Danylo Halytsky Lviv National Medical University

Methodological guidance for practical classes on Internal medicine, including endocrinology, medical genetics. The Individualized Major: Endocrine emergencies. Managing patients with endocrine diseases.

For sixth-year students

Internal medicine

Training specialists of the second (master's) level of higher education

Subject area 22 - Healthcare

Major 222 - Medicine

Lviv 2021

Methodological guidance compiled following educational and qualification characteristics and professional specialist training programs, the experimental curriculum developed based on Credit Transfer System (CTS), discussed and approved at the Methodical Meeting of Endocrinology Department (Protocol No 10 dated February 04, 2021) and approved by the Subject-oriented Methodological Commission for Therapeutic Disciplines of Danylo Halytsky Lviv National Medical University (Protocol No. 5 dated 25.03.2021).

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Theme 1. Managing a patient with chronic complications of diabetes mellitus. Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with diabetes mellitus. Management of a patient with hypoglycemic coma.

1. Topicality

1. Vascular events are one of the common syndromes in the manifestation of diabetes mellitus. In most cases, their intensity specifies the working capacity of patients, prognosis of the disease and the length of life. In this regard, the timely and accurate diagnosis, treatment of diabetic angiopathies acquires important significance in diabetology. The problem of angiopathy is rather interdisciplinary than merely diabetic. It involves ophthalmology, surgery and nephrology. The knowledge of clinical features and treatment policy with different degrees of manifestation of angiopathy in different areas allow preserving the working capacity of patients for a longer period.

   The knowledge of the peculiarities of the course and treatment of emergencies with diabetes mellitus is mandatory for all physicians. The basis for the occurrence and development of acute complications of diabetes mellitus form acute disorders of the vital function of the body: respiratory and blood flow homeostasis etc. These disorders directly threaten life and require immediate assistance. Thus, studying comatose states in the event of diabetes mellitus is extremely important for the training of a future physician. Diabetes mellitus treated with insulin and oral sugar-lowering drugs is often accompanied by the occurrence of hypoglycemic states. Physicians must be aware of the signs of hypoglycemia and immediately provide assistance in the occurrence of hypoglycemic states independent of the origin. The problem of timely diagnosis and delivery of emergency assistance in the occurrence of hypoglycemic states is topical as long as in the absence of treatment they may result in high morbidity rates, the occurrence of posthypoglycemic encephalopathy and disability.

2. Learning goal.

To become acquainted with epidemiological surveys of diabetes mellitus in Ukraine and the world (α=1)

The student must know (α=2):

- Classification of diabetic angiopathies and neuropathies;
- Diabetic retinopathy: process stages, diagnosis, prevention and treatment;

- Diabetic nephropathy (diabetic chronic kidney disease (DCKD)): development stages, diagnosis, treatment and prevention
- Diabetic neuropathy, classification, diagnosis and treatment

- Diabetic foot: classification, diagnosis, treatment;
- Classification of emergencies
- Reasons and pathogenesis of hypoglycemic state and coma
- Clinical manifestations of hypoglycemia and hypoglycemic coma
- Hypoglycemia and hypoglycemic coma treatment strategy and methods in patients with diabetes mellitus

The student should be able to (α=3):

- order the necessary medical examinations to detect diabetic angiopathy (nephropathy, retinopathy, angiopathy of lower extremities), autonomic and peripheral neuropathy;

- justify and formulate a diagnosis of diabetes mellitus and its complications based on analysis of laboratory findings and instrumental methods of examination
- perform differential diagnosis of chronic complications of diabetes mellitus;
- order adequate treatment of chronic complications of diabetes mellitus.
- manage a patient with chronic complications of diabetes mellitus: existing algorithms, standards for the diagnosis and treatment;
- know the peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with diabetes mellitus;
- know the methods of establishing the diagnosis and data analysis, received in the course of the interview and direct examination of patients with hypoglycemic states
- refer for the necessary examination to detect hypoglycemic states and hypoglycemic coma;
- perform the diagnosis and differential diagnosis of hypoglycemic states and hypoglycemic coma;
- apply the hypoglycemic coma modern diagnostic and treatment standards
- define the hypoglycemia and hypoglycemic coma treatment and prevention strategy.

3. Educational goal.

Attract attention to and form the sense of responsibility in students, who will become different types of doctors for the timely detecting and the proper treatment of disease to achieve carbohydrate metabolic compensation as a principal factor preventing complications of chronic diseases, as well as hypoglycemic coma timely diagnosis, differential diagnosis and treatment.

4. Interdisciplinary integration:

Subjects	*To know*	*To be able to*
Previously studied subjects Systemic Anatomy Hominal Physiology Histology Biochemistry Pathoanatomy Pathophysiology	 the topography, the vascularization of the pancreas, the internal secretion of the pancreas, the histologic structure of the island of Langerhans, the carbohydrate metabolism, morphological changes in organs and tissues in patients with diabetes mellitus, pathogenesis of vascular events and comas in patients with diabetes mellitus	
Subjects that will be studied later		Perform a clinical review, order the corresponding diagnostic testing, consultations by allied health professions to verify the diagnosis
Therapy	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diabetes mellitus, hypoglycemic coma	
Pediatrics	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diabetes mellitus and glycemia in children	

Surgery	Peculiarities of the course of diabetes mellitus, hypoglycemia in the event of surgical pathology, timely diagnosis and surveillance of such patients	
Obstetrics & Gynaecology	Peculiarities of the course of diabetes mellitus, the hypoglycemic state during pregnancy, timely diagnosis and surveillance of such patients	
Neurology	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of neurological complication of diabetes mellitus	
Ophthalmology	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diabetic retinopathy	
Intersubject integration	Modern methods of patients' examination, in particular, laboratory, instrumental, adequate treatment strategy	Order the adequate treatment

5. Training subjects:

- Etiology, the pathogenesis of diabetic macro- and microangiopathy, neuropathy, the biochemical effect of hyperglycemia
- Classification of diabetic angiopathies
- Classification of diabetic neuropathies
- The concept of diabetic foot syndrome (classification, diagnostic and treatment approaches).

- Clinical manifestations of vascular events of diabetes mellitus
- Laboratory and instrumental diagnosis of diabetic angio- and neuropathies
- Diabetic angio- and neuropathies treatment methods
- Techniques preventing the development of chronic complications of diabetes mellitus
- Etiology, the pathogenesis, clinical picture of hypoglycemia and hypoglycemic coma
- Diagnosis and differential diagnosis of hypoglycemic coma.
- Management and treatment of hypoglycemic states and hypoglycemic coma.

6. Plan and organizational structure of the class

(see «Introduction»)

7. Materials and methodological support of the class

7.1 Materials of the preparatory stage of the class

Tests (α=2)

1. A teenage girl aged 18 is complaining about thirst, dry mouth, frequent urination. Fasting blood glucose level is 7,8 mmol/L, HbA1c – 9,8 %.
In the course of examination, there was detected acetone breath, dry skin. What diagnosis should be suspected?

A. Type 1 Diabetes Mellitus
B. Type 2 Diabetes Mellitus
C. Diabetes insipidus
D. Impaired fasting glycaemia
E. Gestational diabetes

2. A woman aged 50 visited a family physician. She was complaining about skin and genital itching, some thirst, dry mouth, nighttime urination. Her mother was suffering from type 2 diabetes mellitus. Height 165 cm, weight 90 kg. Daytime Glycemia: 8,4-10,3-12,6-6,9 mmol/L. What provisional diagnosis should be established?

A. Type 1 diabetes mellitus
B. Type 2 diabetes mellitus
C. Impaired glucose tolerance
D Candidiasis
E Dermatitis

3. Macroangiopathy, as the complication of diabetes mellitus, most often affects the vessels of:

A. Brain
B. Lungs
C. Retina
D. Kidneys
E. Liver

4. Which of the following assertions is not true as regards angiopathy of lower extremities?

A. Occurrence of paresthesia
B. Gradual trophic disorder beginning with fingers
C. Leg Pain When Walking
D. Foot temperature decrease
E. Development of gangrene in the foot

5. Which of the following assertions is true as regards bone affection in patients with diabetes mellitus?

A. Dupuytren's contracture
B. Aseptic bone necrosis
C. Hyperostosis
D. Calcification of arthrodial cartilages
E. Seronegative polyarthritis

6. Define anti-hypertensive agents which are the most reasonable for the treatment of early nephropathy in teenagers:

A. ACE inhibitors
B. Loop diuretics.
C. Calcium antagonists
D. B-blockers
E. Statins

7.2. Methodological materials for the principal stage of the class:

Examination protocol, establishing a diagnosis, treatment and prevention

ACTIVITY SECTION	GUIDELINES FOR ACTION
Greeting	Greet and introduce yourself to a patient
Acquaintance	Collect personal information about a patient (full name, sex, age, place of residence, place of work and occupation)
Patient's complaints at the time of examination	Visual impairment, face oedema, limb swelling, a rise in arterial pressure, leg pain, foot ulcer formation

Managing patients with diabetic retinopathy

Diabetic retinopathy (DR) – a microvascular complication of diabetes damaging the back of the eye (retina). At the terminal stage, it can cause blindness.

Stages	***Diagnostic criteria***
I–non-proliferative retinopathy	• No complaints • Normal vision acuity • Retinal microaneurysm, swelling (predominantly in a macular zone), haemorrhage, hard and soft exudative focuses
II – preproliferative retinopathy	• decrease in visual acuity • Alongside with changes, peculiar to I stage, there are vascular malformations (rosary-like, tortuosity, loops, duplications and significant fluctuations of the vessel calibre), a large number of exudates, intraretinal microvascular abnormalities, numerous retinal haemorrhages, scotomas with varying intensity
III–proliferative retinopathy	• a sudden decrease in visual acuity to complete blindness • neovascularisation of the optic disc and other areas of the retina • Vitreous Hemorrhage

	• Fibrous tissue formation in the area of preretinal haemorrhages • Complications of diabetic retinopathy III: • 1. Fractional retinal detachment • 2. Rubeosis iridis • 3. Secondary glaucoma

Diabetic retinopathy study methods:

1. Mandatory:
    - External examination of the eyeball, examination of visual acuity and visual fields once per 6 months
    - Defining the level of ophthalmotonous pressure once a year in patients suffering from diabetes mellitus for 10 or more years
    - biomicroscopy of the eye lens and vitreous body using a corneal microscope
    - direct or indirect ophthalmoscopy with dilated pupil once a year, in the event of discovered complications – every 3-6 months
2. Additional:
    - Photographing the vessels in the eye fundus using a fundus-camera
    - Fluorescein angiography
    - electrophysiological study methods to define the functional status of healthy ophthalmic nerve and retina
    - ultrasound investigation in the event of significant opacities in the vitreous body and eye lens.

In the event of a sudden decrease in visual acuity or the occurrence of any other complaints about the sense of sight, you should be immediately examined by an ophthalmologist.

Diabetic retinopathy treatment:

Must be carried out jointly by endocrinologist and ophthalmologist.

1. Perfect/optimal glycemic control (HbA1c <7,0-7,5%). There is clear dependence between glycemic control and the development of diabetic retinopathy.

2. The use of vasoprotective drugs for treatment and prophylactic purposes has been recognized as poorly effective, especially against the background of inadequate glycemic control.
3. Laser photocoagulation nowadays has become the most effective type of diabetic retinopathy treatment and prevention of blindness. There are used three basic methods of laser photocoagulation: focal laser photocoagulation, barrier laser photocoagulation, panretinal laser photocoagulation.

Algorithm of remedial measures in the event of diabetic retinopathy:

Sight-threatening complications	***Remedial measures***
Non-proliferative diabetic retinopathy	Careful glycemic control
Retinal microbleeds	Laser photocoagulation of lesions
Significant macular oedema	Focal laser photocoagulation
Risk of proliferative diabetic retinopathy	Panretinal laser photocoagulation
Vitreous hemorrhage	Observation versus vitrectomy
Tractional retinal detachment	Vitrectomy
Neovascular glaucoma	Panretinal laser photocoagulation,

The urgency of laser photocoagulation depends on the type and stage of illness (is defined by an ophthalmologist):
Macular oedema or macular retinopathy:

- In the event of acute type – urgently
- In the event of chronic type – within several days

Proliferative diabetic retinopathy:

- In the event of the central type (newly formed vessels on optic disc) – urgently
- In the event of peripheral type (newly formed vessels in other areas of the

retina) – without delay within 1-2 weeks

Preproliferative diabetic retinopathy:

- In the presence of additional risk factors – without delay within several weeks
- In the absence of risk factors – within 2-3 months

Criteria for treatment efficacy: Stabilisation of retinopathy progression

Regular medical check-up –lifetime:

Examination	Frequency	Remedial measures	Preventive measures
Non-proliferative diabetic retinopathy			
Examination by ophthalmologist: without macular retinopathy	Twice a year	Laser photocoagulation	Attaining of perfect /optimal glycemic control of diabetes mellitus. Arterial blood pressure control and correction
with macular retinopathy	Three times a year		
Measuring visual acuity. Measuring ophthalmotonous pressure. Direct ophthalmoscopy Biomicroscopy of the eye lens and vitreous body Fluorescein angiography of the retina Photographing the vessels in the eye fundus	If necessary - more frequent		
Diabetic preproliferative retinopathy			
Examination by ophthalmologist Measuring visual acuity. Measuring ophthalmotonous pressure.	3-4 times a year and if necessary	Laser photocoagulation	Maintenance of perfect /optimal glycemic control of diabetes mellitus.

Direct ophthalmoscopy Biomicroscopy of the eye lens and vitreous body Fluorescein angiography of the retina Photographing the vessels in the eye fundus			Arterial blood pressure control and correction
Diabetic proliferative retinopathy			
Examination by ophthalmologist Measuring visual acuity. Measuring ophthalmotonous pressure. Direct ophthalmoscopy Biomicroscopy of the eye lens and vitreous body Fluorescein angiography of the retina Photographing the vessels in the eye fundus	Urgently, then 3-4 times a year and if necessary	Laser photocoagulation Cryocoagulation Vitrectomy	Maintenance of perfect /optimal glycemic control of diabetes mellitus. Arterial blood pressure control and correction

Managing patients with diabetic nephropathy

Diabetic nephropathy (diabetic chronic kidney disease) - specific renal vessels damage in patients with diabetes mellitus that is accompanied by the formation of nodular or diffuse glomerulosclerosis, the terminal stage of which is characterized by the development of CKD**.**

Classification of diabetic nephropathy (according to Mogensen) and its course

Duration of diabetes mellitus	**Stage**	**Clinical picture**	**Prognosis**
From the onset of disease	I – hyperfiltration, kidney hypertrophy	Increased glomerular filtrate rate up to 160	Possible full regression of changes

		ml/min, enlarged kidneys	
2–5 years	II – beginning of histological changes, change of the structure and functions of the basement membrane	Thickening of the basement membrane, mesangial expansion, absence of albuminuria	Possible partial regression of changes
5–10 (15) years	III – early clinical nephropathy	albuminuria, decrease of glomerular filtrate rate from 160 to 130 ml/min, arterial hypertension	Possible slowdown of changes progression, sometimes regression
10 (15)–25 years	IV – obvious nephropathy	constant proteinuria, decrease of glomerular filtrate rate up to 70 ml/min, then up to 10 ml/min, constant increase in arterial pressure, swelling, lipid storage disease	Possible slowdown of the course of changes progression, sometimes their delay
>15 years	V – kidney failure	increases in creatinine, arterial hypertension	Irreversible progression of changes to the terminal renal insufficiency
GFR - glomerular filtrate rate			

Diagnosis

Chronic kidney disease (CKD) must be actively detected during the screening study because for many years the disease may develop without any objective or subjective symptoms. It is necessary to carry out the clinical urine analysis, determine the

creatinine concentration in serum and microalbuminuria in the urine from time to time in patients with an increased risk of chronic kidney disease, especially in patients with diabetes mellitus or arterial hypertension. In practice, the calculation of GFR but not the determination of creatinine concentration in blood serum, which depends on age and muscle mass, is the best indicator of kidney function.

Supplementary examinations:

1. **Clinical urine analysis**: albuminuria, proteinuria, micro- macrohematuria, casts, leukocyturia, low urine specific gravity.

2. **Blood examination**: anaemia (usually, normocytic and normochromic), an increase of creatinine, urea, uric acid, potassium, phosphates and parathormone, triglycerides, cholesterol concentration, hypocalcemia; metabolic acidosis.

3**. Imaging**: **ultrasound investigation —** kidneys, usually decreased in size (often <10 cm in long axis); exclusion (large kidneys, despite chronic kidney disease) in the event of amyloidosis - nephropathy, diabetic nephropathy, multicystic kidney and nephropathy with HIV infection. Imaging using contrast (for example, CT) is carried out only in the case of an emergency, considering the high risk of contrast-induced nephropathy.

Diagnostic criteria:

The diagnosis of chronic kidney disease is established when during > 3 months, there are preserved morphological or functional kidney diseases (→Definition), or GFR <60 ml/min/1,73 sq.m. The diagnosis of CKD is established in patients with chronic renal disease and GFR <60 ml/min/1,73 sq.m.

Treatment.

Microalbuminuria stage:

carbohydrate metabolism compensation (HbA1c < 7%);
use of angiotensin-converting-enzyme inhibitors (ACE inhibitors) or ARA inhibitors in subpressor doses at normal arterial pressure and in median curative doses – at increased arterial pressure over 130/80 mm Hg - constantly;
correction of dyslipidemia (if any);

a diet with mild restriction of animal protein (no more than 1 gr of protein per 1 kg of body weight);

Proteinuria stage:

Optimal carbohydrate metabolism compensation (HbA1c < 7%);

Maintenance of arterial pressure at a level of 130/80 mm Hg;

first choice drugs

- ACE or ARA inhibitors – constantly

correction of dyslipidemia (if any) – constantly;

restriction of animal protein up to 0,8 gr of protein per 1 kg of body weight – constantly;

prevent from using Nephrotoxic medications (contrasts, antibiotics, non-steroidal anti-inflammatory drugs);

erythropoietin if confirmed;

Chronic kidney disease stage:

carbohydrate metabolism compensation (HbA1c < 7%);

maintenance of arterial pressure at a level of 130/80 mm Hg; first choice drugs - ACE or ARA inhibitors (carefully – if the level of creatinine in blood is more than 330 mcmole/l). The combined antihypertensive therapy is recommended;

Restriction of animal protein up to 0,8 gr of protein per 1 kg of body weight – constantly;

correction of dyslipidemia (if any) – constantly;

treatment of renal anaemia (erythropoietin) – at the level of Hb< 110 gr/l (guided arterial pressure, Hb, Ht, platelets, iron and serum ferritin)

correction of hyperkalemia;

correction of calcium and phosphate metabolism;

hemodialysis;

peritoneal dialysis;

kidney transplantation (within the conditions of specialized centers);

Management of patients with diabetic neuropathy

Diabetic neuropathy (DN)– a complex of clinical and subclinical syndromes, characterized by diffuse or local lesion of peripheral and/or autonomic nerve fibres caused by diabetes mellitus.

