoxicosis is the term used for with thyroiditis since the thyroid gland is not overactive, as in the case of hyperthyroidism.
Thyroid cancer is a thyroid neoplasm that is malignant. It can be treated with radioactive iodine or surgical resection of the thyroid gland. Chemotherapy or radiotherapy may also be used.
Most often the first symptom of thyroid cancer is a nodule in the thyroid region of the neck. However, many adults have small nodules in their thyroids, but typically fewer than 5% of these nodules are found to be malignant. Sometimes the first sign is an enlarged lymph node. Later symptoms that can be present are pain in the anterior region of the neck and changes in voice due to involvement of recurrent laryngeal nerve.
Thyroid cancers can be classified according to their histopathological characteristics. The following variants can be distinguished (distribution over various subtypes may show regional variation):

- Papillary thyroid cancer (75% to 85% of cases) – often in young females – excellent prognosis
- 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 classified as "differentiated thyroid cancer". These types have a 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, was diagnosed enlarged thyroid gland. Patient lives in Carpathians.
Objective review: Thyroid enlarged in all parts. Configuration of the neck was not changed. Consistence 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 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?
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 good." Although she could not date the onset of decreased hearing, she had experienced difficulty listening 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 affect seem 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 decreased hearing. She occasionally had numbness in both hands early in the morning that cleared by 10 AM and at times 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. Establish your diagnosis
2. Order therapy.

Theme 6:

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

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

Quantity of study hours: 5.

1. **Professional motivation**: Thyrotoxicosis includes the following causes: Graves' disease, 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 within the thyroid gland causing an overproduction of thyroid hormones (thyroxine or "T4" and/or triiodothyronine or "T3"). Hyperthyroidism is thus a cause of thyrotoxicosis, the clinical condition of increased thyroid hormones in the blood.
Hyperthyroidism and thyrotoxicosis are not synonymous. For instance, thyrotoxicosis could instead be caused by ingestion of exogenous thyroid hormone or inflammation of the thyroid gland, causing it to release its stores of thyroid hormones.
Graves' disease is the most common cause of thyrotoxicosis, and usually presents itself during early adolescence. It has a powerful hereditary component, affects up to 2% of the female population, and is between five and ten times as common in females as in males. Graves' disease is an autoimmune disease where the thyroid is overactive, producing an excessive amount of thyroid hormones (a serious metabolic imbalance known as hyperthyroidism and thyrotoxicosis). This is caused by thyroid autoantibodies (TSHR-Ab) that activate the TSH-receptor (TSHR), thereby stimulating thyroid hormone synthesis and secretion, and thyroid growth (causing a diffusely enlarged goiter). The resulting state of hyperthyroidism can cause a dramatic constellation of neuropsychological and physical signs and symptoms. Graves' disease is also the most common cause of severe hyperthyroidism, which is accompanied by more clinical signs and symptoms and laboratory abnormalities as compared with milder forms of hyperthyroidism. About 25-30% of people with Graves' disease will 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 resulting in excess production of parathyroid hormone (PTH). The parathyroid hormone regulates calcium and phosphate levels and helps to maintain these levels. Excessive PTH secretion may be due to problems in the glands themselves, in which case it is referred to as primary hyperparathryroidism and

which leads to hypercalcemia (raised calcium levels). It may also occur in response to low calcium levels, as encountered in various situations such as vitamin D deficiency or chronic kidney disease; this is referred to as secondary hyperparathyroidism. In all cases, the raised PTH levels are harmful to bone, and treatment is often needed. Recent evidence suggests that vitamin D deficiency/insufficiency plays a role in the development of hyperparathyroidism. Lithium is associated with an increased incidence of hyperparathyroidism.

Hypoparathyroidism is decreased function of the parathyroid glands, as evidenced by decreased levels of parathyroid hormone (PTH). PTH is required for maintaining adequate calcium levels in the blood, and low PTH levels can therefore lead to hypocalcaemia (low calcium levels), which can have potentially serious consequences.

Hypocalcemic crisis presents with the classical symptomatology of tetany plus extrapyramidal symptoms and a disordering of consciousness extending even to coma. It develops when the concentration of ionized serum calcium declines rapidly, and is very rarely found in chronic hypocalcemia. In terms of its etiology, various 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 thus ionized calcium decreases to only a small extent, 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 involving the decompensation of hypercalcemia, which could have existed for longer periods or could be acute at the first instance 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 the remaining 10%; the majority of 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, prophylaxis of thyroid storm.

4. Integration between disciplines (see Table 18).

Table 18

Integration between disciplines

Discipline	To know	How to do
I. Previous Normal anatomy and physiology, histology, pathology 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.
II. Future Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology, Traumatology	Main clinical signs of thyroid disorders, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment. Main clinical signs of parathyroid gland	To make clinical observation, to recommend proper diagnostic assays, consultation of associative specialists for verification diagnosis, to prescribe medication To prescribe adequate treatment.

III. Integration among disciplines	dysfunction, differential diagnosis, clinical features, laboratory evaluation, technologic facilities, treatment. Contemporary methods of diagnosis and 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.
- Hypercalcemnic crisis (etiology, clinical presentation, treatment).
- Hypocalcemic crisis (etiology, clinical presentation, 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 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
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

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
Hyperthyroid thyroid carcinoma	Somatic gain-of-function mutations in the TSH receptor
Familial non-autoimmune hyperthyroidism	Germline gain-of-function mutations in the TSH receptor
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 you may see 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 play an important role in clinical practice. Amiodarone-induced thyrotoxicosis is more common in iodine-deficient regions, but also occurs in patients with a normal nutritional iodine intake. Amiodarone-induced hypothyroidism is usually seen in iodine-sufficient areas.

Reported incidences of amiodarone-induced thyrotoxicosis vary between 0.003% and 11.5%. In a study involving 1448 patients treated with amiodarone, 30 developed amiodarone-induced thyrotoxicosis. Amiodarone-induced thyrotoxicosis is differentiated into two forms. Amiodarone-induced thyrotoxicosis Type I is caused by increased hormone synthesis because of exposure to high amounts of iodine, amiodarone-induced thyrotoxicosis Type II results from cytotoxic destruction of thyrocytes. Hypothyroidism occurs predominantly in patients with preexisting thyroid autoimmune disease and in areas of normal iodine intake. Amiodarone-induced thyrotoxicosis is more common in men than in women.

The signs of thyrotoxicosis are not apparent in all patients with amiodarone-induced thyrotoxicosis. They may be obscured by the underlying cardiac condition. Some patients have a nodular goiter.

The total or free T4 levels are elevated in euthyroid, hypothyroid and hyperthyroid patients treated with amiodarone because of its inhibition of 5'-monodeiodination. In hyperthyroid patients, TSH is suppressed and T3 is elevated. The distinction between amiodarone-induced thyrotoxicosis Type I and II can be difficult on clinical grounds. The radioiodine uptake is typically low to normal in amiodarone-induced thyrotoxicosis Type I, and low to suppressed in amiodarone-induced thyrotoxicosis Type II. Serum interleukin 6 levels are normal to high in amiodarone-induced thyrotoxicosis Type I and markedly elevated in amiodarone-induced thyrotoxicosis Type II, but there is significant overlap and the test is of insufficient sensitivity. 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 therapy of amiodarone-induced thyrotoxicosis is a challenge (see Table 23). If possible, amiodarone should be discontinued. Patients with type 1 amiodarone-induced thyrotoxicosis are preferably treated with methimazole (initially 40 – 60 mg/day, followed by gradual adjustment of the dose), but the response to thionamides is modest. In selected patients, treatment with potassium perchlorate (1 g/day for 4 to 6 weeks) can be considered. Potassium perchlorate is a drug that can cause aplastic anemia and its use should be limited to patients who cannot be controlled by methimazole, or who are allergic to thionamides. For patients with amiodarone-induced thyrotoxicosis Type II, prednisone (0.5 – 0.7 mg /kg body weight per day) can be used for several months. Because the distinction between amiodarone-induced thyrotoxicosis Type I and II is difficult and not always clear, and because some patients have mixed forms of amiodarone-induced thyrotoxicosis, these therapies are occasionally combined. Patients with a history of amiodarone-induced thyrotoxicosis type II are at risk for developing hypothyroidism if exposed to high amounts of iodide.

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

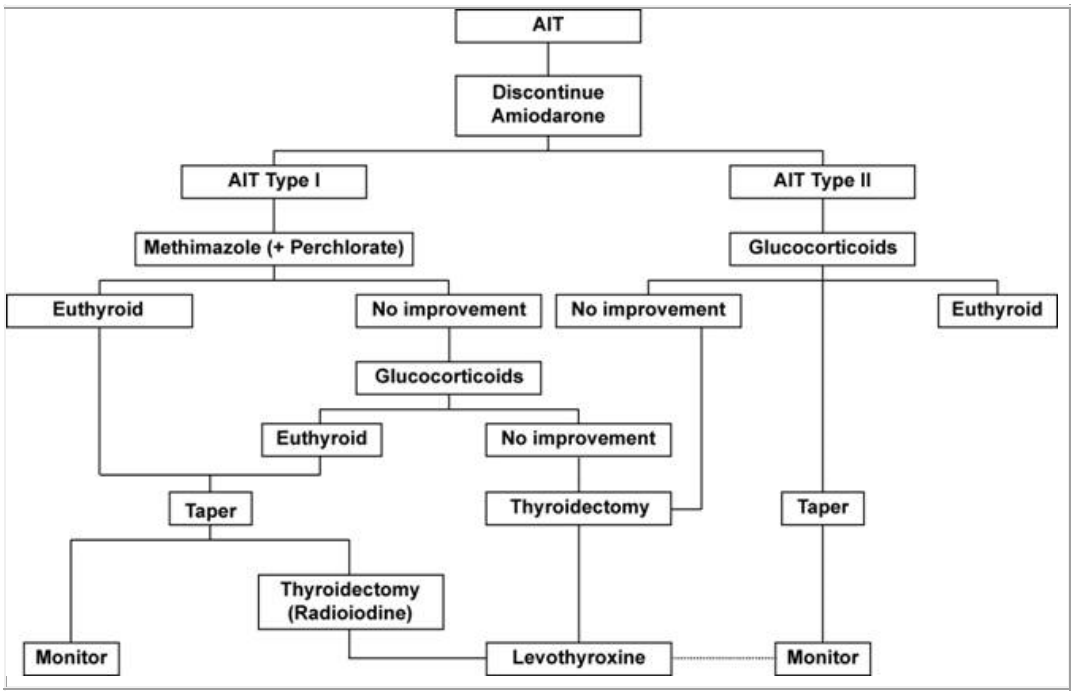


Figure 2. Management of patients with amiodarone-induced thyrotoxicosis (AIT)

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

	Components of Hypercalcemic Syndrome				
Organ	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 potassium loss → hypokalemia	Polyuria, polydipsia, exsiccosis, muscle weakness, arrhythmia	Oliguria, anuria, azotemia	Nephrolithiasis (recurrent), nephrocalcinosis	FHH: hypocalciuria
Intestine	Increased gastric acid secretion, pancreatic enzyme secretion, delayed	Loss of appetite, nausea, vomiting, weight loss, constipation	Increase	Peptic ulcer (recurrent), pancreatitis (calcifying), cholelithiasis	Hyperthyroidism: weight loss

	intestinal transport				
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	Universal (in preference in HHM)	Inhibition of osteolysis	In cases of too fast administration,

		for 2 to 6 days			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, 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 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 denied any 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 exams 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?

Theme 7:

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

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

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

1. **Professional motivation**: Addison's disease (also chronic adrenal insufficiency or chronic primary adrenocortical insufficiency, hypocortisolism, and hypoadrenalism) is a rare, chronic endocrine disorder where the adrenal glands do not produce sufficient steroid hormones (glucocorticoids and often mineralocorticoids). It is characterised by a number of relatively nonspecific symptoms, such as abdominal pain and weakness, but under certain circumstances these may progress to Addisonian crisis, a severe illness in which there may be very low blood pressure and coma. The condition arises from problems with the adrenal gland itself, a state referred to as "primary adrenal insufficiency" and can be caused by damage by the body's own immune system, certain infections or various 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. Despite this distinction, Addisonian crisis can happen in all forms of adrenal insufficiency.
Cushing's syndrome refers to 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. The adenoma causes cortisol levels in the blood to be very high, and negative feedback on the pituitary from the high cortisol levels causes ACTH levels to be very low. Adults may have symptoms of extreme weight gain, excess hair growth in women, diabetes, high blood pressure, and skin problems. Untreated Cushing's syndrome can lead to heart disease and increased mortality.
Primary aldosteronism, also known as primary hyperaldosteronism, is characterized by the overproduction of the mineralocorticoid hormone aldosterone by the adrenal glands., when not a result of excessive renin secretion. Aldosterone causes increase in sodium and water retention andpotassium excretion in the kidneys, leading to arterial hypertension (high blood pressure). An increase in the production of mineralocorticoid from the adrenal gland is evident. It is amongst the most common causes of secondary hypertension, renal disease being the most common.
Primary hyperaldosteronism has many causes, including adrenal hyperplasia and adrenalcarcinoma. When it occurs due to a solitary aldosterone-secreting adrenal adenoma (a type of benign tumor), it is known as Conn's syndrome. In the absence of proper treatment, individuals with hyperaldosteronism often suffer from poorly controlled high

blood pressure, which may be associated with increased rates of stroke, heart disease, 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 excessive amounts of catecholamines, usually noradrenaline (norepinephrine), and adrenaline (epinephrine) to a lesser extent. Extra-adrenal paragangliomas (often described 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 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. Integration between disciplines (see Table 24).

Table 24

Integration between disciplines

Discipline	To know	How to do
I. Previous		

Normal anatomy and physiology, histology, pathology 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 status 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 diagnosis, to prescribe medication To prescribe adequate treatment.
III. Integration among disciplines		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 finfings, diagnosis, treatment.
- Cushing 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 disease.

Addison's disease is named after Dr. Thomas Addison, the British physician who first described the condition in 1849. The adjective "Addisonian" is used to describe features of the condition, as well as patients suffering from Addison's disease.

Addison's disease and other forms of hypoadrenalism are generally diagnosed via blood tests and medical imaging. Treatment involves replacing the absent hormones (oral hydrocortisone and fludrocortisone). Lifelong, continuous treatment with steroid replacement therapy is required, with regular follow-up treatment and monitoring for other health problems.

The symptoms of Addison's disease develop insidiously, and it may take some time to be recognised. The most common symptoms are fatigue, lightheadedness upon standing or while upright, muscle weakness, fever, weight loss, difficulty in standing up, anxiety, nausea, vomiting, diarrhea, headache, sweating, changes in mood and personality, and joint and muscle pains. Some have marked cravings for salt or salty foods due to the urinary losses of sodium. Increased tanning may be noted, particularly in sun-exposed areas, as well as darkening of the palmar creases, sites of friction, recent scars, the vermilion border of the lips, and genital skin. This is not encountered in secondary and tertiary hypoadrenalism.

Medical conditions such as type I diabetes, autoimmune thyroid disease (Hashimoto's thyroiditisand goiter) and vitiligo often occur together with Addison's (often in the setting of Autoimmune polyendocrine syndrome). Hence, symptoms and signs of any of the former conditions may also be present in the individual with Addison's. The occurrence of Addison's disease in someone who also has Hashimoto's thyroiditis is called Schmidt syndrome.