Classification of diabetic neuropathy:

1. Peripheral:

1.1. Somatic
- diffusive symmetric distal sensory-motor neuropathy (called polyneuropathy)
- diabetic amyotrophy (proximal neuropathy causing significant acute disability)
- diffuse motor neuropathy (severe diabetic amyotrophy)
- acute painful neuropathy
- insulin neuritis
- mononeuropathy (damaging peripheral and cranial nerves)

1.2. Vegetative (autonomic) diabetic neuropathy
- cardiopathy
- neuropathy affecting the urinary bladder
- loop of thermal control
- stomach neuropathy
- colonic, enteric, pudendal neuropathy
- cutaneous neuropathy
- asymptomatic hypoglycemia (Hypoglycemia unawareness)
- vasomotor disorders (Charcot joint, neuropathic edema)
- bronchial dystonia
- venous distensibility in the feet
- pupillary reflex disorders
- sexual debility, retrograde ejaculation

2. Central (changes of the brain and spinal cord functions)

- cerebrasthenic syndrome
- encephalopathy
- dyscirculatory disorders of vascular genesis
- myelopathy

Diagnosis:

The examinations aimed at diagnosing diabetic neuropathy in patients with type 1 diabetes mellitus are carried out a year after the occurrence of diabetes mellitus, and in patients with type 2 diabetes mellitus – from the moment the diabetes mellitus was diagnosed.

The list of mandatory examinations to diagnose diabetic neuropathy:

1. Lower limb examination to find symptoms of dry skin, hyperkeratosis, calluses, skin infection, abnormal toenail growths.
2. Evaluation of tendon reflexes (patellar and Achilles reflexes).
3. Evaluation of tactile sensitivity (using monofilament).
4. Evaluation of pain sensitivity (using blunt end needle).
5. Evaluation of temperature sense.
6. Evaluation of proprioceptive sensibility (the Romberg test, used to investigate the cause of loss of motor coordination (sensitive ataxia)).
7. Determination of the vibration perception (using graduated tuning fork).
8. Electromyography (EMG) – stimulation of sensor sural nerve (n. suralis dextr.) and motor nerve (n. peroneus dextr.):
    - action potential amplitude
    - M amplitude of nerve conduction velocity
9. Detection of orthostatic hypotension (arterial blood pressure reduction >30 mm Hg in the event of changing the position from supine to standing).
10. The Valsalva maneuver (heart rate accelerates if you bear down, strain).

Classification of diabetic peripheral neuropathy (DPN)according to the stages of severity

(P.Dyck, P.Thomas, 1999)

DPN grading	*Characterization*
Grade 0. (neuropathy is absent)	There are no symptoms and signs of DPN, autonomic tests are negative, in the course of electromyography (EMG) of sensory and motor peripheral nerves (not less than 2 on one side) no pathologies have been detected.
Grade 1. Subclinical	1A. No symptoms and objective neurological signs of DPN. Existence of any 2 changes, detected in the course of electromyography (EMG) of sensory and motor nerves or positive autonomic tests (the Valsalva maneuver, deep breath test).
	1B. Without symptoms. In the course of clinical examination, there are detected 2 or more objective neurological signs of DPN on one side.
Grade 2. Clinical	2A. Complaints that are peculiar to DPN. Sensory Processing Disorders, movement disorders, autonomic disorders, without signs of weakness in the flexor digitorum brevis (a patient can remain standing on heels).
	2B. The same + signs of weakness in the flexor digitorum brevis (a patient cannot remain standing on heels).
Grade 3. Severe	Neuropathy with performance impairment.

Treatment:

1. Perfect/optimal glycaemic control (HbA1C <7,0-7,5%).
2. Pharmacological therapy:

- **α- lipoic (**thioctic) **acid**

hypoglycemic activity (improvement of insulin sensitivity)

hypolipidemic activity

anti-oxidant action, detoxification activity (including as a donator of SH- groups)

neurotropic action – improves nerve impulse conduction (reduces lipid peroxygenation in peripheral nerves, improves endoneurial blood flow)

improves regeneration (encourages the growth of new nerve fibres)

immunotropic effect (increases the content of all T lymphocyte subpopulations)

- **Vitamin B Complex** in age-specific dosage variances during 2-3 months, a special liposoluble vitamin B1 – BENFOTIAMINUM (100mg 1-2 time(s) a day – for 1-3 months, 2 treatment courses a year).
- Reduction of pain and seizures: nonsteroidal anti-inflammatory drugs, (intramuscular administration every day or every other day №5-10)
- vasodilator (pentoxifyllinum, nicotinic acid products etc).
- metabolic therapy (actovegin, solcoseryl, cytochrome C, instenon, γ-linolenic acid, etc).
- in the event of vegetative disorders symptomatic medication is taken. Its effect is directed to compensation for the function that the organ has lost:

3. Physiotherapy:

- diadinamometry
- inductothermy
- magnetotherapy
- laserpuncture
- nicotinic acid, euphylline, novocaine, proserine electrophoresis provided in the legs
- contrast baths for affected limbs
- lower limb massage

- hyperbaric oxygenation

4. therapeutic exercise

Treatment efficiency criteria: absence of neuropathy clinical manifestations

Regular medical check-up:

Testing		***Regular medical check-up***
Examination, specialists	***Frequency***	
A neurologist with detection of all types of sensitivity (tactile, vibration, pain, temperature, proprioceptive), tendon reflexes	2 times a year	life long
Performance of orthostatic test (endocrinologist)	1 time a year	
The Valsalva maneuver (based on ECG)	1 time a year	
Analysis of heart rate variability	1 time a year, if possible	
Electroneuromyography		
Cardiologist, gastroenterologist, urologist	if necessary	

Management of patients with diabetic foot disease

Diabetic foot disease (DFD) brings together pathological changes of the peripheral nervous system, arterial and microvascular bed, osseous-articular apparatus of the foot and directly threatens the development of ulcerous-necrotic processes and gangrene of the foot.

Classification (formulation of diagnosis)

- Neuropathic form:
  - preulcerative changes and foot ulcer
  - diabetic osteoarthropathy (Charcot's joint)

- neuro-ischaemic form
- ischaemic form

Diagnosis

Mandatory study methods

- past medical history
- lower limb examination
- neurologic examination
- arterial bleeding assessment
- foot and ankle joints X-ray two projection imaging
- microbiological analysis of wound exudate

past medical history

NEUROPATHIC FORM	ISCHAEMIC FORM
long-term course of diabetes mellitus and/or occurrence of ischaemic foot ulcer, amputations in past medical history	long-term course of diabetes mellitus and/or occurrence of ischaemic foot ulcer, amputations in past medical history
alcohol abuse	tobacco abuse

Lower limb examination

NEUROPATHIC FORM	ISCHAEMIC FORM
Dry skin, areas affected by hyperkeratosis in foot overload zones	Pale or cyanotic skin, skin atrophy, often – skin cracking
Specific deformity of foot, toes, ankle joint	Nonspecific toe, foot deformities
Pulse on the pedal arteries has been preserved on both sides	Pulse on the pedal arteries has been reduced or is absent
Painless ulcerous defects in overloaded areas	Acral necrosis, severely painful
Absence of subjective symptoms	Intermittent claudication

Group risks of the diabetic foot disease development

- Patients with distal polyneuropathy at the stage of clinical manifestation of depression of the peripheral nervous system function
- Patients with peripheral vascular diseases of any genesis
- Patients with foot deformity of any genesis
- Patients with diabetic retinopathy and nephropathy

	○ Single patients, aged patients ○ People addicted to the alcohol ○ Smokers
Treatment	**Treatment of neuropathic form with preulcerative changes and foot ulcer** ○ carbohydrate metabolism compensation (HbA 1C < 7%) ○ affected limb unloading (therapeutic and unloading footwear, individual unloading bandage, rocking chair) ○ removal of hyperkeratosis areas and/or initial debridement of ulcerous defect ○ antibiotic therapy provided there are signs of infection and ulcerous defects at stage 2 and deeper ○ the use of modern atraumatic instruments **Treatment of neuropathic form of diabetic foot disease with osteoarthropathy** ○ carbohydrate metabolism compensation (HbA 1C < 7%) ○ affected limb unloading (individual unloading bandage at the acute and subacute stages) ○ antibiotic therapy in the event of ulcerous defects with the signs of infection and wounds at stage 2 and deeper. ○ in the event of ulcerous defects – the use of modern atraumatic instruments for bandaging, which corresponds to the stage of the ulcerative process **Treatment of the ischemic form of diabetic foot disease** 1. Conservative treatment: ○ carbohydrate metabolism compensation (HbA 1C < 7%) ○ smoking cessation ○ the correction of arterial hypertension ○ treatment of dyslipidemia ○ elimination of limb ischemia phenomena: • disaggregant (coagulogram- guided and control of the state of the fundus of the eye), • vasodilators • anticoagulant (coagulogram-guided and control of the state of the fundus of the eye)

	2. Reparative surgery on the arteries under the condition of separation of vascular surgery and/or percutaneous transluminal angioplasty (balloon angioplasty) 3. In the event of ulcerous defects – antimicrobial therapy **Prevention of diabetic foot disease** o Maintenance of the long-term steady-going carbohydrate metabolic compensation (HbA 1C < 7%) o Teaching patients to take care of feet/legs o the early detection of patients that are among the risk group for diabetic foot disease o Wearing orthopedic footwear.

Examination protocol, establishing a diagnosis, hypoglycemia and hypoglycemic coma prevention and treatment

ACTIVITY SECTION	GUIDELINES FOR ACTION
Greeting	Greet and introduce yourself to a patient (if a patient is conscious)
Acquaintance	Collect personal information about a patient (full name, sex, age, place of residence, place of work and occupation)
Patient's complaints at the time of examination and development of hypoglycemia	Identify and present details of patient's complaints. While identifying patient's complaints, pay attention to the availability of: - hunger - general weakness - sweatiness -limb tremor - heartbeats -diplopia - oscitation - numb lips, tongue - motor and psychic agitation -drunk behaviour -unmotivated violent behaviour -loss of consciousness
1. Examination of organs and systems. **2. Patient history.** **3. Life history.**	Evaluate the course of the disease and examine organs and systems. Availability of risk factors and diseases that may cause hypoglycemia: 1. Diabetes mellitus in the past medical history.

	2. Treatment with insulin and sugar-lowering drugs. 3. Pancreatic islet cell tumors can be either noncancerous (benign) or cancerous (malignant). 4. Extrapancreatic tumors. 5. Hepatic disorders and gastrointestinal disease. 6. Autonomic nervous system disorders and central nervous system problems. 7. Other endocrine disorders . 8. Metabolic disease 9. Malnutrition . 10. Heavy physical exertion 11. Reactive hyperinsulinism. 12. Pregnancy and lactation.
Physical examination	When examining a patient, evaluate: 1. general state of the patient: - unconsciousness - retardation - obnubilation - motor and psychic agitation - watery skin, diffuse sweating. 2.Respiration: -normal - accelerated - oscitation 3.Face: -wandering gaze 4.Pupils: -dilated 5. eyebulb tonus: -normal 6.Tongue: -clean - moist 7. Muscle tonus: - limb rigidity - tonic and clonic seizures 8. Pathological reflexes: - bilateral Babinski sign 9.Pulse: -fast -tachycardia

	10. Arterial blood pressure: -normal or elevated 11.Response to glucose intravenous infusion .
Examination plan	Glycemic index glucosuria ketonuria HbA1c C-peptide
Laboratory and instrumental investigations	1 Complete blood count -usually without pathological findings -sometimes leukopenia. 2. Clinical urine analysis: - aglycosuria -absence of acetone - low specific gravity. 3. Biochemical analysis result: - hypoglycemia <2,7 mmol/L (in a patient with poorly controlled diabetes hypoglycemia may develop at higher glycemic indices) -an elevated level of immunoreactive insulin (IRI) (or C-peptide) in the event of insulinoma -positive test with starvation (sample with suppression of insulin secretion).
Treatment	
I. During the prehospital phase or at the admission department	
	1. Bolus dosing of glucose solution 40% (40-60 ml), upon reaching the effect, however, in the event of insufficiency- the dose increases. 2. Prevention of potentially fatal complication-acute Wernicke encephalopathy-pre-administration of Vitamin B1 (100 ml) -2,0 Thiamine bromide solution 5%.
The most common mistakes that are made when providing emergency assistance to patients with hypoglycemia during the prehospital phase or at the admission department.	
	1. Very seldom there is carried out a diagnostic administration of glucose solution 40%, which is mandatory when delivering assistance to comatose patients. 2. Thiamine 100 mg is not pre-administered.

	3. Because of the absence of the possibility during the prehospital phase, there isn't defined the level of glycemia and ketonuria. 4. Give by an intravenous injection (infusion) a high dose of insulin without reasonable grounds!!!	
II. Algorithm of providing assistance to patients with hypoglycemia and hypoglycemic coma in a hospital setting.		
<u>Mild hypoglycemia</u> (without loss of consciousness, which does not require any outside help).	**0-3 min**	Take simple carbohydrates in the amount of 1-2 carbohydrate units: 4-5 lumps of sugar dissolved in water or honey, jam (1-2 tablespoons) or 200ml of sweet fruit juice. If hypoglycemia was caused by administration of prolong insulin, then you should additionally eat 1-2 carbohydrate units of hydrocarbon compounds (a slice of bread, 2-3 spoons of porridge or mashed potatoes).
<u>Severe</u> <u>hypoglycemia</u> (with or without loss of consciousness, however, which requires outside help)	**0-3 min**	1. Intravenous bolus injection 40-80 ml of glucose solution 40%. 2. Intramuscularly or subcutaneously 1 mg of glucagon (HypoKit, GlucaGen),or 0,5ml -epinephrine solution 1%.
	5-15 min	1.If the patient did not regain consciousness, repeatedly administer 60 ml of glucose solution 40%. 2. Intravenous drip infusion glucose solution 5-10%.
	15-30 min	1If the content of glucose exceeds 3 mmol/L and in the event of unconsciousness: a) intravenous drip-feed 100-120 g of Mannitol. b) intravenous bolus injection 2 mg of dexamethasone every 6 hours (to prevent cerebral edema).

Hypoglycemia in babies
clinical signs and treatment

Hypoglycemia in children is characterized by age-related peculiar course. The

following gives evidence of hypoglycemia in newborn babies:

-decrease in glucose level <2,2 mmol/L during the first day

- decrease in glucose level <2,5 mmol/L from the second day.

Under normal conditions, the newborn babies at birth have a considerable amount of glycogen in the liver and muscles and the glucose production rate is 2-3 times more (with a view to body surface area), therefore for the occurrence of hypoglycemia solid reasons are required.

Clinical symptoms of hypoglycemia in newborn babies:

- Adynamia
- Food refusal
- Hypothermia
- Myotonia(a disorder that affects muscles)
- Tremor
- Abnormal cry
- Convulsions
- Comatose state

Hypoglycemia treatment in newborn babies

1. Bolus administration of glucose solution 20% calculated 2-4 ml/kg at the rate of 1ml/min should be used in the event of severe hypoglycemia with the convulsive disorder.
2. Under the condition of common hypoglycemia administer glucose solution 5% at the rate of 5mcg/kg/min until the normalization of blood glucose level.
3. In severe cases with severe hyperinsulinemia a dose may be increased to 15mcg/kg/min.
4. Glucocorticoids 5 mg/kg twice a day

Hypoglycemia in toddlers

Clinical signs of hypoglycemia in children

Symptoms of neurohypoglycemia	**Symptoms of sympathicoadrenal system**
Headache	**Sallow skin**
Sense of fear	**Sweatiness**
Hearing and vision disorder	**Muscular tremor**
Inability to focus	**Hyperreflexia**
Sleepiness	**Increase in arterial pressure**
Convulsive disorder	**tachycardia**
Semicoma	**Agression**

Coma	Hunger

Treatment of hypoglycemic coma in children and teenagers

1. Bolus administration of glucose solution 20% or 40% in the calculation 20-40 ml.
2. In the absence of effect in 15 minutes, repeated administration of the specified dose.
3. In the absence of effect, administer glucose solution 5%. The child is infused until he/she regains consciousness.

7.3. Control materials for the final stage of the class:
Assignments (α=3)

1. What form of diabetic neuropathy is characterized by the presence of acute pain, paresthesia, hyperesthesia and is fully reversible by its nature?
A. acute sensory diabetic neuropathy
B. chronic sensorimotor neuropathy
C. autonomic neuropathy
D. proximal motor neuropathy
E. chronic inflammatory demyelinating polyneuropathy

2. A patient aged 32, who was diagnosed with type 1 diabetes mellitus for the first time is complaining about acute pain in two legs, their hypersensitivity, especially about hip pain, a touch of clothes causes unbearable pain. The pain appeared along with diabetes symptoms. Its intensity increased after the normalisation of blood glucose level. It was accompanied by significant weight loss. Try to establish the provisional diagnosis?
A. type 1 diabetes mellitus, chronic sensorimotor neuropathy.
B. type 1 diabetes mellitus, acute sensory neuropathy.
C. type 1 diabetes mellitus, compressive mononeuropathy of lower limbs
D. type 1 diabetes mellitus, proximal motor neuropathy
E. type 1 diabetes mellitus, asthenoneurotic syndrome.

3. With what complications from among those listed below the diabetic patients are contraindicated in pregnancy?
A. non-proliferative diabetic retinopathy
B. stage 5 diabetic nephropathy
C. stage 1 diabetic neuropathy
D. metabolic liver disease
E. stage 1-2 diabetic neuropathy

4.In the life of a patient aged 40 years old, suffering from a severe form of type 1

diabetes mellitus occurred decompensation, which was accompanied by the development of ketoacidosis. Metabolic diseases were treated with intravenous administration of small amounts of rapid-acting insulin and isotonic sodium chloride solution. In an hour the patient started suffering from headache, sweatiness, heart disorders. Blood sugar – 2,8 mmol/L, content of sodium - 140 mmol/L. What caused such a state?

A. Hyperhydration
B. Hypokalemia
C. Ketoacidotic intoxication.
D. Hyponatremia
E. Hypoglycemia

5. A man, aged 36 years old lost consciousness in the street. He was detected diabetes mellitus patient history. Alcohol breathe. Watery, warm skin. Arterial blood pressure – 140/90 mm Hg, convulsive reflexes. Shallow breathing, preserved eye globe tone, enlarged pupils, hyperreflexia. What medical assistance must be provided?

A. Subcutaneous administration of short-acting insulin 10 units.
B. Intravenous stream introduction of 40-80 ml of glucose solution 40%.
C. Intravenous administration of short-acting insulin 10 units.
D. Intravenous stream introduction of 100-120 ml of glucose solution 40%.
E. Intravenous drip-feed introduction of 500 ml of glucose solution 5 %.