Acute adrenal insufficiency.

Adrenal crisis is a potentially fatal condition associated mainly with an acute deficiency of the glucocorticoid cortisol and, to a lesser extent, the mineralocorticoid aldosterone. Crisis occurs when the physiological demand for these hormones exceeds the ability of adrenal glands to produce them, i.e. in patients with chronic adrenal insufficiency when subject to an intercurrent illness or stress:

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

The most common cause is abrupt withdrawal of steroids; secondary adrenocortical insufficiency occurs when steroids given as therapy have suppressed the hypothalamic-pituitary-adrenal axis.Bilateral adrenal gland haemorrhage can produce adrenal crisis due to severe physiological stressors such as myocardial infarction, septic shock or complicated pregnancy, or with concomitant coagulopathy or thromboembolic disorders. Other causes include autoimmune Addison's disease, tuberculosis, HIV, adrenoleukodystrophy, congenital adrenal hypoplasia, etc.

Risk factors

- Long-term steroids:
    - There have been a few cases associated with high-dose inhaled fluticasone and it may cause suppression at lower doses also.
    - A case has been documented following intra-articular steroid injection.
- There have also been cases after ketoconazole, phenytoin and rifampicin.

Presentation

- The patient is acutely ill with hypotension, especially postural. They may also be very weak and confused.
- Circulatory collapse may be severe with feeble rapid pulse and soft heart sounds.
- Pyrexia is common and may be due to underlying infection.
- Anorexia, nausea, vomiting and severe abdominal pain occur very frequently. This may be severe and present as an apparent acute abdomen.
- The patient may show increased motor activity progressing to delirium or seizures.

Investigations

- Sodium is usually moderately decreased, but may be normal.
- Potassium is usually slightly increased or normal – rarely, markedly increased (risk of arrhythmias).
- Hypoglycaemia, possibly severe, is characteristic.
- Serum cortisol concentrations are normally highest in the early morning hours (04:00 hours – 08:00 hours) and increase further with stress. Serum cortisol concentrations at this time of less than 80 nmol/L are strongly suggestive of adrenal insufficiency.
- A short ACTH stimulation test should be performed in all patients suspected of having adrenal insufficiency:
    - Determine the baseline serum cortisol, then administer ACTH 250 mcg intravenously.
    - Serum cortisol measurements are taken at 30 and 60 minutes after ACTH administration.
    - A rise in serum cortisol concentration after 30 or 60 minutes to a peak of 500 to 550 nmol/L or more is considered a normal response.
- ECG may show prolonged QT interval:
    - This may induce ventricular arrhythmias.
    - Deep negative T waves have been described in acute adrenal crisis.

Management

General principles

- Start treatment immediately based on clinical features and not delayed for confirmation of adrenal function.
- Administration of glucocorticoids in supraphysiological or stress doses is the only definitive therapy.
- Dexamethasone does not interfere with serum cortisol assay and may therefore be the initial drug of choice.
- However, because dexamethasone has little mineralocorticoid activity, fluid and electrolyte replacement is essential.

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 required.
- Continued intravenous replacement of estimated dehydration:
    - Usually 5%+ over 8+ hours.
    - Using 5% dextrose in normal saline.
    - Take into account age, volume, cardiac and renal function.
    - Unlikely 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.
    - Thereafter, the hydrocortisone dose can usually be halved again.
    - With such high doses of glucocorticoid, mineralocorticoids are not required.
    - When dosage is reduced further, add fludrocortisone 0.05-0.2 mg/day, aiming at normotension, normokalaemia and a plasma renin activity in the upper normal range.
- If hypotension persists, give additional corticosteroids and consider vasopressors, e.g. dopamine.
    - Investigate adrenal haemorrhage, especially if the patient is receiving anticoagulants.
    - Reversal of coagulopathy should be attempted with fresh frozen plasma.
- Treat the underlying precipitating disorder, e.g. infection, with antibiotics.
- When testing for adrenal insufficiency and treating at the same time, replace hydrocortisone with dexamethasone added to the infusion together with corticotropin.
- Collect blood and urine for analysis of cortisol and urinary – OH-CS levels.

Prevention

- Early dose adjustments (e.g. doubling the usual maintenance dose) are required to cover the increased glucocorticoid demand in stress.
- Careful and repeated education of patients and their partners is the best strategy to avoid this life-threatening emergency.
- Avoid exposure to chickenpox or measles. If exposed, seek medical advice without delay.
- Patients do not require cover for routine dentistry. Patients undergoing general anaesthesia for procedures may require supplementary steroids depending on the dose and duration of steroid treatment.

Associations

Other underlying associated endocrinopathies, which should be excluded:

- Hypothyroidism may mask the Addison’s disease and the thyroxine replacement may precipitate an acute adrenal crisis.
- On steroid replacement therapy the ‘hypothyroidism’ will resolve.

Death may be caused by circulatory collapse and arrhythmias with hypoglycaemia contributing. Prognosis is the same as for patients without adrenal insufficiency if the precipitating condition is diagnosed and treated appropriately.

Cushing syndrome.

Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity). A common sign is the growth of fat pads along the collar bone and on the back of the neck (buffalo hump) and a round face often referred to as a “moon face”. Other symptoms include hyperhidrosis (excess sweating), telangiectasia (dilation of capillaries), thinning of the skin (which causes easy bruising and dryness, particularly the hands) and other mucous membranes, purple or red striae (the weight gain in Cushing’s syndrome stretches the skin, which is thin and weakened, causing it to hemorrhage) on the trunk, buttocks, arms, legs or breasts, proximal muscle weakness (hips, shoulders), and hirsutism (facial male-pattern hair growth), baldness and/or cause hair to become extremely dry and brittle. In rare cases, Cushing's can cause hypercalcemia, which can lead to skin necrosis. The excess cortisol may also affect other endocrine systems and cause, for example, insomnia, inhibited aromatase, reduced libido, impotence, amenorrhoea/oligomenorrhea and infertility due to elevations inandrogens. Patients frequently suffer various psychological disturbances, ranging from euphoria to psychosis. Depression and anxiety are also common.

Other striking and distressing skin changes that may appear in Cushing’s syndrome include facial acne, susceptibility to superficialdermatophyte and malassezia infections, and the characteristic purplish, atrophic striae on the abdomen.

Other signs include polyuria (and accompanying polydipsia), persistent hypertension (due to cortisol’s enhancement of epinephrine’s vasoconstrictive effect) and insulin resistance (especially common in ectopic ACTH production), leading to hyperglycemia and insulin resistance which can lead to diabetes mellitus. Insulin resistance is accompanied by skin changes such as acanthosis nigricans in theaxilla and around the neck, as well as skin tags in the axilla.

Cushing's syndrome due to excess ACTH may also result in hyperpigmentation,This is due to Melanocyte-Stimulating Hormone production as a byproduct of ACTH synthesis from Pro-opiomelanocortin (POMC). Cortisol can also exhibit mineralcorticoid activity in high concentrations, worsening the hypertension and leading to hypokalemia (common in ectopic ACTH secretion). Furthermore, gastrointestinal disturbances, opportunistic infections and impaired wound healing (cortisol is a stress hormone, so it depresses the immune and inflammatory responses).Osteoporosis is also an issue in Cushing’s syndrome since osteoblast activity is inhibited. Additionally, Cushing’s may cause sore and aching joints, particularly in the hip, shoulders, and lower back.

When Cushing's syndrome is suspected, either a dexamethasone suppression test (administration of dexamethasone and frequent determination of cortisol and ACTH level), or a 24-hour urinary measurement for cortisol offer equal detection rates. Dexamethasone is a glucocorticoid and simulates the effects of cortisol, including negative feedback on the pituitary gland. When dexamethasone is administered and a blood sample is tested, high cortisol would be indicative of 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 novel approach, recently cleared by the US FDA, is sampling cortisol in saliva over 24 hours, which may be equally sensitive, as late night levels of salivary cortisol are high in Cushingoid patients. Other pituitary hormone levels may need to be ascertained. Performing a physical examination to determine and visual field defect may be necessary if a pituitary

lesion is suspected, which may compress the optic chiasm causing typical bitemporal hemianopia.

When any of these tests are positive, CT scanning of the adrenal gland and MRI of the pituitary gland are performed to detect the presence of any adrenal or pituitary adenomas or incidentalomas (the incidental discovery of harmless lesions). Scintigraphy of the adrenal gland withiodocholesterol scan is occasionally necessary. Very rarely, determining the ACTH levels in various veins in the body by venous catheterization, working towards the pituitary (petrosal sinus sampling) is necessary.

Primary aldosteronism.

Aldosterone enhances exchange of sodium for potassium in the kidney so increased aldosteronism will lead to hypernatremia and hypokalemia. Once the potassium has been significantly reduced by aldosterone, a sodium/hydrogen pump in the nephron becomes more active leading to increased excretion of hydrogen ions and further exacerbating the hypernatremia. The hydrogen ions that are exchanged for sodium are generated by carbonic anhydrase in the renal tubule epithelium causing increased production of bicarbonate. The increased bicarbonate and the excreted hydrogen combine to generate a metabolic alkalosis. The high pH of the blood makes calcium less available to the tissues and causes symptoms of hypocalcemia (low calcium levels).

The sodium retention leads to plasma volume expansion and elevated blood pressure. The increased blood pressure will lead to increasedglomerular filtration rate and cause 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 lead to a decrease in aldosterone levels (a very helpful clinical tool in diagnosis of primary hyperaldosteronism).

Aside from high blood pressure manifestations of muscle cramps (due to hyperexcitability of neurons secondary to hypocalcemia), muscle weakness (due to hypoexcitability of skeletal muscles secondary to hypokalemia), and headaches (due to hypokalemia or high blood pressure) may be seen.

Secondary hyperaldosteronism is often related to decreased cardiac output which is associated with elevated renin levels.

Measuring aldosterone alone is not considered adequate to diagnose primary hyperaldosteronism. Rather, both renin and aldosterone are measured, and a resultant aldosterone-to-renin ratio is used for diagnosis. A high aldosterone-to-renin ratio indicates presence of primary hyperaldosteronism.

If plasma levels of renin and aldosterone suggest hyperaldosteronism, CT scanning can confirm the presence of an adrenal adenoma. If the clinical presentation primarily involves hypertension and elevated levels of catecholamines, CT or MRI scanning can confirm a tumor on the adrenal medulla, typically an aldosteronoma.

The treatment for hyperaldosteronism depends on the underlying cause. In patients with a single benign tumor (adenoma), surgical removal (adrenalectomy) is curative. This is usually performed laparoscopically, through several very small incisions. For patients with hyperplasia of both glands, successful treatment is often achieved with spironolactone or eplerenone, drugs that block the effect of aldosterone. With its antiandrogen effect, spironolactone drug therapy may have a range of effects in males, including sometimes gynecomastia. These symptoms usually do not occur with eplerenone drug therapy.

Pheochromocytoma.

The signs and symptoms of a pheochromocytoma are those of sympathetic nervous system hyperactivity, including:

- Skin sensations
- Flank pain
- Elevated heart rate
- Elevated blood pressure, including paroxysmal (sporadic, episodic) high blood pressure, which sometimes can be more difficult to detect; another clue to the presence of pheochromocytoma is orthostatic hypotension (a fall in systolic blood pressure greater than 20 mmHg or a fall in diastolic blood pressure greater than 10 mmHg upon standing)
- Palpitations
- Anxiety often resembling that of a panic attack
- Diaphoresis (excessive sweating)
- Headaches
- Pallor
- Weight loss
- Localized amyloid deposits found microscopically
- Elevated blood glucose level (due primarily to 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 leads to glycogenolysis and gluconeogenesis and thus elevation of blood glucose levels).

A pheochromocytoma can also cause resistant arterial hypertension. A pheochromocytoma can be fatal if it causes malignant hypertension, or severely high blood pressure. This hypertension is not well controlled with standard blood pressure medications.

Not all patients experience all of the signs and symptoms listed. The most common presentation is headache, excessive sweating, and increased heart rate, with the attack subsiding in less than one hour.

Tumors may grow very large, but most are smaller than 10 cm.

The diagnosis can be established by measuring catecholamines and metanephrines in plasma (blood) or through a 24-hour urine collection. Care should be taken to rule out other causes of adrenergic (adrenalin-like) excess like hypoglycemia, stress, exercise, and drugs affecting the catecholamines like stimulants, methyldopa, dopamineagonists, or ganglion blocking antihypertensives. Various foodstuffs (e.g. vanilla ice cream) can also affect the levels of urinary metanephrine and VMA (vanillylmandelic acid). Imaging by computed tomography or a T2weighted MRI of the head, neck, and chest, and abdomen can help localize the tumor. Tumors can also be located using an MIBG scan, which in scintigraphy using iodine-123-marked metaiodobenzylguanidine.

Pheochromocytomas occur most often during young-adult to mid-adult life.

These tumors can form a pattern with other endocrine gland cancers which is labeled multiple endocrine neoplasia (MEN).

Surgical resection of the tumor is the treatment of first choice, either by open laparotomy or else 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 evaluation of hematuria. He had been in exellent health until he awoke 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 reveaeled 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. Anintravenous pyelogram was ordered. The right ureter had a small filling defect which did not totally obstruct the flow of contrast media. Because a questionable left suprarenal mass, 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 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 belly 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 presented within 6 months.

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

Theme 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: "Basics of diagnosis, management, and prophylaxis of main endocrine disorders" in the module 1: "The basis of internal medicine"

Course: 4.
Faculty: medical.
Working place: classroom, hospital wards.
Quantity of study hours: 5.

Quantity of study hours: 5.

1. Professional motivation: Acromegaly/Gigantism is a very rare disease (annual incidence: 3/1.000.000). The syndrome results from a chronic exposure to GH (Growth Hormone) leading to the classic clinical features that the diagnosis seems to be easy.
High exposure to GH produces gigantism in youths prior to epiphyseal fusion and acromegaly in adults. The early diagnosis and intervention may prevent irreversible changes associated with chronic overproduction of GH (as well IGF-1) and may also normalize life expectancy. These patients have an increased mortality rate from systemic sequela of hypersomatotrophism in 2-4 times that of the healthy population. Especially after 45 years of age, an increase of mortality rate from cardiovascular and cerebrovascular atherosclerosis (36-62%), respiratory diseases (0-25%) and malignancies (9-25%) occurs. Death rates tend to be higher when diabetes mellitus or hypertension is associated.
Itsenko-Cushing's disease (from the names of the Ukrainian neuropathologist N. M. Itsenko, 1889–1954, and the American neurosurgeon H. W. Cushing, 1869–1939), a disorder caused by excessive secretion of the pituitary adrenocorticotropic hormone (ACTH) with a consequent increase in adrenal function.
Excessive pituitary function may be caused by a tumor (basophilic adenoma) or by injury to the hypothalamic region of the brain, the site of production of a special substance (corticotropin releasing factor) that intensifies the synthesis and liberation of adrenocorticotropic hormone (ACTH). The symptom complex of Itsenko-Cushing's disease is brought about by the elevated level of secretion of adrenocortical hormones (glucocorticoids, mineralocorticoids, and ketosteroids); manifestations include adiposis (mainly in the region of the pectoral girdle, trunk, abdomen, and face), hypertension, hirsutism (in females), osteoporosis, diabetes mellitus, lowered sexual function, and dryness of the cutaneous integuments.
Diabetes insipidus is a condition characterized by excessive thirst and excretion of large amounts of severely diluted urine, with reduction of fluid intake having no effect on the concentration of the urine. There are several different types of diabetes insipidus, each with a different cause. The most common type in humans is central diabetes insipidus, caused by a deficiency of arginine vasopressin, also known as antidiuretic hormone. The second common type of diabetes insipidus in nephrogenic diabetes insipidus, which is caused by an

insensitivity of the kidneys to antidiuretic hormone. It can also be an iatrogenic artifact of drug use.