6.A patient V., aged 20 years old**,** has been suffering from diabetes mellitus since the age of 12. In the past medical history, brittle diabetes with frequent episodes of hypoglycemia. She was treated with short-acting insulin 8-10 units 4 times a day. As a matter of convenience and to keep the disease secret she started administering herself intermediate insulin 20 units before breakfast and 16 units before bed. As a result, she started suffering from sharp hunger and sweatiness at night time. She felt better after taking simple carbohydrates (sweet tea, candies, biscuits etc). What caused the specified changes in the patient's state of health and what are the manifestations of the disease associated with?

A. hypoglycemic state
B. change of the insulin preparation
C. duration of a disease
D. sexual debut
E. psychological disadaptation

7.A patient N., aged 21 years old**,** has been suffering from diabetes mellitus for 5 years. He is taking short-acting and intermediate insulin. The total daily dose is 42 units. In the morning, 40 minutes following the injection he started complaining about sweatiness, weakness, tremor and general sweating. After a while, he lost

consciousness. What are the possible reasons for his complaints and loss of consciousness?

A. Hypoglycemia
B. Ketoacidotic coma
C. Hyperosmolar coma
D. Cardiac rhythm disorder
E. Vegetative cardiac denervation

8.The following laboratory data are typical for hypoglycemia and hypoglycemic coma:

A. Blood glucose level <2,7 mmol/L
B. Blood glucose level <3,3-5,5 mmol/L
C. Blood glucose level <5.5 mmol/L
D. Increased Plasma Osmolarity <320 mmol/L
E. Hyperkalemia >6,0 mmol/L

9. Emergency medical service team delivered a patient aged 26 years old unconscious from the street to the hospital emergency department with the diagnosis of alcoholic intoxication. There were registered clonic convulsions, watery skin, pathological reflexes. Ordinary breathing. Signs of injection sites on the side surface of the abdomen. Heart rate - 90 per 1 min, arterial blood pressure - 145/90 mm Hg. What provisional diagnosis is the most probable?

A. Hypoglycemic coma
B. Alcoholic coma
C. Ketoacidotic coma
D. Narcotic poisoning
E. Hemorrhagic Stroke

10.A patient D., aged 32, was taking short-acting insulin 4 times a day. After three days he was transferred into a new treatment pattern – intermediate insulin 2 times a day. At 3 a.m. he felt weakness, tremor, excessive sweating and lost consciousness. What provisional diagnosis is the most probable?

A. Hypoglycemic coma
B. Ketoacidotic coma
C. Acute cerebrovascular accident
D. Uremic coma
E. Hyperosmolar coma

11.Terms of hypoglycemic coma development:

A. Urgently
B. For one day

C. For 2-3 days
D. For 10-12 hours
E. For 10-15 days

12.Specify the activities of a patient with diabetes mellitus in the event of a sudden tremor, heartbeats, excessive sweating, faint?

A. Drink a sugar-sweetened beverage
B. Increase the consumption of mineral water
C. Decrease liquid consumption
D. Increase the amount of protein in daily ration
E. Exclude saturated fat from the diet

13.A patient V., 49 has been suffering from diabetes mellitus for 9 years. She has been treated with Glimepiride the daily dose of which is 6 mg, which she takes once a day in the morning. Because of working at a country cottage in summer and eats at random times, during the afternoon she marks excessive sweating, chest pain and compressing retrosternal pain, heartbeat. Name the most probable cause for the occurrance of these symptoms of illness?

A. Hypoglycemic states
B. Long-term work at a country cottage
C. Eating at random times
D. High dose of sugar-lowering drug
E. Dehydration.

14.A patient D, aged 34 years old, has been suffering from type 1 diabetes mellitus for 10 years. At the party, he drank 300 ml of alcohol (in particular, horilka) before eating then ate a little bit. In a while, he started to demonstrate belligerency towards surrounding people without any reason and finally lost consciousness. What immediate relief must be provided to the patient?

A. intravenous bolus administration of 40-60 ml glucose solution 40%
B. intravenous drip-feed of glucose solution 5%
C. intravenously administer 20 units of insulin + glucose solution 5%
D. intravenous bolus administration of 40-60 ml glucose solution 40% + 30 units of insulin
E. intravenous drip-feed of 200ml sodium bicarbonate 3,4%.

15. A patient N., aged 38 years old, was transferred to the hospital unconscious. According to the emergency physician, the patient demonstrated psychic and motor agitation at home. In the course of transportation to the hospital, the patient suddenly lost consciousness. According to the past medical history the patient has been suffering from type 1 diabetes mellitus for many years and treated with insulin. The

patient eats at random times because of the need for frequent business trips. In the course of physical examination: unconscious, watery skin, dilated pupil, convulsive tic; respiratory rate 20 per 1 min; Ps -90 in 1 min, rhythmical; arterial blood pressure 150/90 mm Hg. Cardiovascular and respiratory systems are within normal limits. Soft abdomen. Positive Babinski sign. What is the most provisional diagnosis?

A. Hypoglycemic coma
B. Ketoacidotic coma
C. Hyperosmolar coma
D. Lactic acidosis
E. Diabetes mellitus decompensation with acute renal failure

16.A patient D., aged 36 years old, referred to the physician complaining about periodic weakness, hunger, gained 6 kg in the last 2 years. In the morning being at a doctor's office, there occurred an attack, which was accompanied by bulimia, tremor and the patient finally lost consciousness. During the examination: blood sugar 2,0 mmol/L. After administration of 40ml glucose solution 40% attack was stopped. What is the most provisional diagnosis?

A. Insulinoma
B. Type 1 diabetes mellitus
C. Type 2 diabetes mellitus
D. Glucagonoma
E. Phaeochromocytoma

17.To the hospital emergency department of the central clinical hospital there was taken a patient aged 48 years old unconscious. Clinician-observed: watery skin, injection signs on hips and shoulders. Shallow breathing. Ps- 100 per 1 min, rhythmical; arterial blood pressure 160/40 mm Hg. Brisk muscle tone and tendon reflexes. Clonic seizure of limb muscles. What patient's state is the most probable?

A. Hypoglycemic coma
B. Ketoacidotic coma
C. Hyperosmolar coma
D. Lactic acidosis
E. Insulin-induced cerebral coma

18.A patient S., aged 40 years old, who has been suffering from type 1 diabetes mellitus for 15 years, against the background of compensation, after taking Anaprilin because of tachycardia, starts suffering from long-term hypoglycemia cases, approximation of which he does not feel. What treatment policy in this particular case is the most reasonable?

A. Replace Anaprilin with calcium antagonist
B. Replace Anaprilin with Obsidan

C. Reduce insulin dose
D. Reduce Anaprilin dose
E. Increase the dietary intake of carbohydrates.

Protocol № 1 clinical considerations for a patient

Patient's full name _____
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_____
Age _____ Occupation_____
patient's complaints _____
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past medical history _____
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Patient's life history _____
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Results of physical examination of the patient: _____
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Provisional diagnosis: _____
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What diseases may require the performance of differential diagnosis?
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Examination plan: _____
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Results of laboratory and instrumental examination:
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Substantiation of clinical diagnosis: _____
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Clinical diagnosis: _____
Prior disease:
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Complications: _____

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Intercurrent diseases: _____
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Prognosis: _____
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Workng capacity: _____
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Treatment: _____
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medicamentous therapy: _____
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glycaemic control: _____

Marking of mastering practical skills

Order No.	Skills and procedures	Signature of the student/ adviser
1	Practical skills	
1.1.	Know how to interview, perform a physical examination of a patient with diabetes mellitus	
1.2.	Be able to analyze the laboratory examination data	
1.3.	Know how to assign a sugar- lowering therapy to a patient with diabetes mellitus	
2.	Know how to assign the diabetes complication treatment pattern	
2.1.	Diabetic retinopathy	
2.2.	Diabetic nephropathy	
2.3.	Diabetic neuropathy	
2.4.	Diabetic foot disease	

_____
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Theme 2: Management of patients with uncompensated diabetes mellitus (ketoacidosis). Management of a patient with hyperglycemic (ketoacidotic) coma.

1. Topicality .

Diabetes mellitus today is a global medical and social contemporary problem. This is an epidemic of non-infectious disease. It takes third place according to the prevalence rate after cardiovascular morbidity and malignant tumors. The reasons for early disability and death of patients with diabetes mellitus include chronic and acute complications that develop in the event of decompensation of the disease.

1. **Learning goal.**

Teach the students the contemporary methods of management of a patient with uncompensated diabetes mellitus, how to implement contemporary diagnostic standards, treat and prevent diabetes mellitus based on the management of patients with diabetes mellitus under inpatient treatment and outpatient clinic.

The student must know (α=2):

- The definition of the concept of diabetes mellitus, impaired glucose tolerance, impaired fasting glycaemia.
- Etiology and pathogenesis of type 1 and type 2 diabetes mellitus.
- The risk of cardiovascular and neurological complications, prognosis and working capacity of patients with diabetes mellitus.
- Main reasons for diabetes mellitus decompensation.
- Management (examination, treatment) of patients with diabetes mellitus, the role of internal organs pathology in the development of diabetes mellitus decompensation.
- Diabetes mellitus compensation criteria.
- Recommendations for the selection of the modern methods of insulin therapy (traditional, intensified,pump therapy) and insulin analogue. Prescription of sugar-lowering tablets.
- Etiology and pathogenesis of ketoacidotic coma.
- Clinical manifestations of ketoacidosis, diagnosis and differential diagnosis of comatose states.
- Treatment policy in the event of diabetes mellitus detected for the first time and in the occurrence of ketoacidotic states.
- Type 2 diabetes mellitus treatment algorithm (A Consensus Report from American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) 2019)
- Principal provisions of care delivery protocols with a specialization in «Endocrinology», (order of the Ministry of Health of Ukraine No.574 dated 05.08.2009).

The student should be able to (α=3):

- Interview and examine patients with diabetes mellitus .
- Measure and evaluate a level of capillary and venous blood glucose.
- Conduct a capillary blood glucose tolerance test, as well as appraise the value of glycated hemoglobin, fructosamine, C-peptide, glycosuria, ketonuria.
- Differentiate between different types of diabetes mellitus
- Draw up a plan of examination of a patient with diabetes mellitus, justify the application of the main examination techniques, define indications for their performance.
- Based on analysis of laboratory findings and instrumental methods of examination, justify and formulate the diagnosis of diabetes mellitus and its complications.
- Prescribe a corresponding medication to treat type 1 and type 2 diabetes mellitus and its complications.
- Detect and provide assistance in the event of diabetic ketoacidosis.
- Diagnose ketoacidotic coma.
- Conduct differential diagnosis of different types of comatose states.
- Apply modern diabetic ketoacidotic coma diagnostic and treatment standards.
- Provide medical assistance in the event of ketoacidotic coma.
- Demonstrate that the medical professional has moral and deontological principles.

2. Educational goal.

Attract attention to and form the sense of responsibility in students, who will be different types of doctors, for the timely detecting and the proper treatment of non-compensated states of disease to achieve carbohydrate metabolic compensation as a principal factor preventing complications of chronic diseases as well as timely performing diagnosis, differential diagnosis and treatment of hyperglycemic ketoacidotic coma.

4. Interdisciplinary integration:

Subjects	*To know*	*To be able to*
Previously studied subjects		
Systemic Anatomy	the topography, the vascularization of the pancreas,	
Hominal Physiology	the internal secretion of the pancreas,	

Histology Biochemistry Pathoanatomy Pathophysiology	the histologic structure of the island of Langerhans, the carbohydrate metabolism, morphological changes in organs and tissues in patients with diabetes mellitus, pathogenesis of vascular events and comas in patients with diabetes mellitus	
Subjects that will be studied later		Perform a clinical review, prescribe the corresponding diagnostic testing, consultations by allied health professions to verify the diagnosis
Therapy	Clinical picture, diagnosis, differential diagnosis, treatment of different types and conditions of diabetes mellitus, hyperglycemic coma	
Pediatrics	Clinical picture, diagnosis, differential diagnosis, treatment of different types and conditions of diabetes mellitus, hyperglycemic coma in children	
Surgery	Peculiarities of the course of different types and conditions of diabetes mellitus in the event of surgical pathology, timely diagnosis, prevention and treatment of patients with decompensated diabetes mellitus	
Obstetrics & Gynaecology	Peculiarities of the course of different types and conditions of diabetes mellitus during pregnancy, timely diagnosis and surveillance of such patients	
Neurology	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of neurological complication of diabetes mellitus	
Ophthalmology	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diabetic retinopathy	
Intersubject integration	Modern methods of patients' examination, in particular, laboratory, instrumental, adequate treatment strategy	Prescribe the adequate treatment

5. Training subjects:

- Etiology and pathogenesis of type 1 and type 2 diabetes mellitus.
- Main reasons for diabetes mellitus decompensation.
- Diabetes mellitus decompensation criteria.
- Etiology and pathogenesis of hyperglycemic ketoacidotic coma.
- Clinical picture of ketoacidotic coma.
- Differential diagnostics of comatose state in patients with diabetes mellitus.
- Management (examination, treatment) of patients with diabetes mellitus, the role of internal organs pathology in the development of diabetes mellitus decompensation.
- Sugar-lowering therapy depending on the diabetes mellitus type and severity level. Recommendations for the selection of treatment.
- Treatment policy in the event of diabetes mellitus detected for the first time and in the occurrence of ketoacidotic states.
- Ketoacidotic coma treatment algorithm

7. Materials and methodological support of the class.

7.1 Materials of the preparatory stage of the class

Tests (α=2)

1. A patient, aged 56 years old after treatment of diabetic ketoacidosis started suffering from weakness, cardiac pain and heart failure. He was treated with insulin, sodium bicarbonate.Blood glucose 4,5 mmol/L, plasma potassium - 2,9 mmol/L, plasma sodium - 148 mmol/L. The most probable cause for such a state.
   A. Hypokalemia;
   B. Normal response to insulin administration;
   C. Hyperlactacidemia
   D. Hypoglycemia
   E. Alkalosis

2. A boy aged 9 years old is suffering from diabetes mellitus. 30 minutes after insulin injection he started

complaining about sweatiness, weakness, ringing in the ears. In some minutes he lost consciousness. What laboratory tests he must be referred to first of all?

A. Define the glucose blood level
B. Define blood electrolytes
C. Define total blood protein
D. Define acetone in urine;
E. Define ketone bodies

3. Lactic acidosis in patients with diabetes mellitus is possible under the following circumstances:

A. Treatment with biguanides
B. Treatment with sulfanilamide derivatives
C. Treatment with acarbose drugs
D. Treatment with glitazones
E. Treatment with glinides

4. Ketonuria in patients with diabetes mellitus occurs:

A. In the event of decompensated diabetes mellitus
B. In the event of simple sugar intake
C. In the event of fat intake
D. In event of fructose intake
E. In the event of metformin overdose

5. The diagnosis of diabetes mellitus in the state of decompensation is established in the following cases:

A. In the event of hyperglycemia and presence of urine ketones
B. If the patient's breath smells like acetone
C. Dry skin, polyuria, brown tongue coating
D. If the daily urine exceeds 5 L
E. When a patient with diabetes mellitus is unconscious

6. Decompensated diabetes mellitus. Diabetic precoma is established according to the following clinical and laboratory data:

A. Hyperglycemia, ketonuria, communication with a patient becomes complicated
B. Hyperglycemia, ketonuria, pain on palpation
C. Hyperglycemia, ketonuria, hepatomegaly with pain on palpation
D. Hyperglycemia, ketonuria, leucocytosis in blood test
E. Hyperglycemia, ketonuria, nausea, cyclic vomiting

7. Typical laboratory changes in diabetic comatose patients:

A. Hyperglycemia, ketonuria
B. Hyperglycemia, increased plasma osmolarity
C. Significantly increased blood lactate level
D. Lactacidosis, increased erythrocyte sedimentation rate
E. Hyperkalemia

8. A patient S , aged 26 years old has been suffering from diabetes mellitus since the age of 14. Brittle diabetes with frequent episodes of hypoglycemia. The patient is treated with short-acting insulin 6 – 8 units 4 times a day. To keep the disease secret she started administering herself intermediate insulin 18 units before breakfast and 14 units before bed. As a result, she started suffering from sharp hunger and sweatiness at night time. She felt relief after eating sweets. What are the changes in the patient's state of health related to?