Diabetes mellitus and diabetes insipidus are two entirely separate conditions with unrelated mechanisms. Both cause large amounts of urine to be produced (polyuria), and the term diabetes is derived from the Greek name for this symptom. However, diabetes insipidus is either a problem with the production of antidiuretic hormone (cranial diabetes insipidus) or kidney's response to antidiuretic hormone (nephrogenic diabetes insipidus), whereas diabetes mellitus causes polyuria via a process called osmotic diuresis, due to the high blood sugar leaking into the urine and taking excess water along with it.

The incidence of diabetes insipidus in the general population is 3 in 100,000. The name refers to the inability to retain fluid (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. Although the clinical syndrome resulting from hyperprolactinemia has been recognized in women since ancient times, the biochemical condition is a relatively new disorder as human prolactin was only purified and verified to be distinct from human growth hormone in 1971.

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

In women, a high blood level of prolactin often causes hypo-oestrogenism with anovulatory infertility and a decrease in menstruation. In some women, menstruation may disappear altogether (amenorrhoea). In others, menstruation 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, as the hormone promotes tissue changes in the breast. Intercoursemay become painful because of vaginal dryness.

In men, the most common symptoms of hyperprolactinaemia are decreased libido, erectile dysfunction, infertility and gynaecomastia. Because men have no reliable indicator such as menstruation to signal a problem, many men with hyperprolactinaemia being caused by an adenoma may delay going to the doctor until they have headaches or eye problems caused by the enlarged pituitary pressing against nearby optic nerves. They may not recognize a gradual loss of sexual function or libido. Only after treatment do some men realize they had a problem with sexual function. Because of hypoestrogenism and hypogonadism (low testosterone), hyperprolactinaemia can lead to osteoporosis.

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

For instance, hypopituitarism is the decreased secretion of one or more of the eight hormones normally produced by the pituitary gland at the base of the brain. If there is decreased secretion of most pituitary hormones, the term panhypopituitarism is used. The signs and symptoms of hypopituitarism vary, depending on which hormones are undersecreted and on the underlying cause of the abnormality.

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced 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 likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness. Evidence to support the view that some obese people eat little yet gain weight due to a slow metabolism is limited; on average obese people have a greater energy expenditure than their thin counterparts due to the energy required 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 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 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,
- order adequate treatment in the case of acromegaly and gigantism,
- perform differential diagnosis of Itsenko-Cushing 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 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 about obesity.

4. Integration between disciplines (see Table 25).

Table 25

Integration between disciplines

Discipline	To know	How to do
I. Previous		
Normal anatomy and physiology, histology, pathology 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.
II. Future		
Internal medicine Pediatrics Surgery Obstetrics & Gynecology Neurology, Ophthalmology	Main clinical signs of piyuitary 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 diagnosis, to prescribe medication
III. Integration among disciplines	Contemporary methods of diagnosis and treatment	To prescribe adequate observation and treatment.

5. Contents of the lesson.

- Physiology and pathophysiology of the endocrine brain and hypothalamus.
- Adenohypophysis: classification.
- Acromegaly and gigantism: etiology, pathogenesis, clinical picture, laboratory investigations, diagnosis and differential diagnosis, therapy.
- Itsenko-Cushing disease: development, symptoms and signs, laboratory finfings, 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 (underlain pathologies), diagnosis, 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
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. Ovelwhelming secretion of GH in adolescence
B. Ovelwhelming secretion of GH in old age
C. Ovelwhelming secretion of GH in adults
D. Ovelwhelming 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 in frequency of pituitary adenomas, accounting for about 17% of them. It is often caused by a pituitary adenoma GH secreting (99%), but other causes has been described such asa rare form caused by hypersecretion of GHRH from an ectopic source (pancreatic islet or carcinoid tumors) or from within the central nervous system such as ganglyoneuroma (called eutopic). Even more rare form is a nonpituitary GH secreting tumor documented in a few lung tumors and in those called ectopic pituitary tumor. GH secreting pituitary adenomas are often over 1cm in diameter when the diagnosis is established. Arising from the lateral wings of the anterior pituitary. Rarely is due to a microadenoma.
About 15% of GH secreting tumors also hypersecrete prolactin, explaining the clinical manifestation of hyperprolactinemia also seen in these patients.
By microscopy the pituitary adenomas are classified as presented 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 oversecretion of GH in acromegaly has an abnormal dynamic control. Secretion remains episodic, however the duration, amplitude and number of secretory episodes are elevated. The characteristic nocturnal surge is absent and there are abnormal responses to suppression and stimulation. TRH and GnRH may cause GH release whereas these substances do not stimulate normal secretion. (These factors are very helpful to make the diagnosis)
Distinctive features and pathologic findings associated with GH excess usually begin in the third or fourth decade and progress insidiously. The mean age at diagnosis is 42 years and equally in sex incidence. Typically the duration of symptoms is usually 5–10 years before the diagnosis.
Soft tissue proliferation is one of the early manifestations. Leading to the classic features: enlargement of the hands, feet and facial features, the most common complaint of the patients.
In adults, the syndrome is characterized by local overgrowth of bone (skull, mandible). Linear growth does not occur because of prior fusion of the epiphyses of long bones. Many younger may have hypogonadism associated which delays epiphyseal closure. The combination of elevated IGF-1 and hypogonadism leads to a striking acceleration of linear growth.
This bony and soft tissue changes are also associated by other systemic disorders of endocrine, cardiovascular and respiratory systems.

The major problem of the treatment in when the patients come to medical attention. The tumor is typically in a very aggressive phase producing headache, visual field changes and/or hypopituitarism (resulting from the mass effect).
Signs and symptoms of GH excess are listed 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 normal level of serum GH is 3 to 5 ng/ml. More than 10 ng/ml is found in 90% of patients with acromegaly. Although children and younger can have normal levels of GH or even up to 50 ng/ml.
However, a single measurement is not entirely reliable, though GH is secreted by pituitary in spurts and its concentration can vary widely. At a given moment, an acromegalic may has normal GH levels, whereas a GH level in a health person may be 5 times higher specially in conditions as: stress, sleeping time, exercise.