A. hypoglycemia
B. sexual debut
C. change of insulin preparation
D. pregnancy
E. psychological disadaptation

7.2. Methodological materials for the principal stage of the class:

Examination protocol, establishing a diagnosis, treatment and prevention

ACTIVITY SECTION	**GUIDELINES FOR ACTION**
Greeting	Greet and introduce yourself to a patient
Acquaintance	Collect personal information about a patient (full name, sex, age, place of residence,

	place of work and occupation)
Patient's complaints at the time of examination	Identify and present details of patient's complaints. While identifying patient's complaints, pay attention to the availability of: - dipsesis - polypliagia - polyuria, nycturia - dry mouth - weight loss - skin itching - leg pain
Individual and family medical history, examination of organs and systems	Specify the course of the disease, examine organs and systems. 1.Availability of risk factors. While interviewing pay attention to the information about: - overweight (≥ 25 kg/sq.m.); -occurrence of diabetes mellitus in the past medical history; - sedentary lifestyle; - age over 45; - arterial hypertension; - hypercholesterolemia, hypertriglyceridemia; - atherosclerosis, gout, chronic liver, kidney, cardiovascular disease (chronic heart diseases, infarcts,strokes in the past medical history); - chronic periodontitis and furunculosis; - metabolic syndrome; - glycosuria episodes against the background of stress situations; - gestational diabetes in the past medical history; - mothers of children with developmental anomalies; - polycystic ovary syndrome; - long-term diabetes drugs intake 2. Availability of symptoms of target organs affects: - brain and vision: headache, dizziness, visual deterioration, transitory ischaemic attack, sensory or motor impoverishment; - heart: heartbeats, chest pain, short breath, leg swelling; - kidney: thirst, polyuria, nycturia, haematuria; - peripheral artery: cold extremities, intermittent claudication .
Physical examination	While examining a patient evaluate the patient: 1. body weight 2. waist measurement 3 body mass index (BMI) While examining the patient pay attention to the availability of: 1. Signs of affecting target organs: - peripheral artery (acrotism, weak pulse or asymmetry of pulse, cold extremities, ischemic injuries, skin injuries); - heart (localization and character of the apex beat, arrhythmia, pulmonary rale, peripheral oedemas); - brain (cervical venous hum, motor and sensory impoverishments); - eye retina (according to fundoscopy, if possible).
Examination plan	blood glucose level, urine, ketonemia, ketonuria, HbA1c, C-peptide, fructosamine
Laboratory and instrumental investigations	1. Evaluate the level of: - fasting glucose; - cholesterol total (XC), XC high-and low - density lipoprotein (HDL, LDL) and triglycerides (TG) in blood serum; - potassium in blood serum; - uric acid and creatinine in blood serum; - microalbuminuria, - Hb A1c, C-peptide, fructosamine
Formulating a diagnosis	Intermediate severity or severe type 1 (type 2) diabetes mellitus (mild form for type 2) in the event of compensation (subcomensation, decompensation) or - Diabetes mellitus resulted from ...(specify the reason) diabetic microangiopathies: - Retinopathy (specify the stage in the left eye (OS), in the right eye (OD); condition after laser photocoagulation or operative therapy (if any) since ... - nephropathy (specify the stage)

	Diabetic neuropathy (specify the form) Diabetic macroangiopathy: - Coronary artery disease (specify the form). - Cardiac decompensation (specify the stage according to NYHA). - Cerebrovascular disease (specify which ones). - Peripheral angiopathy (specify the type and stage) arterial hypertension (specify the stage) Dyslipidemia (if any) Concurrent diseases.
Treatment plan	Make a treatment plan, which must include non-drug and drug therapy
Non-drug therapy	
	Give a recommendation on lifestyle modification: - Reduce weight in the event of obesity or overweight; - Limit the consumption of easily digested carbohydrates; - Reduce alcohol intake; - Regularly do dynamic physical exercises; - Limit salt intake up to 3 g/day in the event of arterial hypertension; - Limit saturated fat and cholesterol intake; - Give up smoking; - Include to the daily diet the food products rich in vegetable fibre.
Drug therapy	
Drug therapy methods	1. Based on carbohydrate metabolism evaluation in a patient who did not previously undergo treatment, decide on the necessity to start drug treatment; 2. Decide upon the medication that is worth prescribing to a patient based on his previous treatment history, availability of complications and concomitant pathology, indications and counterindications for the prescription of specific drugs (See Section "Oral sugar-lowering drugs), as well as their value; 3. When choosing the medication, take into account the evidence-based guidelines according to the data of the supervised investigations.
Oral sugar-lowering drugs	
Secretagogues Sulfonylurea medications	*Mechanism of action:* stimulate insulin secretion; *Data of the supervised investigations:*strength of recommendations 1. *Indicated:* in the event of type 2 diabetes mellitus with predomination of insufficient insulin secretion (no obesity)with inefficiency of diet and physical exercises. *Counterindicated* in the event of type 1 diabetes mellitus, ketoacidosis, pregnancy, lactation, chronic renal disease.
Meglitinides	*Mechanism of action:* stimulate insulin secretion; *Data of the supervised investigations:* strength of recommendations 2. *Indicated* in the event of type 2 diabetes mellitus with predomination of insufficient insulin secretion (no obesity) and expressed hyperglycemia after eating with the inefficiency of diet and physical exercises. *Counterindicated* in the event of type 1 diabetes mellitus, ketoacidosis, pregnancy, lactation, chronic renal disease.
Sensitizer Biguanides	*Mechanism of action*: reduction of glucose production from the liver; reduction of the insulin resistance of muscular and fat tissue. *Data of the supervised investigations:* strength of recommendations 1. *Indicated:* in the event of type 2 diabetes mellitus with predomination of insulin resistance (with obesity) and fasting hyperglycemia with the inefficiency of diet and physical exercises.
Thiazolidinediones	*Counterindicated* in the event of type 1 diabetes mellitus, ketoacidosis, pregnancy, lactation, chronic cardiac, hepatic, renal failure, anemia, alcohol abuse, elderly age. *Mechanism of action*: reduction of insulin resistance of muscular and fat tissue, reduction of glucose production from the liver. *Data of the supervised investigations: strength of recommendations* 2. *Indicated* in the event of type 2 diabetes mellitus with predomination of insulin resistance with the inefficiency of diet and physical exercises. *Counterindicated* n the event of type 1 diabetes mellitus, ketoacidosis, pregnancy and lactation, hepatopathy (high ALT >2,5times) severe heart, renal failure.
Alpha-glucosidase inhibitor	*Mechanism of action*: reduced absorption of carbohydrates in the intestine. *Indicated:* in the event of type 2 diabetes mellitus with predomination of hyperglycemia with the inefficiency of diet and physical exercises. *Counterindicated* in the event of type 1 diabetes mellitus, ketoacidosis, pregnancy, lactation, gastrointestinal pathology.
Modern sugar-lowering drugs	
Incretin modulators:	*Mechanism of action*: glucose-mediated sugar-lowering effect, cardio – and angioprotective effect, deceleration of gastric emptying, hepatoprotective effect.

glucagon-like peptide-1receptor agonist dipeptidyl peptidase 4 inhibitors	*Data of the supervised investigations:* strength of recommendations 2. *Counterindicated* in the event of type 1 diabetes mellitus, ketoacidosis, pregnancy, lactation, gastrointestinal pathology, chronic pancreatitis
Sodium-glucose Cotransporte r-2 (SGLT2) Inhibitors	Increase elimination of glucose from kidneys

Management of patients with diabetic ketoacidosis	
Diagnosis	**Main reason for the occurrence of ketoacidotic states-** absolute relative insulin deficiency **Provocative factors:** - concomitant disease (acute inflammatory processes, acute exacerbation of chronic disease, contagious diseases). - Violation of treatment regimen (missing or refusal from insulin administration, errors in prescription or administration of insulin dose, administration of insulin after its expiration date or if it was stored under inappropriate conditions, etc.) - inadequate control over blood glucose level. - surgical intervention and traumas. - pregnancy - untimely diagnosis of diabetes mellitus . - untimely prescription of insulin therapy in the event of type 2 diabetes mellitus. - chronic therapy with insulin antagonists (glucocorticoids, diuretins etc.). - stress. **1. Clinical picture:** -thirst; - polyuria (followed by oligo- and anuria); - worsening dry skin and mucous membranes; -weakness, adynamia; -Headache; - absence of appetite, nauses, vomiting; - acetone breath **2. Complete blood count** - leucocytosis **3. Common urine test** - glycosuria; ketonuria; proteinuria (inconstantly). **4. Biochemical blood assay** - hyperglycemia; hyperketonemia; the increase of urea and creatinine nitrogen (inconstantly). **5. Acid and alkaline state** - Decompensated metabolic acidosis.
During the prehospital phase or at the admission department:	
Treatment	**1. Rehydration with insulin therapy:** -short-acting insulin 20 units –intramuscularly (controlled ketones in blood and urine glucose) - saline solution 0,9% by intravenous administration at a rate of 1L/hour.
At the intensive therapy unit	
	1. Rehydration • saline solution 0,9% (at the level of sodium plasma <150 mmol/L): 1st hour – 1 L isotonic sodium chloride solution; 2nd 3rd hour – 0,5 L of isotonic sodium chloride solution; further until elimination of dehydratation, 0,25-0,5 L/hour isotonic sodium chloride solution; • in the event of glycemia <14 mmol/L – glucose solution 5 – 10%, possible together with the physiological solution ; • colloid plasma expanders (in the event of hypovolemia -systolic pressure – <80mm Hg) **2. Insulin therapy: low dose regime** short -cting insulin, initial dose 10-16 units intravenous bolus, then there is administered 0.1 unit/kg/hour intravenous drip-feed,

	subcutaneous administration of insulin at a rate of 3-4 units/hour only under the condition of reduced glycemia 14 mmol/L and with normal findings of acid-alkali balance or **intensification of basal-bolus insulin therapy scheme**. **3. Correction of electrolytic violations** (renewal of potassium deficiency) Depends on kidney functional status and initial level of kalemia: if the potassium level is less than 3 mmol/L intravenous drip-feed 3 g/hour KCl 4% solution, in the event of kalemia 3-4 mmol/L – 2 g/hour, in the event of kalemia 4-5 mmol/hour – 1,5 g/hour
	4. Correction of metabolic acidosis Insulin therapy – is an etiological treatment of **metabolic acidosis** with ketoacidotic states. If in an hour after rehydratation, using colloid solution and insulin therapy shock remains and pH still is < 7,0, there is indicated intravenous administration of sodium bicarbonate in the calculation of 1-2 mmol/kg of the body weight: half a dose is administered within 30 min, and the other one — within 1–2 hour.Additional administration of potassium solution is mandatory. Upon reaching pH ≥ 7,0 the administration of sodium bicarbonate is ceased. **5. Prevention of Disseminated Intravascular Coagulation Symptoms.** Heparine 2500-5000 units (controlling blood clotting time) is administered twice during the first day **6. Treatment and prevention of contagious diseases** There are prescribed broad-spectrum antibiotics in age-specific dosage variances.

7.3. Control materials for the final stage of the class:
Assignments (α=3)

1. A woman aged 79 years old has been suffering from type 2 diabetes mellitus for 20 years. She has been treated with DIABETON MR 90 mg a day. Besides, she has been suffering from arterial hypertension. Every day she takes Ramipril 10 mg and Arifon® Retard 1 table (daily). The patient also suffers from permanent ciliary arrhythmia, 2 stage pulmonary heart disease. She is taking furosemide 80 mg once in 3 days. Fasting glycemia 8,5 mmol/L, prandial - up to 13,7 mmol/L, glycated hemoglobin 8%. To improve carbohydrate metabolism parameters there was added to the treatment metformin 500 mg after breakfast and supper. In a week after taking medication there increased weakness, dyspnea,swelling in the feet. Fasting glycemia 7,5 mmol/L, prandial 10,3 mmol/L. What is the deterioration in the patient's condition related to?

A. Development of lactic acidosis
B. hypokalemia resulted from taking furosemide
C. Decreased fasting glycemia
D. Decreased prandial glycemia
E. Polypragmasy

2. A patient aged 76 years, has been suffering from type 2 diabetes mellitus for 18 years. She has been treated with micronized glibenclamide at a dose of 10,5mg a day. The last week because of the absence of the medication the dose was decreased to 3,5 mg a day. In a week of treatment, she felt excessive thirst, weakness, excessive sleepiness. In the course of examination – excessive skin dryness. The skin straightens with difficulties after wrinkle. Glycemia 28 mmol/L, glycosuria 40 g/L, ketonuria is not revealed.What diagnosis would you establish?

A. Hyperosmolar coma
B. Type 2 diabetes mellitus at the decompensation stage
C. Lactic acidosis
D. Diabetic precoma
E. Transient disorders of cerebral circulation.

3. A patient aged 18 years old has been suffering from type 1 diabetes mellitus since the age of 4. He has been treated with short-acting and intermediate insulin. He was transferred to the treatment with insulin produced by another manufacturer at a dose, which is 20% less than the previous ones. Because of the fear of hypoglycemia, the patient increased the quota limit of simple carbohydrates in the daily diet. In 3 days after permanent treatment he started suffering from excessive thirst, there increased the amount of passed urine, he started suffering from pain in the epigastrium and nausea. What are the changes in the patient's clinical course of disease related to?

A. decompensation of diabetes mellitus
B. FARMASULIN H idiosyncrasy
C. FARMASULIN N idiosyncrasy
D. insulin preparation dose reduction
E. diet violation

4. A woman aged 55 years old has been suffering from type 1 diabetes mellitus for 2years. She has been treated with glibenclamide at a daily dose of 10 mg in the morning and 5 mg at lunchtime. Because of too much work in the garden

in summer and poor nutrition, she changed the regime of taking the preparation in the course of the day. She was taking the total dose (15 mg) after a hearty supper. She started suffering from excessive sweating at night, cardiac pain, heartbeats, faintness, she woke up very often at night. She controlled cardiac pain with validol (up to 10 tablets at the same time) and drinking sweet fruit juice. What were the patient's symptoms of illness caused by?

A. hypoglycemia
B. long-term work in the garden
C. long-term staying in the sun
D. change of the usual regime of taking glibenclamide
E. change of the dietary regime

5. A patient K, aged 65 years old, has been suffering from type 2 diabetes mellitus for 20 years. Against the background of acute cerebrovascular accident, there occurred hyperglycemia 56 mmol/L, severe dehydration, hyperchloremia, hypernatremia. ketonemia and ketonuria are absent. Specify the provisional diagnosis:

A. hyperosmolar coma;
B. acute renal failure;
C. Diabetic hyperketonemic coma;
D. recrudescence of chronic renal disease;
E. hyperlactacidemic coma.

6. A patient with diabetes mellitus lost consciousness at the table during a party. Before that, he was drinking much alcohol and almost did not eat. What treatment should be prescribed by the physician first of all?

A. glucose 40% intravenous bolus
B. glucose 5% intravenous drip-feed
C. glucose 40% and insulin intravenous drip-feed
D. glucose 5% and insulin intravenous bolus
E. alkali solutions intravenous drip-feed

7. A patient was transported by ambulance to the resuscitation department unconscious. There was found the Diabetic Patient ID Card. Kussmaul stertorous breathing, acetone breath, dry skin, a decrease in skin turgor, pinched face, periosteal reflexes are absent, reduced eye bulb tonus. The blood content of lactic acid is 1,2 mmol/L (norm 0,62-1,3 mmol/L), glycemia 29 mmol/L. The development of what emergency can be suspected?

A. lacticidemic coma .
B. hyperosmolar coma.
C. hypoglycemic coma.
D. ketoacidotic coma.
E. uremic coma

Protocol of clinical considerations for a patient

Patient's full name _____
_____
_____
____
Age _____
Occupation_____
Patient's complaints
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Past medical history
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Patient's life history _____
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Results of physical examination of the patient: _____

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Provisional diagnosis:
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What diseases may require the performance of differential diagnosis?
1._____
2. _____
3. _____
4. _____
5._____
Examination plan: _____
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Results of laboratory and instrumental examination:
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Substantiation of clinical diagnosis: _____
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Clinical diagnosis: _____
Prior disease:
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Complications:
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concomitant disease: _____
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Prognosis: _____
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Working capacity:
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Treatment: _____
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medicamentous therapy: _____
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glycaemic control:
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Marking of mastering practical skills

Order No.	Skills and procedures	Signature of the student/ adviser
1	Practical skills	
1.1.	Know how to interview, perform a physical examination of a patient with diabetes mellitus	
1.2.	Be able to analyze the laboratory examination data	
1.3.	Know how to assign a sugar-lowering therapy to a patient with diabetes mellitus: tablets, a traditional and functional insulin therapy	
2.	Emergencies	
2.1	Be able to provide assistance in the event of ketoacidotic state	

Theme 3. Management of a patient with goitre. Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with thyroid problems. Treatment of a patient with thyrotoxic crisis.

3. Topicality

Goitre is a clinical concept characterizing the enlargement of the thyroid gland in size or volume, presence of nodular goitre. It develops because of genetic liability under the influence of triggers.

Triggers are usually represented by adverse environmental factors: iodine and selenium deficiency, the activity of goitrogenic substances, tobacco smoking etc. Goitre often accompanies the range of such pathological conditions as diffuse toxic goitre, nodular goitre, chronic autoimmune thyroiditis or it may result from medical interventions and some medication intake.

Goitre may be either diffuse (when the total volume increases) or nodular (in the event of the presence of local additional inclusions (adenomas, carcinomas, calcificates, in some cases – large cysts in thyroid tissue (TT)).

The scope of *iodine deficiency* and its consequences impresses. According to estimates of WHO, about 2 billion people or 30% of the world population live in areas severely affected by iodine deficiency. The total number of those suffering from endemic goitre reaches 740 million people, and those with infantile hypothyroidism – 11 million people. Herewith, the cases of discernible infantile hypothyroidism are quite fairly deemed to be «the tip of the iceberg», considering that less severe intellectual disabilities (not always diagnosed) occur much more frequently. The course of endemic goitre, which from olden times has been the most common and the best-known sign of iodine deficiency, may be complicated by the development of local compression syndrome, iodide-induced thyrotoxicosis and/or malignant change. Thus, the problem of iodine deficiency has been recognized as the immediate global problem, as long as all the specified disorders to a large extent determine not only the health status of the population but also the intelligence level of society. It is worth additionally emphasizing that under the condition of chronic iodine deficiency there significantly increases the risk of the thyroid gland radiation-induced pathology development in the event of industrial disasters.

Thyroiditis - a group of thyroid gland diseases that differ in etiology and pathogenesis, morphological pattern and clinical course. Thyroiditis is a general term that refers to "inflammation of the thyroid gland". The occurrence and clinical importance of types of thyroiditis also significantly differ. In most cases, physicians face different types of chronic autoimmune thyroiditis, which is considered to be the most common autoimmune human disease. It often causes thyroid gland functional disorders (usually the development of hypothyroidism), which defines the main clinical aspect of this pathology. Subacute thyroiditis like granulomatous and lymphocytic are second by frequency. Notwithstanding their full-blown symptoms in most cases, they do not leave any persistent disorders behind. Other types of

thyroiditis occur much less frequently.

Thyrotoxicosis – a syndrome with which there are observed clinical and/or biochemical manifestations of the excessive content of thyroid hormones in blood independent of the causative factor. About 90% of cases of thyrotoxicosis fall on diffuse toxic goitre and thyroid gland functional autonomy. Diffuse toxic goitre (Graves-Basedow disease) is one of the most severe diseases, which is a genetically determined system pathology of autoimmune genesis, which is manifested by diffuse thyroid disease and hyperthyreosis, often in combination with extrathyroidal pathology (infiltrative ophthalmopathy, dermopathy). Timely diagnosis enables adequate treatment, preventing the development of many severe complications of thyrotoxicosis both chronic (cardiomyopathy, encephalopathy, myopathy, osteoporosis, cachexia) and acute (thyrotoxic crisis). The similarity of clinical symptomatology necessitates the differential diagnosis of thyrotoxicosis syndrome with numerous cardiovascular diseases, diseases of the nervous and other systems, which may be a difficult task, however, so necessary from the perspective of medical tactics.

It is believed that *thyroid cancer* is a rare disease, which is about 1–1,5 % of all malignant neoplasms, however, among endocrine tumors it occurs the most frequently. For the recent 25 – 30 years, numerous notifications show the increase of thyroid cancer cases in many countries, especially among youth. In Europe over 20000 new thyroid cancer cases are diagnosticated every year and 1500–2000 patients die from this disease. In Ukraine, during a year about 2500 new patients are detected. About 27000 patients are registered as such that have undergone treatment and 10–12 patients per 1 million of the population die.

Malignant thyroid neoplasms are quite specific and extremely diverse according to their biological attribute. On the one hand, it often leads to diagnostic errors and long–time ineffective treatment with different specialists (endocrinologists, surgeons, pediatricians, phthisiologists, otolaryngologists).

On the other hand, the timely delivered adequate treatment of thyroid cancer provides quite good long-term results. It is expediated by both the low malignant potential, peculiar to most of these tumors, and the compliance with up-to-date standards of their diagnosis and treatment. Nevertheless, there occur tumors with quite aggressive behaviour, which are life-threatening conditions.

4. Learning goal.

To become acquainted with spreading of diffuse and nodular nontoxic goitre, hypothyroidism, thyroiditis, thyroid cancer in Ukraine and the world (α=1).