Because of these problems, more accurate diagnosis can be done when GH is measured under conditions in which GH secretion is normally suppressed. So, physicians often use: oral glucose tolerance test (OGTT), IGF-1 measurement, TRH and GnRH tests.
OGTT is the best test to confirm the disease. Since its simplest and most specific dynamic test.
IGF-1 Measurement: (normal ranges vary in different laboratories) is an indirect measurement of GH. Since IGF-1 levels are much more stable over a day, they are often more particle and reliable of the measurements of GH levels. An other advantage of this exam is showing activity of the disease.
*TRH & GnRH Tests: a*fter 500μg I.V. of TRH or 100μg I.V. of GnRH, GH will increase in most patients with acromegaly. TRH can release GH in 70-80% of acromegalic patients. Its major advantage is when the OGTT shows a boderline response. Its response require a TRH receptor presence in the tumor.
After GH or IGF-1 has diagnosed acromegaly, other exams can be done:

1. Tumor Localization

In all patients, MRI (90% have more than 1cm in diameter) can show tumor localization and size. The finding of a normal MRI is very rare. In this case, the next procedure is considering an extrapituitary ectopic source of GHRH or GH. If the scans suggest diffuse pituitary enlargement or hyperplasia, ectopic GRH should be suspect. Typical skull RX (thickening of the calvarium) of an acromegalic patient pituitary macroadenoma (MRI)

2. Heel Pad Measurement

Usually more than 22mm and must be measured with lateral RX
Surgical therapy is the gold standard of GH-secreting tumors because of its aggressive behavior. And must be done as the primary choice in all patients who are otherwise acceptable surgical risks. The surgical modality can be transsphenoidal (the better) or craniotomy (in case of extrasellar enlargement of the adenoma)
The effectiveness of this therapy by using a value of 10 ng/ml or less was 73%. And it is more successful when the tumor is restricted to sella.
Radiation therapy is indicated to patients whom surgery failed to achieve normal GH levels or patients with high risk of surgery.
Medical therapy is sometimes used to shrink large tumors before surgery.

- Dopaminergic Analogues

These medications are derived from ergoline family: bromocriptine, pergolide. In at least 50% of acromegalic, dopamine action is presumably through a dopamine D2 receptor mediated mechanism, thus suppressing GH secretion.
This is the major limitation of this treatment and 15% have the coexistence of prolactin hypersecretion. Since D2 are not so dense as in the prolactinomas. Thus, the goal on reducing the size of the tumor when using these drugs is just 10-15% in contrast to 70-80% of the prolactinomas. Furthermore, this kind of treatment is the 3rd choice.
Bromocriptine is divided in 2-3 doses of about 15-60mg daily and reduces GH secretion from some pituitary tumors. Side effects include GH upset, nausea, vomiting, light headedness when standing and nasal congestion. These effects can be reduced or eliminated if medication is started at a very low dose at bedtime, taken with food, and gradually increased to the full therapeutic dose.

- Somatostatin analogues (Octreotide)

As explained below with the use of dopaminergic analogues, the use of octreotide also depends on the presence of somatostatine receptors in the adenoma. But 10-30% of acromegalic has low density of these receptors. This drug must be injected under the skin every 8 hours about 300 μg/daily for effective treatment. In 50% a reduction of GH levels < 5ng/ml occurs. And those patients who initially had GH < 20ng/ml, the levels of GH and IGF-1 become normalized in 95%.

In many patients, GH levels fall within one hour and headaches improve within minutes after the injection. Several studies have shown that octreotide is effective for long-term treatment. Also has been successfully to treat patients with acromegaly caused by non-pituitary tumors.

Because it inhibits gastrointestinal and pancreatic function, long term use causes digestive problems such as decreased gastrointestinal motility, nausea, gas, abdominal pain, fat malabsortion, acholic stools, colelitiasis in one third of patients. And 25% develop gallstones. May also causes glucose intolerance, although scientists have found that in some acromegalic with diabetes, the drug improves blood sugar control.

The levels of GH and also improved clinical and metabolic parameters.

At the present time the treatment of choice is surgery. Pharmacotherapy is not yet an acceptable alternative to surgery. It's indicated when neither surgery nor radiotherapy was successful and/or there were contra-indications for the patient.

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

Table 28

Features of Itsenko-Cushing syndrome

Etiologies	**Symptoms**
Iatrogenic	Mood changes (depression and euphoria)
Steroid therapy (most common cause)	Easy bruising
Central Cause	Weakness
Pituitary adenoma	Weight gain
Adrenal Cause	Amenorrhea
Adrenal Adenoma	Back pain
Adrenal Hyperplasia	
Adrenal Malignancy (15%)	
Ectopic Source	
Malignancy (Small Cell Carcinoma of the lung: 15%)	
Signs	**Labs**
Truncal Obesity (90%)	Screening Test
Hypertension (85%)	24-hour Urinary free cortisol level (preferred)
Glucose Intolerance (80%)	Urine 17-Ketosteroid excretion
Hirsutism (70%)	Urine 17-Hydroxysteroid excretion
Wide, purple abdominal and thigh striae (65%)	Serum Cortisol
Osteoporosis (55%)	Low dose Dexamethasone Suppression Test
Moon facies	Dexamethasone 1 mg at 11pm
Buffalo hump (Thoracic kyphosis)	Plasma Cortisol in following 8 AM
Myopathy	Night-time Salivary cortisol testing
Plethoric face	Distinguish between pituitary, adrenal or ectopic cause
Supraclavicular fat pad development	
Hypertrichosis	Plasma ACTH
Peripheral Edema	High dose Dexamethasone Suppression Test (8 mg)
Hypertension	

Radiology	Management
CT or MRI Cone down Sella Turcica Pituitary adenoma CT abdomen Adrenal tumor	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 in the presence of hypercortisolism is strong evidence for an adrenal tumor.

A high or high normal baseline plasma ACTH level in the presence of hypercortisolism is strong evidence for either pituitary or ectopic production of excessive ACTH. As a group, patients with Cushing's disease have significantly lower ACTH levels than do patients with ectopic ACTH production. However, so much overlap exists that the ACTH level cannot reliably distinguish 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 main value of this test is to confirm the diagnosis of autonomous adrenal neoplasia once hypercortisolism with a low or low-normal plasma ACTH has been confirmed. Lack of suppression confirms the diagnosis.

Overnight 8-mg test. The most convenient way to do the high-dose dexamethasone suppression test is to obtain a baseline 8 a.m. plasma cortisol determination. Administer 8 mg of dexamethasone at 11 p.m. and obtain a 6-8 a.m. plasma cortisol the next morning. A reduction of plasma cortisol to less than 50% of the baseline value is considered significant suppression.

Two-day test. The alternative test is the 2-day high-dose dexamethasone suppression test. It is less convenient than the overnight test and no more accurate; its use can be confined to difficult diagnostic cases when more data may be helpful. A baseline 24-hour urine is collected for 17-OHCS, free cortisol, and creatinine. Then dexamethasone is administered, 2 mg orally every 6 hours for 2 days (20 μg/kg every 6 hours for children). On the second day a repeat 24-hour urine collection is obtained; 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 cannot reliably 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, significant cortisol suppression with high-dose dexamethasone favors pituitary Cushing's disease but cannot clinch the diagnosis without further testing.

2. Distinguishing adrenal adenomas from hyperplasia.

Plasma 18-hydroxycorticosterone (18-OHB). Patients with low plasma potassium and renin and a high 24-hour urinary aldosterone excretion need further evaluation to distinguish whether they have an adrenal adenoma or hyperplasia. This discrimination is made most accurately by obtaining both plasma 18-OHB and aldosterone levels: a single plasma level of 18-OHB is obtained; levels higher than 85 ng/dl are diagnostic of an adrenal neoplasm. Accurate 18-OHB determinations are now available. A plasma aldosterone level of greater

than 20 ng/dl is additional evidence for an adrenal neoplasm.

Cushing's disease refers to hypercortisolism secondary to excess production of ACTH from a corticotrophic pituitary adenoma. This causes the blood ACTH levels to be elevated along with cortisol from the adrenal gland. The ACTH levels remain high because a tumor causes the pituitary to be unresponsive to negative feedback from high cortisol levels.

Treatment involves X-irradiation of the pituitary region. Symptomatic treatment includes the administration of agents that lower blood pressure, antidiabetic preparations, and substances that inhibit adrenal function (amphenone, metopyrone). Subtotal or total adrenalectomy may be performed and followed by the administration of adrenal hormones.

Diabetes insipidus

- Central diabetes insipidus

The most common form of serious diabetes insipidus, central diabetes insipidus, results from damage to the pituitary gland, which disrupts the normal storage and release of ADH. Damage to the pituitary gland can be caused by different diseases as well as by head injuries, neurosurgery, or genetic disorders. To treat the ADH deficiency that results from any kind of damage to the hypothalamus or pituitary, a synthetic hormone called desmopressin can be taken by an injection, a nasal spray, or a pill. While taking desmopressin, a person should drink fluids only when thirsty and not at other times. The drug prevents water excretion, and water can build up now that the kidneys are making less urine and are less responsive to changes in body fluids.

- Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus results when the kidneys are unable to respond to ADH. The kidneys' ability to respond to ADH can be impaired by drugs-like lithium, for example-and by chronic disorders including polycystic kidney disease, sickle cell disease, kidney failure, partial blockage of the ureters, and inherited genetic disorders. Sometimes the cause of nephrogenic diabetes insipidus is never discovered.

Desmopressin will not work for this form of diabetes insipidus. Instead, a person with nephrogenic diabetes insipidus may be given hydrochlorothiazide (HCTZ) or indomethacin. HCTZ is sometimes combined with another drug called amiloride. The combination of HCTZ and amiloride is sold under the brand name Moduretic. Again, with this combination of drugs, one should drink fluids only when thirsty and not at other times.

- 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 results in an abnormal increase in thirst and fluid intake that suppresses ADH secretion and increases urine output. Desmopressin or other drugs should not be used to treat dipsogenic diabetes insipidus because they may decrease urine output but not thirst and fluid intake. This fluid overload can lead to water intoxication, a condition that lowers the concentration of sodium in the blood and can seriously damage the brain. Scientists have not yet found an effective treatment for dipsogenic diabetes insipidus.

- Gestational diabetes insipidus

Gestational DI occurs only during pregnancy and results when an enzyme made by the placenta destroys ADH in the mother. The placenta is the system of blood vessels and other

tissue that develops with the fetus. The placenta allows exchange of nutrients and waste products between mother and fetus.

Most cases of gestational diabetes insipidus can be treated with desmopressin. In rare cases, however, an abnormality in the thirst mechanism causes gestational diabetes insipidus, and desmopressin should not be used.

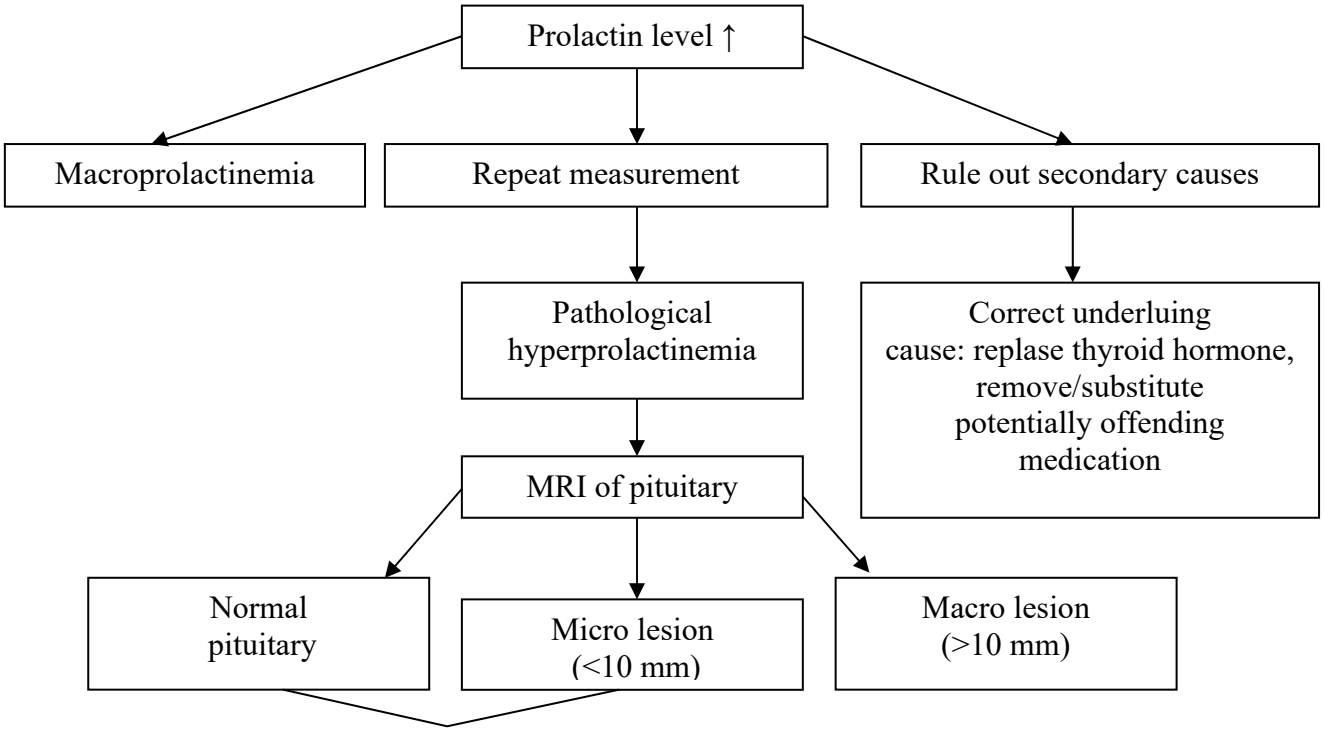
Prolactin and its disorders (see Fig.3)

Prolactin-secreting adenomas are divided into 2 groups: (1) microadenomas (more common in premenopausal women), which are smaller than 10 mm and (2) macroadenomas (more common in men and postmenopausal women), which are 10 mm or larger.

If the prolactin level is greater than 100 ng/mL or less than 250 ng/mL, the evaluating physician must decide whether a radiographic study is indicated. In many cases, with the availability of MRI scanners, imaging is performed earlier and at lower prolactin levels to rule out a non–prolactin-producing tumor.

When the underlying cause (physiologic, medical, pharmacologic) cannot be determined and an MRI does not identify an adenoma, idiopathic hyperprolactinemia is diagnosed.

Another potential cause of hyperprolactinemia is macroprolactinemia. Most prolactin in the bloodstream is monomeric (approximately 85%). However, dimeric and polymeric forms may also coexist. Macroprolactinemia is the apparent increase in serum prolactin without typical symptoms. In this condition, serum prolactin molecules can polymerize and subsequently bind to immunoglobulin G (IgG). This form of prolactin is unable to bind to prolactin receptors and exhibits no systemic response. In the asymptomatic patient with hyperprolactinemia, this condition should be considered. The discovery of macroprolactinemia could save the patient the inconvenience and cost of an in-depth evaluation for a microadenoma. Consult laboratory personnel for any special collecting requirements. Women with macroprolactinemia are able to conceive. This condition generally requires no treatment (Fig. 4).