The student must know (α=2):

- biological effect of thyroid hormones on human organism and mechanism of thyroid function regulation;
- determination and risk factors of the major thyroid disorders;

- symptoms and signs of the major thyroid disorders;
- diagnostic criteria of the major thyroid disorders;
- thyroid enlargement classification;
- methods of assessment of thyroid function;
- Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with thyroid problems

The student should be able to (α=3):

- to diagnose endemic and sporadic goitre, hypothyroidism, autoimmune, acute, subacute thyroiditis, thyroid cancer, decide upon treatment policy and (if possible) the preventive measures;
- carry out the differential diagnosis of thyroid disorders;
- examine neck and thyroid;
- palpate cervical glands;
- effectively use the possibilities of public and personal preventive measures of iodine deficiency disorders (IDD).
- perform diagnosis and differential diagnosis of thyrotoxic crisis
- determine treatment policy in the event of thyrotoxic crisis

3. Educational goal.

To formulate deontological principles of working with patients suffering from endocrine pathology. To attract students' attention to the influence of environmental factors on the development of certain thyroid disorders. To form the sense of responsibility for the timeliness of diagnosis, completeness of examination and selection of treatment policy for patients with different types of thyroid disorders especially the one, which may threaten life and health.

4. Interdisciplinary integration:

Subject	*To know*	*To be able to*
Previously studied subjects		
Systemic anatomy	Anatomy of the thyroid gland	
Hominal physiology	synthesis, transportation, effects, thyroid hormones' secretion regulation;	
Histology	embryogenesis, histological structure of the thyroid gland;	
Pathoanatomy	Classification and nature of pathomorphological	Evaluate results of pathohistological

	changes of the thyroid gland ;	examination of the thyroid gland;	
Pathophysiology	Etiology and pathogenesis of iodine deficiency disorders, hypothyroidism, thyroiditis, thyrophyma		
Pharmacology	Iodine-containing drugs, thyroid hormones, anti-inflammatory drugs;	Fill the corresponding prescriptions	
Radiology	ultrasonography, scintigraphy, radiodiagnosis of thyroid disease .	Evaluate results of corresponding examinations	
Subjects that will be studied later			**Subjects that will be studied later**
Internal diseases	Changes of the internal organs in the event of thyroid diseases, their differential diagnosis, basic treatment methods;	Carry out clinical examination of a patient, palpate the thyroid gland; assign the necessary diagnostic examinations and consulting of associated medical specialists to verify the diagnosis, interpret the results (conclusions).	
Pediatrics	Peculiarities of the course of the pathology of the thyroid gland at an early age;		
Surgery	Surgical management of thyroid disease		
Obstetrics & Gynecology	Peculiarities of the course of thyroid		

	diseases across pregnancy, their influence on fetal development;	
Neurology, psychiatry	psychoneurological symptoms of thyroid disease	
Intrasubject integration	Modern methods of clinical, laboratory and instrumental examination of patients with hormonal diseases.	Carry out differential diagnosis of thyroid diseases with other pathology, assign adequate treatment

5. Training subjects:

- Definition and epidemiology of iodine deficiency disorders.
- Pathogenesis, clinical manifestations and diagnosis of endemic goitre.
- Modern approaches to endemic goitre treatment.
- Clinical aspects of other iodine deficiency disorders.
- Iodine deficiency disorders prevention: forms, methods, control.
- Sporadic goitre: etiology, pathogenesis, clinical manifestations, diagnosis, treatment.
- Definition, epidemiology and classification of hypothyroidism.
- Etiology and pathogenesis of different types of hypothyroidism.
- Clinical manifestations and diagnostic criteria of thyroid hypofunction; atypical hypothyroidism.
- Principles of hypothyroidism treatment across different age groups.
- Congenital hypothyroidism: pathogenesis, the neonatal screening, peculiarities of substitution therapy.
- Clinical and morphological classification, etiology, pathogenesis, clinical manifestations, diagnosis, treatment of thyroiditis.
- Etiology, pathogenesis, clinical picture, diagnosis of toxic diffuse goiter;
- Etiology, pathogenesis, clinical picture, diagnosis, differential diagnosis and treatment of thyrotoxic crisis.
- Epidemiology, causative factors, morphological classification of thyroid tumors.
- Clinical picture of different thyroid cancer types.
- Possibilities and restrictions of the thyroid cancer diagnosis methods.

- Modern methods of thyroid cancer treatment.
- Regular medical check-up of patients with thyroid cancer. Prognosis.

6. Plan and organizational structure of the class
(see «Introduction»)
7. Materials and methodological support of the class.
7.1. Materials for the preparatory phase of the class
5. Tests (α=2)
1. Within the framework of the neonatal screening program, a newborn baby was diagnosed with hypothyroidism. At what age the baby may be assigned the substitution therapy?
A.Since the 1st month of the new baby's life.
B.Since the 3d month of the new baby's life.
C.Since the 6th month of the new baby's life.
D.After termination of breastfeeding.
E.Transfer the baby into the artificial feeding, and then prescribe Levothyroxine.

2.Define the most informative laboratory parameter for the diagnosis of primary hypothyroidism:
A.Thyrotropic hormone
B.General thyroxin.
C. Free thyroxin.
D. Triiodothyronine.
E. Antibodies level to thyroid peroxidase.

3.To the characteristic symptoms of hypothyroidism refer all but…
A. Bodyweight gain
B. Warm skin
C. Emotional disequilibrium
D. Tachycardia
E. Exophthalmos

4.Choose the drug that does not inhibit thyroid hormone synthesis:
- Thiamazolum
- Propylthiouracil
- High iodine doses
- Carbimazole
- Dexamethasone

7.2. Learning materials for the main stage of the lesson:

Levels of enlargement of the thyroid gland (WHO, 1986)

[used in the clinical practice].

Grade of enlargem	Characteristics:
0	No goitre (the volume of elements does not move beyond the size of distal phalanx of the patient's thumb);
Ia	Goitre is detected only on palpation and is invisible when the p fully tilts the head backwards;
Ib	Palpable goitre, however, it is visible only when the patient tilts the head backwards; (including the nodule in the eve enlargement of the thyroid gland);
II	Palpable goitre. It is visible with the head in a normal position
III	A large goitre that is visible at a distance of 5 m and more

Levels of enlargement of the thyroid gland (WHO, 1994)

[used in the epidemiological studies].

Grade of enlargement	Characteristics:
0	No goitre
I	Palpable, however, invisible goitre
II	Palpable and visible goitre

Laboratory methods of study of the thyroid gland are divided into the following groups:

Markers of the functional status: thyrotropic hormone (TSH), general thyroxin, free thyroxin, general triiodothyronine, free triiodothyronine • *Markers for the autoimmune disease: anti-thyroglobulin autoantibodies, anti-thyroid peroxidase autoantibodies, TSH receptor antibodies* • *Markers for oncologic pathology: thyroglobulin, calcitonin*

Diagnostic value of thyroid hormone levels

Thyroid function	fT_3	fT_4	TSH
Preserved (euthyroidism)	Normal	Normal	Normal
Subclinical dysfunction	Normal	Normal	• elevated (subclinical hypothyroidism); • lowered (subclinical thyrotoxicosis)

Manifest thyrotoxicosis	Elevated	Elevated	Lowered
Manifes hypothyroidism	Lowered/ normal	Lowered	• elevated (primary hypothyroidism); • lowered/normal (secondary or tertiary hypothyroidism)

Iodine consumption rate (the International Council for Control of Iodine Deficiency Disorders (ICCIDD), 2005)

Contingent	The need for iodine, mcg/day
Babies at the age of 0 – 59 months	90
Children at the age of 6 - 12	120
Children over 12 and adults	150
Women across pregnancy and lactating women	250

Hypothyroidism –a clinical syndrome caused by a long-term, persistent deficiency of thyroid hormones in the human body or the decrease of its biological effect in tissues.

Classification.

According to the level of lesion:

1. Primary (thyrogenic)
2. Secondary (hypophyseal), tertiary (hypothalamic)
   a. panhypopituitarism
   b. isolated TSH deficiency
   c. disorders of the hypothalamus and pituitary gland
3. Tissue (transport, peripheral) – resistant to thyroid hormones; hypothyroidism in the event of nephrotic syndrome.

By origin:

1. Congenital:

a. Developmental abnormalities of the thyroid gland: dysgenesis (agenesia, hypoplasia, dystopia, ectopia);

b. dishormonosis: congenital enzymopathies, accompanied by thyroid hormone biosynthesis disorders; impaired sensitivity TSH;

c. congenital panhypopituitarism;
d. transient;
- iatrogenic;
- caused by mother's thyroid-blocking antibodies;
- idiopathic

6. Acquired:

- thyroiditis, (autoimmune thyroiditis, hypothyroid phase, subacute viral),
- postprocedure (thyroid surgery),
-iatrogenic (radioiodine therapy and thyrostatic drugs, thyrostatic drugs) endemic goitre

According to the course:

1. transient
2. subclinical (minimal thyroid deficiency)
3. manifest

According to the compensation status:

1. Compensated
2.Decompensated

Complications: thyrogenic nanism, encephalopathy, cretinism, polyneuropathy,
myopathy, hypothyreoid coma, sexual development disorders (delayed puberty or precocious sexual development) etc.

Diagnostic criteria:

1. Clinical:

- different stages of cognitive decline
- stunted growth (thyrogenic nanism)
- delayed puberty or precocious sexual development
- dry and pale skin
- fragile, dry hair
- swollen face, limbs, tongue
- brachycardia

2. Paraclinical tests:

- Complete blood count: anemia, sometimes accelerated erythrocyte sedimentation rate)

- Increase in cholesterol level of blood, b- lipoproteid
- Electrocardiography (ECG): sinus bradycardia (during the first months of life pulse rate may be normal), voltage decrease, conduction delay, systolic lengthening

Thyroid visualization during its ultrasound investigation.

- Hormonal diagnosis:
- In the event of subclinical hypothyroidism: high TSH level (higher than 2,5 mU/l, however, lower than 10 mU/l) with the normal level of free thyroxin and absence of clinical symptomatology.
- In the event of manifest hypothyroidism: high TSH level – higher than 10 mU/l and decrease of free thyroxin; - In the event of secondary hypothyroidism the level of TSH is within normal limits or decreased, a decrease of free thyroxin.- X-Rays of the hands: delayed skeletal maturation, epiphyseal dysgenesis – To diagnosticate autoimmune thyroiditis as the reason for hypothyroidism: anti-thyroid peroxidase antibodies (TPOAb) – 2-3 times higher than the upper normal level.

Prevention of iodine-deficient conditions and treatment of endemic goitre

Types	**Means**
Prevention:	
Mass	Table salt iodizing (40 g of potassium iodate per 1 t of salt); as an alternative – bread, water, oil iodizing;
Individual	Prescription of drugs containing iodine to the population groups or private persons with increased demand for iodine: children, teenagers, pregnant and breastfeeding women; carried out by taking medicines containing potassium iodide (Iodid-Farmak, Jodomarin), multivitamin preparations that meet the daily demand for iodine.
Treatment	
drug	• drugs containing iodine: children – 100 mcg/day, teenagers and adults (< 45) – 200–400 mcg/day for 6-12 months; • drugs containing levothyroxine (L-thyroxin, Euthyrox) in suppressive regimen providing the level of TSH

surgical	• blood plasma 0,2–0.5 mI U/L; • thyroid hormone preparations in combination with iodides (patient-specific). In the event of large goitre; mechanical compression of neck; nodular types of goitre, that do not respond to drug treatment under substantiated suspicion in malignant change.

Nodular/multinodular nontoxic goitre

Morphological classification	• colloid proliferative goitre; • follicular adenoma; • adenocarcinoma; • cystic lesion; • focal thyroid lesion..
Main clinical manifestations	Often absent. There may be observed neck discomfort, the sensation of a foreign body,visible swelling.
Complications	• compression syndrome with other organs functional disorders; • malignant change; • development of Iodide-induced thyrotoxicosis (in regions that were affected by iodine deficiency).
Diagnosis	• ultrasound investigation, including Doppler sonography; • US-guided FNAB–indicated with nodules > 1 cm; • Definition of TSH, if needed fT4, fT3 ; • scintigraphy – at suspicion on functional autonomy of the thyroid gland; • X-ray radiography, computed tomography, magnetic resonance examination – in the presence of compression syndrome.

Treatment policy	• case follow-up – control every ≈ 6 (six) months (ultrasound investigation, where required –in. methods); • suppressive therapy L-T 4 with a view to 2,0-2,5 mcg/kg/day, which in the regions affected by iodine deficiency it is worth combining with drugs containing iodine (as in the event of an endemic goitre); low efficiency in general; • surgical treatment – as indicated (see above).

Thyroiditis. Classification (clinical and morphological)

Acute thyroiditis	• *purulent;* • *nonpurulent..*
Subacute thyroiditis	• granulomatous thyroiditis; • lymphocyte thyroiditis: ○ post-partum thyreoiditis; ○ spontaneous thyroiditis
Chronic thyroiditis	• autoimmune (lymphocyte): ○ hypertrophic (Hashimoto thyroiditis); ○ Ord's thyroiditis (Idiopathic hypothyroidism); ○ focal; • fibrous (Riedel's thyroiditis (also known as Riedel struma)); • specific (tuberculosis, sarcoidosis etc).

Differential diagnosis for thyroiditis

	Acute purulent	Subacute granulomatous	Subacute lymphocytic	Autoimmune	
				hypertrophic	hypertrophic
Beginning	Acute	Acute	Acute	Gradual	Gradual
Neck pain	+++	+++	–	+/–	–
Hyperthermia	+++	++	–	–	–

Thyroid gland	Enlarged, contains, indurated acutely painful zones	Enlarged, painful, indurated, often one-sided	More often diffusely enlarged, indurated, painless	diffusely enlarged, indurated, pseudo-nodular	Does not palpate
Functional disorder	–	+++	+++	++	+++
Antithyroid antibodies	–	+	++	+++	++
Cytological Findings	Granulocyte	Multinucleate giant cells	Lymphocytes	Lymphocytes	–

Notes: (+) – seldom, (++) – often, (+++) – very often.

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Classification of thyrotoxicosis

Etiology	1. Thyrotoxicosis, associated with the hyperproduction of thyroid hormones of the thyroid gland (hyperthyroidism): • Graves-Basedow disease (diffuse toxic goitre); • functional autonomy of the thyroid gland (toxic thyroid nodule). 2. Thyrotoxicosis, associated with the hyperproduction of thyroid hormones outside the thyroid gland: • hormone-responsive thyroid cancer metastasis. 3. Thyrotoxicosis, not associated with the hyperproduction of thyroid hormones: • drug-induced thyrotoxicosis; • thyrotoxic phase of destructive thyroiditis (subacute, post-partum).
Severity	1. Subclinical (hidden, latent) – random level of TSH is lowered, the concentrations of fT_4 and fT_3 are within normal limits; clinical manifestations are generally absent.

	2. Manifest – concentration of fT_4 and/or fT_3 is elevated; manifestation range varies from oligosymptomatic to the comprehensive clinical picture. 3. Complicated, including thyrotoxic crisis.
Stage	• compensation; • subcompensation; • decompensation

Frequency of clinical signs in patients with diffuse toxic goitre

Symptom	%	Symptom	%
Goitre	85–100	Ocular symptoms	50–70
Tachycardia	85–100	Muscle weakness	60–80
Irritability	80–95	Hyperkinesis	50–80
Tremor	70–90	Increased appetite	40–60
Sweaty warm hands	60–80	Infiltrative ophthalmopathy	30–50
Hyperhidrosis	70–90	Frequent rectal discharge	20–40
Hypersensitivity to heat	70–80	Atrial fibrillation	2–10
Systolic blood pressure increase	60–80	Infiltrative dermopathy	2–3
Fatigue	80–90	Decreased appetite	≈ 23
Body weight loss	60–80	Dysmenorrhea	3–5
Thyroid bruit heard over the systolic	60–70	Gynecomastia	≈ 5
Dyspnea	60–70	Body weight gain	≈ 5

Thyroid Eye Disease

Symptoms	Signs
Dalrymple	wide open palpebral fissure
Graefe	the lagging of the upper eyelid on the downward rotation of the eye
Stellwag	sign of infrequent or incomplete blinking
Mebius	rare congenital neurological disorder
Kocher	upper eyelid retraction, a strip of sclera between eyelid margin and iris

Krause	The intensity of brightness of the eye

Treatment methods for diffuse toxic goitre

Treatment methods	**Indications**
Medicamentous: *Pathogenetic therapy* Antithyroid drugs (thyrostatic drugs)	• always taken: either as an independent method or as a preparation for radical intervention.
symptomatic medication	
β- adrenoceptor blocking agent	• usually taken along with thyrostatic drugs.
High doses of iodine	• preoperative preparation; • treatment of the thyrotoxic crisis.
Glucocorticoids	• severe course of the disease, insufficient response to thyrostatic drugs; • preoperative preparation; • endocrine ophthalmopathy.
Sedating	• taken almost always.
Surgical	• a large goitre; • compression syndrome; • substernal goitre; • severe forms of thyrotoxicosis, complicated by atrial fibrillation; • absence of steady compensation for medicamentous therapy; • liability to recurrence; • thyrostatic medication intolerance; • presence of thyroid nodule > 2 cm.
Radioactive iodine therapy	• age over 40 (in the USA and some European countries - over 18); • middle and severe course with low efficiency of medicamentous therapy; • severe complication or concomitant pathology, which substantially

	increases the risk of surgical intervention; • postsurgical recurrence of toxic goitre; • patient's refusal from surgical treatment;

Thyrostatic therapy – practical recommendations

Conditions	Means	Goal
Initial treatment ▪ moderate clinical activity; Control every 2–4 weeks.	▪ thiamazol 10–30 mg/day; ▪ carbimazole 15–40 mg/day; ▪ propylthiouracil 100–300 mg/day.	Compensation (normalization of concentrations of fT_4 and fT_3).
▪ High clinical activity; Control every 2–4 weeks.	▪ thiamazol 20–40 mg/day; ▪ carbimazole 30–60 mg/day; ▪ propylthiouracil 300–500 mg/day.	Compensation (normalization of concentrations of fT_4 and fT_3).
Maintenance therapy (12–18 months); Control every 6–12 weeks.	▪ thiamazol 2,5–10 mg/day; ▪ carbimazole 5–15 mg/day; ▪ propylthiouracil 50–100 mg/day.	Persistent euthyroidism (TSH ≈ 0,3–1,0 mIU/L).
Cessation of therapy ▪ *remission* ▪ *recurrence*	Control every 3–4 months. Curative treatment.	Persistent euthyroidism (TSH ≈ 0,3–2,0 mIU/L).

Thyrotoxic crisis is a life-threatening condition that may develop in a patient with non-compensated thyrotoxicosis. It is characterized by the marked aggravation of its clinical signs and worsening of homeostasis disorders. In the absence of adequate treatment, a patient usually dies. Infections, traumas, severe diseases or surgical treatment of diffuse toxic goitre without corresponding antithyroid drugs are usually the provocative factors.

In the event of rapid deterioration in a patient's condition with hyperthyroidism, it is always necessary to keep in mind a possible occurrence of the thyrotoxic crisis. Symptoms of the disease that caused the thyrotoxic crisis may come into the picture. In typical situations, the clinical course of thyrotoxic crisis is characterized by occurrence in stages.

1. Prodromal signs, which include agitation, insomnia (sleep hallucinations and other psychic dysfunctions), massive weight loss, intensification of muscle tremors and hyperhidrosis, fever, nausea and vomiting; most of them are caused by hyperactivity of the sympathoadrenal system.

2. Developed crisis, the defining attributes of which includes a conspicuous aggravation of thyrotoxicosis symptoms, primarily on the part of nervous, cardiovascular and digestive systems, signs of dehydration, worsening multiple organ failure and development of the comatose state.

The classic clinical picture of thyrotoxic crisis is so vivid and notable that it is enough to see once to remember for the rest of your life. It includes fever (up to 38–41 °C), hyperhidrosis, severe tachycardia, cardiac insufficiency, tremor, nausea and vomiting, diarrhea, dehydration, extreme excitation, delirium or coma. In 90 % of cases of the central nervous system, disorders occur. At the first stage symptoms of motor and psychic agitation predominate: patients are worrying, emotionally unstable (they are crying, attack, laugh), hyperactive and not goal-oriented in their behaviour, possible development of mental affection. With the progression of crisis such state changes by retardation, apathy, emotional enfeeblement, pronounced muscular weakness. It is important to remember that psychoneurological manifestations of thyrotoxic crisis have also prognostic significance, as long as their rapid progression, usually, is a premonitory symptom of comatose state. Thyrotoxic myopathy manifests as reduction of tone and rapid fatigability of the muscles of the neck, shoulder –blades, arms and legs, more seldom — face and trunk. There may be observed pains, involuntary jerks, convulsions and hypokalemic paroxysmal paralysis episodes. Excessive sweating, promptly intensifying dehydration. Symptoms on the part of the gastrointestinal tract include nausea, vomiting, decreased appetite, crampy abdominal pain, uncontrollable diarrhea and as a result - body weight loss.

Hepatomegaly and abnormal liver function tests often result from cardiac insufficiency, however, there was sometimes observed jaundice with necrosis involving hepatocytes. Heart rate (up to 140– 200 per 1 min) and pulse pressure increases, short breath occurs. Permanent atrial fibrillation may lead to congestive heart failure among people, who did not suffer from heart diseases in the past medical

history. Vascular collapse often becomes a harbinger of a patient's death.

Thyrotoxic crisis treatment protocol

1st hour	1. Provision of complete physical and mental rest. 2.In the event of agitation - Droperidol (1-2 ml solution 0,25%) intramuscularly and/or Dimedrol solution 1% 1 ml intramuscularly or Seduxen 2-3 ml solution 0,5% intramuscularly or chloral hydrate given by enema , if necessary every six hours. 3. Urgently mercazolilum 60 mg by mouth or intranasal feeding tube added to glucose 5%. 4. Hydrocortisone 200-400 mg (prednisolone 60-90 mg) intravenous bolus, cocarboxylase 200 mg added to 0,5 L glucose 5% or physiological solution by drop infusion. 5. In the event of low arterial blood pressure cordiamine 2 ml subcutaneously or Dopamin (80 mg of Dopamin soluted in 200 ml of glucose solution 5% and administered by intravenous drip-feed at the rate from 2 to 10 mcg/kg/min.). 6. Anaprilin by mouth 80 mg or 5 ml administered by slow IV injection (in the event of elevated or normal arterial pressure). 7. Reserpinum 1 ml solution 0,25% administered by slow IV injection. 8. Continuous oxygen therapy.
2nd hour	1. In 1 hour after taking mercazolilum - Lugols solution 1% 30-50 drops added to milk, in the event of vomiting Lugols solution is given by enema added to sodium chloride physiological solution or by intravenous administration 5 ml added to 0,5 L of glucose solution 5% or sodium chloride physiological solution. Instead of Lugols solution, there may be intravenously administered 5-10 ml of sodium iodide 10%. 2. Contrykal 40000 units in 50 ml of sodium chloride physiological solution by intravenous administration. 3. Ascorbic acid 50 ml of solution 5% added to 500 ml sodium chloride physiological solution by intravenous drip-feed. 4. Hydrocortisone 75-100 mg intramuscularly (in the event of low arterial blood pressure by intravenous drip-feed added to sodium chloride physiological solution). 5. In the event of non-stop vomiting by intravenous bolus administration 10 ml sodium chloride solution 10%. 6. In the event of hyperthermia - 2-4 ml Analgin solution 50%, 2 ml Dimedrol solution1% intramuscularly.

	7. Neohaemodes 400 ml, rheopolyglucin 400 ml or glucose solution 5% 500 ml by intravenous drip-feed. The total amount of fluid during the second hour -1L.
3rd hour	1. broad-spectrum antibiotic. 2. glucose solution 5% or sodium chloride physiological solution, Neohaemodes by intravenous drip-feed. The total amount of fluid during the third hour 0,5 L.
4 – 6th hour	1. Hydrocortisone 75-100 mg intramuscularly. 2. Mercazolilum 30 mg by mouth every 4 hours. 3. Anaprilin 80 mg by mouth every 4-6 hours. 4. Reserpinum 1 ml solution 0,25% intravenously every 4-6 hours. 5. Oxygen therapy.
• Later on the therapy is conducted considering the patient's state of health. Every eight hours there is repeatedly administered Lugols solution, glucocorticoids, every 4-6 hours - β - blockers. Total amount of fluid in the course of the day does not exceed 2-3 L. • In the event of crisis symptoms elimination during the second day: Mercazolilum 10-20 mg three times a day by mouth; Lugols solution in 30 drops 3 times a day added to milk; Anaprilin in 40 mg 2-3 times a day; Hydrocortisone 75 mg or prednisolone 30 mg intramusculary. • To replenish the metabolic cost there are intravenously administered nutritional substances containing carbohydrates and proteins. Thyrotoxic crisis and its consequences are treated for not less than 7-10 days until the complete elimination of clinical and metabolic disorders.	

Peculiarities of the clinical course of the morphological variant of thyroid cancer

Histological variant	**Clinical features**
Papillary	is the most common (≈ 65–80%). It progresses slowly. It often takes many years. It is multifocal in 25-30% of cases. It develops predominantly among young patients, in particular, children. Metastasizing occurs in a mainly lymphogenic way (40–50% of observations),first and foremost in cervical nodes.
Follicular	It is second in terms of occurrence (10–25%). It is clinically rather more aggressive, however, its course is usually long-term. It usually occurs among middle-aged people (maximum 50 years old). Predominantly hematogenous spread (11–20%, primarily in bones) and seldom in regional lymph nodes (5–6%).

Poorly differentiated	Frequency 4–7%. According to the morphological structure, clinical course and prognosis it falls in between differentiated and anaplastic types of thyroid cancer. It mainly occurs in patients over 50 years old, often infiltrates into adjacent tissues and is metastasizing (30–50%).
Medullary	Frequency 5–10%. There are two types of this tumor – sporadic (70–80%) and familial (20–30%). It secretes large quantities of calcitonin as well as other bioactive substances: serotonin, prostaglandin, corticotropin-like peptides etc. According to the degree of malignancy, the tumor approximates poorly differentiated thyroid cancer.
Anaplastic	It seldom occurs (1–5%). In most cases at an elderly age.It is fast-growing, early infiltrates into the adjacent organs, which is accompanied by the development of compression syndrome, wide-spreading. Only single patients live more than 6 months.

Diagnosis and treatment of thyroid cancer

Diagnosis	• ultrasound investigation of the thyroid gland and regional lymph node basins; • US-guided FNAB; • Definition of calcitonin, TSH, fT_4 , fT_3 where required ; • X-ray radiography, computed tomography (CT), magnetic resonance examination (MRT) – in the event of compression syndrome.
Differential diagnosis	Other diseases that manifest as focal abnormalities (their clinical course is the same as the course of a nodular goitre).
Treatment	In the event of highly-differentiated: thyroidectomy + radioiodine therapy + suppressive therapy L-T_4. In the event of other types: thyroidectomy (sometimes widened) + modified cervical lymphadenectomy, sometimes – external beam radiation and/or chemotherapy (partial effect).
Monitoring	• Neck ultrasound; • Determination of thyroglobulin (differentiated cancer);

	• Determination of calcitonin and/or carcinoembryonic antigen (CEA) (medullary thyroid cancer); • Control of TSH, if necessary fT_4 , fT_3 ; • scintigraphy – to verify the residual thyroid tissue and distant metastases (differentiated cancer); • if necessary – other examinations.

7.3. Control materials for the final stage of the class

Assignments (α=3)

1.A man, aged 45 years old visited an endocrinologist. He was complaining about a feeling of cervical compression at the left. Clinician-observed: enlarged thyroid caused by enlargement at the left, in the place there was palpated a nondistinctively separated solid painless nodular lump 3 cm in diameter. There was carried out a fine needle biopsy of the node. A punctate contained polygonal and spindle tumor cells. Immunocytochemically– negative response to thyroglobulin and positive response to calcitonin. Establish the diagnosis.

A. Papillary carcinoma.
B. Follicular carcinoma.
C. Medullary carcinoma
D. Anaplastic thyroid cancer
E. Tumors of other histogeneses.

2. A patient S., aged 20 years old is living in a mountainous area. She was detected the first stage of diffuse enlargement of the thyroid. Laboratorially: TSH 2,2 mIU/L (N: 0,3–4,0), free thyroxin 1,36 ng / dl (N: 0,93–1,7), anti-TPO < 10 IU/mL (N:< 100). What treatment approach in this particular case is the most pathogenetically substantiated?

A.Levothyroxine
B. Potassium iodide
C. Levothyroxine + potassium iodide
D. Surgical treatment
E. Antioxidants

3. A patient underwent surgical treatment because of diffuse toxic goitre. Before the beginning of the operation heart rate 96 beats/min, arterial blood pressure 125/70 mm Hg. The next day her state of health suddenly deteriorated: the patient was excited, there was observed mental obtundation, heartbeating, excessive sweating, vomiting. Heart rate 166 beats/min., ciliary arrhythmia. Arterial blood pressure 80/40 mm Hg.

Temperature 39^0 C. What is the most provisional diagnosis?

A. Postoperative sepsis
B. Acute respiratory failure
C. Thyrotoxic crisis
D. Hypoparathyroidism
E. Acute cardiovascular insufficiency

4. A man, aged 58 years old, in the course of palpation in the right lobe of the thyroid gland was detected an indefinite nodular mass Ø 3 in diameter, with dense consistency. In the course of ultrasound examination, it was detected that it has a decreased echogenicity, indistinct boundaries, microcalcifications and intensified blood flow. What is the most provisional diagnosis?

A. Nodular nontoxic goitre.
B. Thyroid cancer
C. Nodular toxic goitre
D. Subacute thyroiditis
E. Acute non-purulent thyroiditis

5. A patient S., aged 40 years old was detected the second stage diffuse euthyroid goitre without compression symptoms. There are no intercurrent diseases. Which of the following treatment methods is the most reasonable?

A. Glucocorticoids
B. Immunomodulators
C. Surgical treatment
D. Thyroid hormones
E. Antioxidants

6. A patient S., aged 52 years old is complaining about body weight gain, weakness faecal retention, memory impairment. Objective findings: dry skin, mild facial and limb swelling. Heart rate 60 beats per minute, arterial blood pressure 110/60 millimetres of mercury. Ultrasound investigation: the thyroid gland volume 2,6 c.m., decreased echogenicity, inhomogeneous structure. Laboratorially: TSH 23,2 mIU/L (N: 0,3–4,0), thyroglobulin (TG) and thyroperoxidase (TPO) antibodies are moderately increased. It is the most probable that the patient has been suffering from

A. Endemic goitre, euthyroidism
B. Autoimmune thyroiditis (Hashimoto disease) hypothyroidism
C. Autoimmune thyroiditis (atrophic), hypothyroidism
D. Hypothyroidism caused by iodine deficiency
E. Ligneous thyroiditis

7. A patient is complaining about annoyance, hyperhidrosis, hand tremor, heartbeats, bodyweight loss with preserved appetite. Enlarged thyroid gland up to the second stage, elastic, painless. The following symptomatology is best matched to:
A. diffuse toxic goitre
B. neurasthenia
C. autoimmune thyroiditis
D. hypothyroidism
E. hypoparathyroidism

8. A patient underwent surgical treatment because of diffuse toxic goitre. Before the beginning of the operation heart rate 96 beats/min, arterial blood pressure 125/70 mm Hg. The next day her state of health suddenly deteriorated: the patient was excited, there was observed mental obtundation, heartbeating, excessive sweating, vomiting. Heart rate 166 beats/min., ciliary arrhythmia. Arterial blood pressure 80/40 mm Hg. Temperature 39^0 C. What is the most provisional diagnosis?
A.Postoperative sepsis
B.Acute respiratory failure
C.Thyrotoxic crisis
D.Hypoparathyroidism
E.Acute cardiovascular insufficiency

9.In the comprehensive treatment of the thyrotoxic crisis there are prescribed the following drugs except for…

A. Propranolol
B. Lugols solution
C. Adrenalin
D. Cordiamin
E. Glucose solution 40%

15. Which of the following signs are peculiar to thyrotoxic crisis?
A. Hypothermia
B. Thyroid hormones level decrease
C. Pretibial myxedema .
D. Increase of cortisol level in blood.
E. Tachycardia
F. Decrease calcium blood level.

16. What is glucose intolerance in the event of thyrotoxic crisis stipulated by?

A. Excessive glucose uptake in the intestinal tract.
B. Intensified glycolysis.
C. Acceleration of gluconeogenesis.
D. Contra-insulin effect of thyroid hormones.
E. Pancreas excretory function disorder.

17. Which of the following drugs tends to slow down the transformation of thyroxin into triiodothyronine in the treatment of thyrotoxic crisis?

A. Propranolol
B. Noradrenaline
C. Thiamazol
D. Prednisolone
E. Potassium iodide

18. To the hospital ward there was admitted a patient aged 39 years old. She was diagnosed with Paroxysmal Ciliary Arrhythmia. In the course of examination: asthenic consistency, watery skin, stage 3 diffuse goitre, ciliary arrhythmia, heart rate up to 200 per minute, pulse deficit up to 40, arterial blood pressure 180/60 mm Hg. It is known from the past medical history that she has been suffering from the disease for about a year. She gradually became weaker, lost weight (20 kg a year), started suffering from sweating and tachycardia. Psychentonia caused the occurrence of Paroxysmal Ciliary Arrhythmia. What is the provisional diagnosis?

A. Thyrotoxic crisis
B. Stage III toxic diffuse goiter in the course of decompensation, ciliary arrhythmia.
C. Cardiac type vegetovascular dysfunction
D. Hypertensic crisis
E. Miocardiosclerosis, ciliary arrhythmia.

19. A patient Ts., aged 55 years old, is complaining about dyspnea with a light load, persistent heartbeats, sweating, massive weight loss, hand tremor. In the course of examination: heart rate 128 beats per min, arrhythmic pulse, arterial blood pressure 160/70 mm Hg, intensified I cardiac sound, accentuation of II sound over the pulmonary artery. ECG: ciliary arrhythmia, T deflection is smooth in all chest leads. Blood count and erythrocyte sedimentation rate are within normal limits. Diagnosis?

A. coronary heart disease, atherosclerotic cardiosclerosis, ciliary arrhythmia. chronic heart failure (CHF) I.
B. infectious-allergic myocarditis, ciliary arrhythmia, chronic heart failure (CHF) I.

C. thyrocardiac disease, ciliary arrhythmia, chronic heart failure (CHF) I.
D. acute diffuse myocarditis, chronic heart failure (CHF) I.
E. thyrotoxic crisis

20. A patient aged 37 years old was taken to resuscitation department. According to relatives, for a year (except for the last two months) he was taking thiamazole. The general state of the patient is critical. Sudden psychomotor agitation. Warm waterly hyperemic skin, body temperature $39,4^0$ C, shallow breathing. Heartbeat 180 beats/min, ciliary arrhythmia, arterial blood pressure 100/40 millimeter of mercury, preprandial glycemia 5,6 mmol/L, acetone in urine. What is the provisional diagnosis?

A. Thyrotoxic crisis.
B. Hyperosmolar coma.
C. Hypoglycemic coma.
D. Hyperlactacidemic coma.
E. Ketoacidotic coma

21. A patient underwent surgical treatment because of diffuse toxic goitre. Before the beginning of the operation heart rate 96 beats/min, arterial blood pressure 125/70 mm Hg. The next day her state of health suddenly deteriorated: the patient was excited, there was observed mental obtundation, heartbeating, excessive sweating, vomiting. Heart rate 166 beats/min., ciliary arrhythmia. Arterial blood pressure 80/40 mm Hg. Temperature 390 C. What is the most provisional diagnosis?

A. Postoperative sepsis
B. Acute respiratory failure
C. Thyrotoxic crisis
D. Hypoparathyroidism
E. Acute cardiovascular insufficiency

Assignment 1. A woman, aged 44 years old is complaining about apathy, slowness, memory impairment, chills, dry skin, fecal retention, facial swelling. She has been considering herself ill for a year. Objective findings: temperature 36,0°C, heart rate – 56 beats per minute, arterial blood pressure – 110/80 mm Hg ECG: voltage reduction, a decrease of P wave and flattening of T wave. Enlarged thyroid gland because of enlargement of all the regions is visible with the normal position of the neck. It is moderately indurated and non-homogenous, painless. Laboratory examination: free thyroxin – 7,5 pmol/l (N: 10–23), TSH – 16,4 mIU/L (N: 0,3–4,0), TPO antibodies – 640 mIU/L (N: <100). Ultrasound investigation: diffusely decreased echogenicity, markedly inhomogeneous structure, with no tissue masses.

- Formulate the diagnosis (nosology, the nature of structural and diffuse changes of the thyroid gland).
- Define and explain the optimal treatment policy.

Assignment 2. A patient, aged 35 years old in the course of medical examination was detected a nodule in the right thyroid lobe. No complaints. Negative family history. From the past medical history, it is known that as a teenager he was undergoing numerous X-ray examinations because of a cervical spine injury.

Objective findings: the lower part of the right lobe takes the nodular mass ≈ 2,5 cm in diameter. It has a dense consistency, is nodular, movable and painless. The left lobe is not enlarged. It is soft and homogeneous. Cervical glands do not palpate.

- What is the most provisional diagnosis?
- What tests he must be referred for and which one is the most informative?

Protocol No. 3 of clinical considerations for a patient

Patient's full name _____

Age _____ Occupation_____

patient's complaints _____

past medical history _____

Patient's life history _____

Results of physical examination of the patient: _____

Provisional diagnosis: _____

What diseases may require the performance of differential diagnosis?