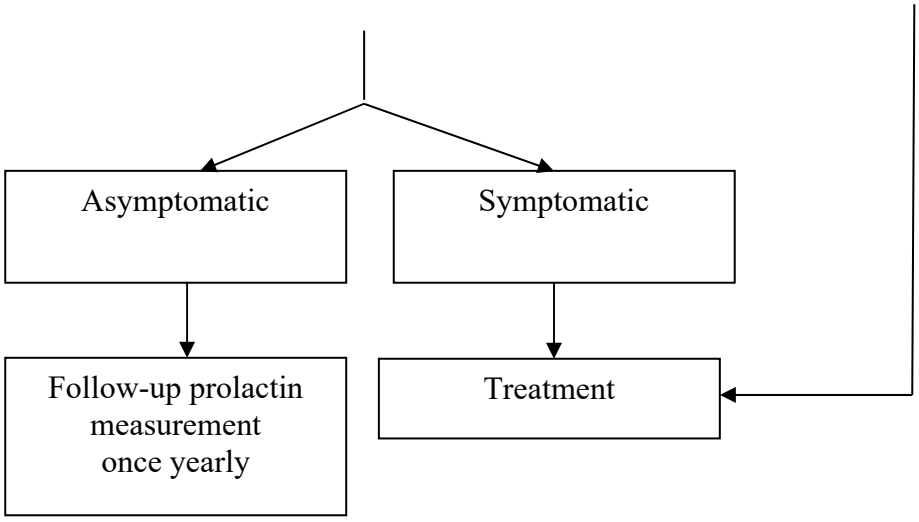
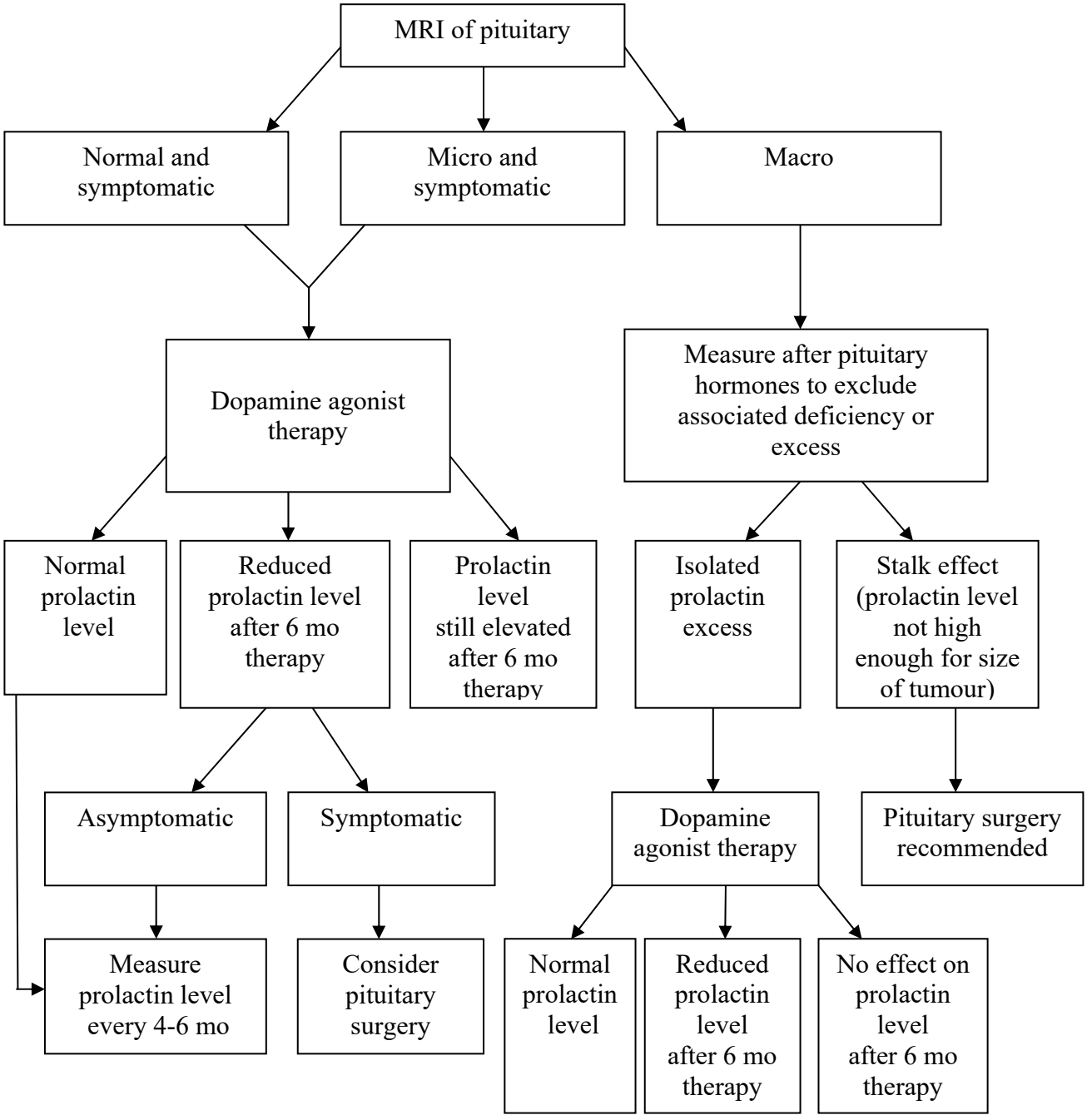


Figure 3. Approach to diagnosos of hyperprolactinemia.



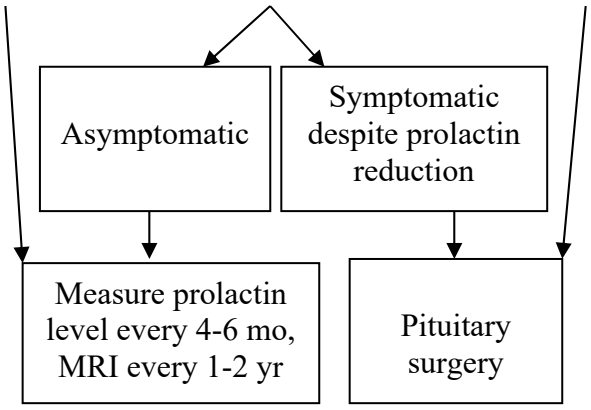


Figure 4. Approach to management of hyperprolactinemia.

Treatment is usually medication with dopamine agonists such as cabergoline, bromocriptine (often preferred when pregnancy is possible), and less frequently lisuride. A new drug in use is norprolac with the active ingredient quinagolide.
Vitex agnus-castus extract can be tried in cases of mild hyperprolactinaemia.
Regarding management of hyperprolactinemia in pregnancy

- There is no evidence of increased teratogenicity associated with bromocriptine or cabergoline use during pregnancy
- Similarly. There is no evidence of increased risk of abortion or multiple pregnancies with dopamine agonist use
- If the tumour size before pregnancy is < 10 mm dopamine agonist therapy is stopped during pregnancy because the risk of tumour expansion is low
- If the tumour size before pregnancy is ≥ 10 mm bromocriptine use is advised during pregnancy to avoid significant tumour expansion
- All patients should be evaluated every 2 months during pregnancy
- Formal visual field testing is indicated in patients with symptoms or a history of macroadenoma
- If visual field defects develop despite dopamine agonist treatment, early delivery or pituitary surgery should be considered

METABOLIC SYNDROME
The term “metabolic syndrome” refers to a clustering of specific cardiovascular disease (CVD) risk factors whose underlying pathophysiology is thought 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)
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

Although the WHO and ATP III definitions generally identify the same individuals, important differences have been found. That is why individual may be classified as having the syndrome by one definition but not by the other one.

Taking into account this problem and other discordances ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) recommend the following:

1. Providers should avoid labeling patients with the term “metabolic syndrome,” as this might create the impression that the metabolic syndrome denotes a greater risk than its components, or that it is more serious than other cardio-vascular disease risk factors, or that the underlying pathophysiology is clear.
2. All cardio-vascular disease risk factors should be individually and aggressively treated.
3. Until randomized controlled trials have been completed, there is no appropriate pharmacological treatment for the metabolic syndrome, nor should it be assumed that pharmacological therapy to reduce insulin resistance will be beneficial to patients with the metabolic syndrome.

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, being 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 subject suffered 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, eye 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 eye 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?

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