Examination plan: _____

Results of laboratory and instrumental examination:

Substantiation of clinical diagnosis: _____

Clinical diagnosis: _____

Prior disease:

Complications: _____

Intercurrent diseases: _____

_____
_____
_____
Prognosis: _____
_____
_____
Workng capacity: _____
_____
_____
_____
Treatment: _____
_____
_____
_____
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_____
Medicamentous therapy: _____
_____
_____
_____
_____

Marking of mastering practical skills

Order No.	Skills and procedures	Signature of the student/ adviser
1	Practical skills	
1.1.	Know how to interview, perform a physical examination of a patient with thyroid disorders	
1.2.	Be able to analyze the laboratory and instrumental examination data in patients with pathology of the thyroid gland	
1.3.	Know how to prescribe medication in the event of patients with thyrotoxicosis syndrome, hypothyroidism of thyroiditis and iodine deficiencies.	
2.	Emergencies	
2.1	Be able to provide assistance in the event of thyrotoxic crisis	

Theme 4: Management of a patient with arterial hypertension syndrome in the endocrine practice. Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with arterial hypertension. Treatment of a patient with adrenal insufficiency.

1. Topicality.

Arterial hypertension continues to be one of the most immediate problems in medicine. In Ukraine, up to 21% of the adult population suffer from this disease. High frequency of complications leads to the decrease of life duration and increase of disability of the population. Therefore early diagnosis and corresponding therapy before the occurrence of the complications remain the top priority problem. The medical and social significance of the program justified the adoption of the National program of prevention and treatment of arterial hypertension in Ukraine.

In practical work, physicians often face difficulties in performing differential diagnoses of arterial hypertension with different etiology. As long as arterial blood pressure is controlled and maintained using the range of endocrine mechanisms, the role of hormones, involved in its regulation, the most clearly manifests in the event of their excess or deficiency. Arterial hypertension symptoms are the most specific to adrenal pathology (korticosteroma, phaeochromocytoma, aldosteronoma) and pituitary-hypothalamic areas of the human brain (Cushing's disease, diencephalic syndrome). According to epidemiological studies, arterial hypertensions, caused by primary aldosteronism, are defined in 0,3-1,5% cases, Cushing's disease – 0,1-0,6%, phaeochromocytoma – 0,1-0,3%, thyroid pathology – 0,2-3,3%. Arterial hypertension, caused by diabetic nephropathy, occurs in 20-40% of patients with diabetes mellitus, which in the general structure equals to 1,8-4,2%.

2 Learning goal.

To teach the students how to manage patients with endocrine arterial hypertension syndrome, apply in practice modern diagnostic, treatment and prevention procedures related to the development of complications resulted from endocrine arterial hypertension under inpatient and outpatient treatment.

To become acquainted with endocrine pathology accompanied by the increase in arterial pressure (α=1).

The student must know (α=2**):**

- The definition of the concept of endocrine hypertension, classification.
- Etiology, the pathogenesis of arterial hypertension (AH) of adrenal genesis.
- The clinical picture of phaeochromocytoma, Conn's syndrome (primary aldosteronism), Cushing's disease.
- Etiology, the pathogenesis, clinical picture of arterial hypertension of pituitary-hypothalamic genesis (Cushing's disease).
- Etiology, the pathogenesis, clinical picture of parathyroid arterial hypertension (hyperparathyroid).
- Etiology, the pathogenesis, clinical picture of thyroid arterial hypertension (hyperthyreosis).
- Etiology, the pathogenesis, clinical picture of arterial hypertension in patients with type 1 diabetes mellitus caused by diabetic nephropathy, type 2 – caused by insulin resistance and diabetic nephropathy).
- Management (examination, treatment) of patients with arterial hypertension syndrome of endocrine genesis.
- Etiology, the pathogenesis, clinical picture, diagnosis, differential diagnosis of acute adrenal insufficiency.
- Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with arterial hypertension.

The student should be able to (α=3**):**

- Interview and examine patients with arterial hypertension syndrome.
- Measure and evaluate the arterial hypertension level.
- Work-up differential diagnosis of arterial hypertension syndrome in patients with endocrine diseases.
- Draw up a plan of examination of a patient with arterial hypertension syndrome, justify the application of the main examination techniques, define indications for their performance.

- Know how to test and evaluate the functional test (low- and a high-dose dexamethasone suppression tests, spironolactone loaded test).
- Reveal, justify and formulate a diagnosis of the underlying disease arterial hypertension is a symdrome of based on analysis of clinical, laboratory findings and instrumental methods of examination
- Prescribe the corresponding treatment for symptomatic hypertension.
- perform diagnosis and differential diagnosis of acute adrenal insufficiency.
- Prescribe and provide treatment of acute adrenal insufficiency
- Demonstrate that the medical professional has moral and deontological principles.

3. Educational goal.

Attract attention to and form the sense of responsibility in students, who will become different types of doctors for the timely detecting, diagnosis, differential diagnosis and the treatment of diseases the course of which includes arterial hypertension as well as timely diagnosis, differential diagnosis and treatment of acute adrenal insufficiency.

4. 4. Interdisciplinary integration:

Subjects	*To know*	*To be able to*
Previously studied subjects		
Systemic Anatomy	the topography, the vascularization of endocrine glands	
Hominal Physiology	function of endocrine glands	
Histology	the histologic structure of endocrine glands,	
Biochemistry	hormone metabolism	
Pathoanatomy	morphological changes in endocrine glands,	
Pathophysiology	pathogenesis of diseases accompanied by arterial hypertension and acute adrenal insufficiency	
Subjects that will be studied later		Perform a clinical review, prescribe the corresponding diagnostic testing, consultations by allied health professions to verify the diagnosis
Therapy	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diseases accompanied by arterial hypertension and acute adrenal insufficiency	
Pediatrics	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of diseases accompanied by arterial hypertension and acute adrenal insufficiency in children	
Surgery	Peculiarities of the course of diseases accompanied by arterial hypertension and acute adrenal insufficiency, in the event of surgical pathology – timely diagnosis and management of such patients	
Obstetrics & Gynaecology	Peculiarities of the course of diseases accompanied by arterial hypertension and acute adrenal insufficiency during pregnancy, timely diagnosis and surveillance of such patients	
Neurology	Clinical picture, diagnosis, differential diagnosis, treatment, prevention of neurological complications of diseases accompanied by arterial hypertension and acute adrenal insufficiency	
Intersubject integration	Modern methods of patients' examination, in particular, laboratory, instrumental, adequate treatment strategy.	Order the adequate treatment

7. Training subjects:

- Classification of arterial hypertension .
- The concept of arterial hypertension, caused by endocrine pathology.
- Etiology, the pathogenesis of arterial hypertension (AH) of adrenal genesis.
- Clinical manifestations of phaeochromocytoma, Conn's syndrome (primary aldosteronism), Cushing's disease.
- Etiology, the pathogenesis, clinical picture of arterial hypertension of pituitary-hypothalamic genesis (Cushing's disease).
- Etiology, the pathogenesis, clinical picture of parathyroid arterial hypertension (hyperparathyroid).
- Etiology, the pathogenesis, clinical picture of thyroid arterial hypertension (hyperthyreosis).
- Etiology, the pathogenesis, clinical picture of arterial hypertension in patients with diabetes mellitus caused by diabetic nephropathy.
- Management (examination, treatment) of patients with acute adrenal insufficiency .

6. Plan and organizational structure of the class

(see «Introduction»)

7. Materials and methodological support of the class

7.1 Materials of the preparatory stage of the class

Tests (α=2)

1. It is not peculiar to the course of arterial hypertension in patients with phaeochromocytoma.:
   A. Paroxysms of full-blown arterial hypertension up to 200-300 mm Hg with simultaneous increase of systolic and diastolic arterial blood pressure
   B. Effective therapy with ordinary hypertensive drugs
   C. Effect of α- adrenoceptor blocking agent .
   D. Crisis ends with much urine flow
   E. Crisis may be accompanied by neurovegetative syndrome

2. arterial hypertension develops in the event of all the diseases but:
   A. Conn's syndrome
   B. phaeochromocytoma
   C. Cushing's syndrome
   D. adrenal insufficiency
   E. Cushing's disease

3. To detect Conn's syndrome there may be made:
   A. spironolactone test
   B. low-dose dexamethasone suppression tests
   C. high-dose dexamethasone suppression tests
   D. adrenocorticotropic hormone stimulation test
   E. prednisolone suppression test

4. What arterial blood pressure is the most peculiar to uncomplicated diffuse toxic goitre?
   A. Increased systolic and decrease diastolic arterial blood pressure
   B. Increased systolic and diastolic arterial blood pressure
   C. Increased diastolic and normal systolic arterial blood pressure
   D. Increased diastolic and decreased systolic arterial blood pressure
   E. Decreased systolic and diastolic arterial blood pressure

5.Choose the preparation class («the gold standard») for the decrease of arterial hypertension level in a patient with diabetic nephropathy:
   A. Angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin receptor antagonist
   B. selective agonist of imidazoline receptors
   C. β- adrenoceptor blocking agents
   D. calcium channel antagonists
   E. thiazide diuretics

7. Drug therapy to treat arterial hypertension in patients with primary aldosteronism includes:
   A. Verospiron (spironolactone) 200-400 mg/d
   B. Hydrochlorotiaside100-200 mg/d
   C. Indapamide 2,5-5 mg/d
   D. Chlortalidone 25-50 mg/d
   E. Furosemide100-200 mg/d

8. Choose the drug class from among «first-line drugs» to decrease arterial hypertension level in patients with Basedow's disease:
   A. Angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin receptor antagonist
   B. Beta-blocker
   C. Selective alpha-adrenoblockers
   D. Centrally acting drugs
   E. Vasodilator

9. Arterial blood pressure level increase in the event of dyshormonal cardiomyopathy is accompanied by all the symptoms but…:
   A. Arterial blood pressure increase
   B. Cardialgia

C. Heart beat
D. Orthostatic hypotension
E. Changes in ECG

10.Which of the following symptoms is not peculiar to Cushing's disease?
A. Obesity
B. Osteoporosis
C. Arterial hypertension
D. Lymphopenia
E. Arterial hypotension

11. What levels of 17- ketosteroids (KS) and 17-ketogenic steroids (KGS) (urinary glucocorticoid metabolites) will confirm Cushing's disease after taking a high-dose dexamethasone suppression test?
A. First high, however, significantly decrease after the test
B. First lowered, however, significantly increase after the test
C.First high, and actually do not change after the test
D. First lowered, and actually do not change after the test
E. First within normal limits, however, significantly increase after the test

7.2. Materials and methodological support of the class:

Acute adrenal insufficiency (Friderichsen-Waterhouse syndrome)

Etiology: acute adrenal insufficiency may be caused by acute thrombosis or adrenal artery embolization, adrenal apoplexy. This complication usually results from acute infection processes (meningococcaemia, pneumococcal and staphylococcal bacteremia, diphtheria, poliomyelitis), some systemic diseases (polyarteritis nodosa, systemic lupus erythematosus). Systemic adrenal hemorrhage may occur in the event of a difficult or complicated delivery, in the event of acute disseminated intravascular coagulopathy syndrome. Its course may be similar to the Addisonian crisis – acute decompensation of chronic primary and secondary adrenal insufficiency, congenital adrenal hyperplasia (adreno-genital syndrome).

The clinical course of acute adrenal insufficiency:

1. Cardiovasculare – dominates collapse, hypotonia, the manifestation of cardiovascular inefficiency: cyanosis, hypothermia, muffled heart sounds, the pulse of poor volume.

2. Entero-intestinal – food refusal, nausea, vomiting (often non-stop), diarrhea, extended spastic stomachache, symptoms and signs of the acute abdomen».

3. Neuropsychic – adynamia, asthenia, depression, delirium with visual hallucinations. Possible meningeal symptom, convulsions similar to epileptic ones. Gradually there is impaired consciousness: retardation, dimout, stupor. Caused by the development of brain edema.

Friderichsen-Waterhouse syndrome develops faster, in some hours, its proceeds with lightning speed.

Diagnostic criteria:

1. Electrolyte disorders: hyperkalemia - more than 5 mmol/L, hyponatremia - less than 140 mmol/L, hypochloremia - less than 90 mmol/L. The correlation between sodium and potassium exceeds 20.
2. Hormone disorder: cortisol and aldosterone level decrease in the event of adrenocorticotropic hormone level increase. Because of the instantaneous development of acute state there is usually no time to determine the level of different hormones.
3.Changes in general clinical tests: leucocytosis, eosinophilia, hematoglobulin level increase, hypoglycemia. ketonuria, proteinuria, cylindruria (hyaline and granular casts), leucocytosis, microhematuria.
4. Symptoms of hyperkalemia according to figures provided by ECG.

Treatment of Friderichsen-Waterhouse syndrome:

1. Long-term corticosteroid therapy.
2. Intravenous fluid therapy
3. Etiotropic treatment – antibacterial, antitoxic.
4. Symptomatic treatment – cardioprotector, hepatoprotective agent, vitamins, sedating and other medication if medically required

DIAGNOSTIC PROCEDURE IN HYPERCORTICOIDISM
(diseases and Cushing's syndrome)

Diagnostics	**Physical examination** **Signs hypercorticoidism:** • persistent hypertension (diastolic) with resistance to antihypertensive drugs; • Headache, visual deterioration; • Dysplasia in obese patients (apron belly, facial fullness ("moon red face"), thin extremities, dowager's hump); • mottled skin, thin skin with pink stretch marks and pustular skin conditions; • dysmenorrhea, hirsuties, lowering of lowering; • Myocardiodystrophy with signs of circulatory inefficiency; • Osteoporosis (bone ache, pathologic fracture). **Laboratory tests** **1. Blood count:** ↑ red blood cells ↑ leucocytes ↓ lymphocytes ↓ eosinophils ↑ blood sugar ↓ potassium ↑ sodium ↑ alkaline phosphatase **2. Urinary test:** proteinuria, leukocyturia, glycosuria **3. Determination of the content of 17-pregnenoldione and 17- ketosteroids in daily urine:** (increased excretion) **4. Hormonal studies** ↑ Cortisol (Blood) adrenocorticotropic hormone: within normal limits or increased in the event of Cushing's disease, decreased in the event of the syndrome **Functional loading tests:** -low-dose dexamethasone suppression test (2mg/day x 2 days) - high-dose dexamethasone suppression test(8 mg/day x 2 days) **Additional study methods** Lumbar spine X-ray imaging (L1–L4): (osteoporosis), suprarenal gland ultrasonic monitoring, Computed tomography, pituitary gland and suprarenal gland magnetic resonance examination.
Treatment	1. Pathogenetic conservative: - radiation therapy - hypothalmic-pituitary-adrenal secretion inhibitor (bromergocryptin, cyproheptadine, reserpine) - suprarenal cortex steroidogenesis inhibitors: chloditane, mitotane 2. Symptomatic treatment (arterial blood pressure correction): - ACE inhibitor, sartans - diuretics: thiazide, nonthiazide, loop in combination with aldosterone antagonist (spironolactone) 3.Surgical treatment: a) Cushing's disease - pituitary transsphenoidal adenomectomy; in the event of large tumor or diffuse hyperplasia – transsphenoidal total hypophysectomy b). primary adrenal Cushing's syndrome: - adenoid tumors and carcinoma (removal of tumor) -in the event of hyperplasia - bilateral adrenalectomy - ectopic ACTH-dependent Cushing's syndrome: tumor extirpation, if managed to find

DIAGNOSTIC PROCEDURE IN ALDOSTERONOMA
(primary hyperaldosteronism, Conn's syndrome)

Diagnostics	***Physicalен examination*** ▪ arterial hypertension syndrome (AH): arterial blood pressure ↑, headache, visual deterioration ▪ neuromuscular syndrome: myasthenia, paresthesia, paresis, muscle weakness, convulsions ▪ Potassium panic kidney syndrome: Excessive thirst, polyuria, nycturia, development of chronic pyelonephritis ***Laboratory tests*** **1. Urinary test:** hyposthenuria, alkaline reaction**,**

	polyuria **2. Biochemical blood assay:** hypokalemia < 3,5 mmol/L (it is determined three times), hypernatremia **3. endocrine profile** ↑ aldosterone >120 pg/ml ↓ renin **4. Functional loading tests:** Verospiron (spironolactone) loading test 100 mg 4 times a day for 3 days. The level of potassium increases > 1 mmol/L. ***Additional study methods*** ECG (brachycardia, arrhythmia, AV delay, Q–T lengthening, U pathologic, ST depression,T-wave inversion. Adrenal ultrasound investigation (adenoid tumor or adrenal hyperplasia), computed tomography, adrenal magnetic resonance examination (adrenal adenoma).
Treatment	1. Conservative treatment (is given under the condition of bilateral hyperplasia of the suprarenal cortex, if the surgical treatment cannot be provided, as well as when after the surgical intervention hypertension remains): – to decrease arterial blood pressure there is intravenously administered Dibasol 8-12 ml 1%, magnesium sulphite – 10-20 ml 20%. For arterial blood pressure flashing down – administer Clophelinum - 1,0 ml 0,01%. In the absence of effect – take Pentamine 2-3 ml 5%. – to compensate for potassium deficiency there is administered potassium chloride solution. In the event of severe hypokalemia, it is necessary to administer up to 10-14 g of potassium chloride during a day. – aldosterone blockers (spironolactone; verospiron) at a dose of 200-400 mg/d followed by the decrease of dose to 50 mg/day. – calcium antagonists (amlodipine, nifedipine), ACE inhibitors (captopril, enalapril, lisinopril) are added if the above-specified treatment given during 2 weeks has no effect. 2. Surgical treatment is given under the condition of diagnosticated aldosteronoma (removal of affected adrenal). Preoperative preparation of a patient must include the prescribed aldosterone antagonist (spironolactone; verospiron) at a dose of 400-600 mg/day for 2-3 weeks

DIAGNOSTIC PROCEDURE IN PHEOCHROMOCYTOMA

Diagnostics	***Physicaleи examination*** arterial hypertension syndrome (AH): (Peroxisomal (classical) form, stable with crises, stable crises free form): - paroxysm of full-blown arterial hypertension up to 200-300 mm Hg with simultaneous increase of systolic and diastolic arterial blood pressure (crisis occurs spontaneously; it is sometimes promoted by exercise or emotional stress, hypothermia, abdominal palpation, it lasts during several dozens of minutes. Attack suddenly stops, arterial blood pressure decreases to the normal figures or lower, there is registered sleepiness, warming and pinky skin, polyuria; – There is no effect from treatment with ordinary hypotensive intermediates. The only effect is from α- adrenoceptor blocking agents. ▪ cardiac syndrome during a crisis Heartbeat, cardiac pain, dyspnea, rhythm disorder (tachycardia, extrasystole, wandering pacemaker). ▪ Abdominal syndrome during a crisis Epigastric pain, nausea, vomiting, excessive salivation, which is changed for dry mouth, diarrhea. ▪ neurovegetative syndrome during a crisis The feeling of fear, anxiety, internal tremor, chill, diaphoresis, face and chest skin pallor, headache, polyuria. ***Laboratory tests*** **1. Blood count during a crisis:** leucocytosis, hyperglycemia. **2. Urinary test** *Paroxysmal form:* Urine for three hours after the crisis for vanillylmandelic acid and catecholamines. *Permanent form:* Daily urine for vanillylmandelic acid and catecholamines 2 times (3 days before determining there are discontinued all the medical preparations) **3. Functional loading tests** Histamine test: administer 0,1 ml histamine solution. 0,1% – it is considered positive in the event of arterial blood pressure increase by 30-40 millimeter of mercury during 2-3 min. Cerucal test: there is intravenously administered Cerucal 2,0 ml added to normal saline - it

	is considered positive in the event of systolic pressure increase by more than 40 millimeter of mercury, diastolic – by 40 millimeter of mercury . Tropaphenum, prazosin test:administration of tropaphenum 10 mg in the event of phaeochromocytoma decreases arterial blood pressure by 60-40 millimeter of mercury. ***Additional study methods:*** Adrenal ultrasound investigation and computed tomography (adrenal adenoma (90%) computed tomography of extraadrenal tumors (10%): sympathetic ganglia, retroperitoneal space, mediastinal space, lower pelvis, plexuses of the abdomen.
Treatment	1. Conservative treatment: Treatment in the period between crises: - nonselective blockers of α - adrenoreceptors (phenoxybenzamine) – initial dose 10 mg/d, further increase up to 20-120 mg/d; - selective blockers α_1 – adrenoreceptors: prazosin (4-20 mg/d), doxazosin (1-16mg/d) - alpha+beta – adrenoblockers : Carvedilol (625-50 mg 2 times/day), labetalol (50-200 mg/ day); - to increase therapeutic effect there are prescribed ACE inhibitors (enalapril), calcium antagonists(amlodipine). 2.Surgical (adrenalectomy) Preoperative preparation of a patient must include the prevention of hypertensic crises: α - adrenoblockers (Regitinum, Phentolaminum, Cardura, Dalfaz, Prazosin, Doxazosin). In the event of severe tachycardia, there are prescribed β - adrenoblockers.
Emergency assistance in the event of pheochromocytoma crisis	I. Create a patient calm conditions of staying at a hospital (excluding exercise or emotional stress, hypothermia, excessive heat), elevate the head of a bed for orthostatic pressure reduction. II. To decrease the arterial pressure (AT): **1.** Alpha-adrenoceptor blocking agent: 2-4 mg phentolamine hydrochloride or 1-2 ml Tropodifene solution 2 $^0/_0$ concomitantly added to 20,0 isotonic sodium chloride solution. Then the medication is administered every 5 minutes until the arterial blood pressure reduces,and in the event of ints decrease and stabilization there is administered intramuscularly at the same dose every 2-4 hours with gradual crossover to tablets of alpha adrenoreceptors selective blockers: Prazosin 20 mg/d, Doxazosin 16 mg/d, Kamiren 16 mg/d, Cardura 16 mg/d, Dalfaz 16 mg/d. **2.** In the event of severe stable tachycardia (more than 120 beats/min), arrhythmia there is administered beta–adrenoblockers by intravenous infusion: propranolol intravenously, by drop infusion 2-5 mg at a speed of 0,1 mg/min; Esmolol by intravenous drop infusion 250-500 mcg/kg/min., then 50-100 mcg/kg/min for 4 minutes; Visken intravenously 5 ml (1 mg) added to glucose solution 20ml by stream infusion; Alpha-beta – adrenoblocker labetalol 20 mg by bolus injection during 2 min. Then repeatedly administer every 10 minutes 20-80 mg until getting the result (total maximum dose – 300mg). In the event of drop infusion, labetalol 200 mg is added to 200 ml glucose solution 5 $^0/_0$ and administered at a speed of 1-2 ml/min. III. In the event of collapse development (adrenaline-secreting phaeochromocytoma) - noradrenaline by intravenous drop infusion (2-4 mg, added to 1000 ml glucose solution $5^0/_0$) IV. In the absence of treatment effect with alpha – and beta adrenoblockers during 3 hours, there is indicated emergency operation – removal of adrenal adenoma or extraadrenal chromaffin tumor.

Protocol of clinical considerations for a patient

Patient's full name _____
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Age _____ Occupation_____
patient's complaints _____
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past medical history _____
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Patient's life history _____
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Results of physical examination of the patient:
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Provisional diagnosis: _____
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What diseases may require the performance of differential diagnosis?
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Examination plan: _____
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Results of laboratory and instrumental examination:
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Substantiation of clinical diagnosis:
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Clinical diagnosis: _____
Prior disease:
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Complications:
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Intercurrent diseases:
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Prognosis: _____
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Working capacity:
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Treatment:
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Medicamentous therapy: _____
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Arterial blood pressure control: _____

Marking of mastering practical skills

Order No.	Skills and procedures	Signature of the student/ adviser
1	Practical skills	
1.1.	Know how to interview, perform a physical examination of a patient with arterial hypertension syndrome	
1.2.	Be able to analyze the laboratory examination data	
1.3.	Know how to prescribe chromotherapy in the event of patients with arterial hypertension syndrome.	
2.	Emergencies	
2.1	Be able to provide assistance in the event of pheochromocytoma crisis	

7.3.Control materials of the final stage of the class

Assignments (α=3)

1. A patient K., aged 5 years old has been complaining about diarrhea, decreased appetite and increased demand for salt, sleep disorder. A boy is talking to friends who are absent at the moment. Clinician-observed: brown hyperpigmented skin on elbows and knees; arterial blood pressure 75/40 mm Hg., Ps106 beats/min. His physical growth and sexual development are retarded. The level of Na – 126 mmol/L, chlorides 74 mmol/L, cortisone 80 nmol/L(N 130 – 360). What is the most provisional diagnosis?

A. Chronic adrenal insufficiency.
B. Acute adrenal insufficiency.
C. Bacterial food poisoning.
D. Acute pancreatitis.
E. Acute cholecystitis.

2. A patient suffering from meningococcal meningoencephalitis suddenly started suffering from decreased arterial blood pressure, resistace to sympathomimetic, brachycardia, nausea, vomiting. What is the provisional diagnosis?

A. Acute adrenal insufficiency (Friderichsen-Waterhouse syndrome)
B. Internal hemorrhage
C. Bacterial food poisoning
D. Addisonian crisis
E. complete atrioventricular block

3. A woman aged 46 years old after the near-total resection of the thyroid gland started suffering from the increased arterial blood pressure up to 145/100 mmHg, facial paresthesia, paresthesia in arms and legs, breathing disorder, retrosternal pain, gastrocnemius muscle spasms. What medicine should be prescribed to the patient?

A. Calcium preparations
B. Neuroleptic agent
C. Tranquilizer
D. Nitrates
E. Beta-blockers

4.A man aged 45 years old visited a therapeutist. He was complaining about chest pain, increased arterial blood pressure up to 150/ 95 mmHg, visual impairment, enlargement of hands and feet. What disease must be excluded ?

A. Cushing's disease
B. Acromegaly
C. Hyperparathyroidism
D. Hypothyroidism
E. Paget's disease

5.A woman R. aged 43 years old, is complaining about heartbeat, heart disorder, short breath in the event of insignificant physical exercise, legs swelling, weight loss. It is seen from the past medical history that when she was pregnant at the age of 20 she was suspected the development of rheumatic heart disease. In recent years she was followed up by a therapeutist because of increased arterial blood pressure. Clinician-observed: the condition is relatively satisfactory. Poor nutrition. Arrhythmic heart rate 84 beats/min., arterial blood pressure 160/95 mmHg. Arrhythmic, muffled heart sounds, systolic murmur, heart rate 120 beats/min. Laboratory: blood counts – white blood cells - $4{,}5 \cdot 10^{9}$, blood sedimentation rate – 5 mm/hour, thyrotropin blood level is below normal, T_3 level is above normal. ECG – ciliary arrhythmia, tachysystole form. What is the most provisional diagnosis?

A. Diffuse toxic goitre
B. Rheumatism, mitral valve regurgitation
C. Coronary artery disease, diffuse cardiosclerosis with rhythm disorder
D. hypothyroidism, endocrine genesis myocardiodystrophy
E. Postmyocarditis cardiosclerosis

6. A patient aged 47 years old is undergoing medical examination because of frequent episodes of arterial blood pressure increase 280/140 mm Hg in recent months. Family medical history related to arterial hypertension is negative.In the morning she is complaining about intensive headache, heartbeat, anxiety. Arterial blood pressure 300/160 mm Hg, heart rate– 128 beats/min. Earlier in the event of similar states there was registered hyperglycemia, leucocytosis, after the removal of crisis there is reported polyuria. Choose preparation class to remove this hypertensive crisis:

A. **α**-adrenoblockers
B. β-adrenoblockers
C. Calcium antagonists
D. Angiotensin-converting enzyme inhibitors
E. Diuretic

7. A patient V., aged 18 years old was referred by the military commissariat to be determined the medical fitness. Clinician-observed: man's body proportion, height 175 cm, weight 105 kg, obesity, fat tissue is distributed relatively evenly, with the predominant fat deposit on face, abdomen, limbs, there is determined bilateral fat deposit, the skin of hips, shoulders, abdomen is covered with a significant amount of pale pink linear atrophy. Heart rate 78 beats per minute, arterial blood pressure 155/90 mmHg. Internal organs are within normal limits. External genital organs were properly formed, conform with the age. In the X-ray picture of the Turkish saddle – there are not observed any destructive changes. Prolactin, cortisone, luteinizing hormone, follicle-stimulating hormone, testosterone are within normal limits. What is the reason for the occurrence of arterial hypertension in a patient?

A. Adiposo-genital dystrophia
B. Prolactinoma
C. Cushing's disease
D. alimentary-constitutional type
E. Biemond syndrome

8. In the endocrinology department there is examined a woman aged 42 years old because of sudden weight gain (20 kg for the last 6 months), arterial blood pressure increase, menstrual disorder, headache. The above-described symptoms appeared after the prior virus infection. On outpatient basis, there was determined TSH level, T3 (general triiodothyronine), T4 (free thyroxine), adrenal hormones, and done an ECG. There was not recorded any significant deviation from the norm. What additional examinations the patient needs to undergo to determine the reason for the weight gain?

A. Ultrasonography of adrenal glands
B. Chest X-ray examination
C. Craniography
D. Determine the creatinin level in blood
E. Determine the potassium, sodium level in blood

9. A patient aged 35 years old a year ago was diagnosed with hypertensive disease accompanied by crises. She was not treated. After the long-term excessive physical effort (doing the laundry) there suddenly appeared the feeling of fear, excitation, heart beat, head megalgia, chest, epigastrium, lumber pain, frequent urination, nausea, vomiting. Watery skin. Pale face. Ps - 170/min., rhythmical. Clear heart tones. Arterial blood pressure - 220/110 mmHg. Blood sugar level - 7,2 mmol/L, leucocytosis, erythrocytosis. What is the most provisional diagnosis?

A. Pheochromocytoma crisis .
B. Hypertensive crisis
C. Myocardial infarction .
D. Thyrotoxic crisis
E. Hypothalamic crisis

10. A teenager aged 16 years old, for 2 years has been complaining about increased arterial blood pressure, weight gain, the occurrence of striae atrophicae on shoulders, abdomen and hips, facial hair. Cortisol levels in blood serum – increased. What is the most provisional diagnosis?

A. Endocrine and metabolic factors in obesity
B. Corticosteroma
C. Juvenile dispituitarism
D. Cushing's disease

E. Alimentary obesity

11. A patient S., aged 38 years old, has been complaining about a persistent headache, thirst, extreme fatigue, increased arterial blood pressure and weight gain (46 kg in the space of 3 years). He connects the disease with flu.During examination: height – 176 cm, body weight – 143 kg, distribution of the fat tissue: predominantly on a trunk, hips, abdomen, multiple cherry-coloured linear atrophy. Arterial blood pressure - 180/100 mm Hgт. What is your provisional diagnosis?

A. III alimentary-constitutional adiposity III ст.
B. Hypothyroidism
C. diencephalic syndrome, neuroendocrinal
D. hypothalamic obesity III ст.
E. Cushing's disease

12. A patient L, aged. 17 years old does not complain. During medical examination at the military commissariat, there was revealed increased arterial blood pressure up to 150/100 mmHg on one arm and 140/80 mmHg on the other. The patient is overweight. The distribution of the fat tissue is homogenous. An insignificant amount of stretch marks of abdomen, hips, and chest. The condition of the internal organs is within normal limits. Blood counts and urinary tests are without pathological findings. Which of the following diagnoses corresponds to this particular case?

A. Hypothalamic amenorrhea in the adolescence
B. Hypertensive disease
C. Aortic coarctation. Symptomatic geodynamic hypertension
D. vegetative-vascular dystonia
E. None of the above-mentioned diagnoses

13. A patient 38 years old, has been complaining about weight gain by 30 kg in the space of the last 7 years. She is suffering from headache, increased appetite. Carbohydrates predominate in the daily diet. For 5 years the patient has been suffering from arterial hypertension. Clinician-observed: height - 172 cm. Body weight - 112 kg, Waist measurement 94 cm. Ps – 78/min, arterial blood pressure - 170/100 mmHg. Liver by 2 cm protrudes below the costal margin. Pastosity of cnemis. Blood sugar in 2 hours after eating. - 8,1 mmol/L, Blood cholesterol 7,8 mmol/L.

What is the main reason for the development of metabolic disorders in the patient?

A. insulin resistance
B. overactivity of hypothalamus activity
C. hyperglycemia
D. hypercholesterolemia

E. Production of thyroid hormones decrease

14. Medical advice was seeking a patient suffering from insulin-dependent diabetes for 20 years. She was complaining about arterial blood pressure instability (90/60 mmHg in the morning,200/100 mm Hg in the evening), orthostatic hypotension, severe tachycardia, which is not corrected with digitaloids, beta-blockers, calcium antagonists. What is your provisional diagnosis?

A. Diabetic Autonomic Neuropathy
B. Endocrine myocardiodystrophy
C. Diabetic microangiopathy affecting blood vessels that supply the myocardium
D. Diabetic microangiopathy affecting coronary arteries
E. Myocarditis

Assignment.

A patient aged 35 years old has been complaining about weight gain (20-25 kg in the last 2-3 years), ovarian menstrual cycle disorder, facial hair, frequent arterial blood pressure increase up to 180/100 mm Hg, headache, visual impairment, occasional, dry mouth, leg numbness. Clinician-observed: hypersthenic type, height 165 cm, weight 110 kg, fat face, neck and trunk. Cyanotic round face with hypertrichosis. The skin is covered with fastering rash, various claret-coloured linear atrophy is on hips and sides of the trunk. Glycemia 8,8 mmol/L. Urine glucose 1%.

1. What is the most provisional diagnosis?
2. What additional examinations need to be done to confirm a diagnosis?

Theme 5: Management of a patient with hypothalamic-pituitary system diseases (acromegaly, hyperprolactinemia, diabetes insipidus) and metabolic disease (obesity). Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with hypothalamic-pituitary system diseases and obesity.

1. Topicality: acromegaly – a pathological increase of some parts of the body, related to the overproduction of somatotrophic hormone (growth hormone) by anterior pituitary as a result of its tumor involvement. It occurs in adults. Its symptoms include an enlarged face, feet and hands, persistent headache and joint pain, sexual dysfunction and a decrease in fertility. The increase of somatotropic hormone level in blood leads to early death from oncological, pulmonary, cardiovascular disease. In patients over 45 years old the death rate from cardiovascular and cerebrovascular complications increases by 36-62%, respiratory disease - by 0-25% and malignant tumor by 9-25%.

Gigantism (or somatomegaly) develops in children with an incomplete process of ossification in the skeletal system, more often it occurs in male teenagers. It may be diagnosed at the age of 9 to 13 years old and progresses throughout the whole physiologic growth period. At the beginning, it is manifested by the increase of muscle strength, and then muscle weakness and asthenia prevail. Other hormonal manifestations of gigantism include diabetes insipidus, hypo and hyperthyroidism, diabetes mellitus. The death rate in such patients depends on the occurrence of lower extremity pathologic fracture and in the event of diabetes mellitus or hypertension overlay.

Diabetes insipidus (DI) – a disease caused by the disorder of neurohypophyseal hormone vasopressin (antidiuretic hormone (ADH)) synthesis, transportation and secretion. It is characterized by polyuria, plasma osmolarity increase. It is manifested by excessive thirst and polyuria. There are central diabetes insipidus (or hypothalamic) and nephrogenic diabetes insipidus. If the cause of the disease is not identified (about 30% of cases), then idiopathic central diabetes insipidus is implied.

Hyperprolactinemia – female amenorrhea-galactorrhea syndrome and male hypogenitalism, which occurs in the event of prolactin hypersecretion by the pituitary body. Causative factor includes pituitary tumor (micro- or macroadenoma), prolactin parasecretion because of taking certain medication, blocking dopamine activity (neuroleptic agents, cerucal etc.), antifertility agents (estrogens); untreated primary hypothyroidism. The increased prolactin level causes the decrease of gonadotropins secretion. In females, high prolactin level in the blood often causes menostasis, infertility, nipple discharge, loss of libido (sex drive). In males, the most widespread symptoms of hyperprolactinemia include the decrease in libido, erectile dysfunction, infertility and gynecomastia. Sometimes patients with hyperprolactinemia mainly

complain only about infertility as long as other symptoms do not trouble them. Sometimes in the event of adenoma active growth, a patient may suffer from visual impairment and tunnelling of vision caused by pressure generation in optic chiasma. As a result of hypestrogenism and hypogenitalism (low testosterone), hyperprolactinemia may cause osteoporosis and increase the occurrence of pathologic fractures.

Obesity is a disease that manifests itself as an overaccumulation of fat in the body and it may have a negative effect on health as long as it leads to the reduction of life span and /or increase of health issues. Body mass index (BMI), that compares the correlation between weight and height must be 18-24 kg/sq.m, in a patient with BMI 25-29 there is diagnosed excess weight, and in the event, BMI is over 30 kg/sq.m. there is confirmed obesity.

In the event of obesity there increases the probability of development of various diseases, in particular, cardiac diseases, type 2 diabetes mellitus, obstructive sleep apnoea, some types of cancer and osteoarthritis. Obesity is most often caused by the combination of dietary regimen disorder, decrease of physical activity, genetic predisposition, some drugs usage.

2. Learning goal.

Offer the students insights into the following issues: acromegaly and gigantism, Cushing's disease, hyperprolactinemia, hypopituitarism, diabetes insipidus, somatotrophic deficiency, gonadopathy, congenital disorders of sexual differentiation, sexual development disorders, obesity, metabolic syndromes and their connection with other concomitant diseases (hypertensive disease, diabetes mellitus) (α =1).

The student must know (α= 2)**:**

- Etiology, the pathogenesis, clinical symptomatology, laboratory tests and treatment of acromegaly and gigantism;
- Etiology, the pathogenesis, clinical symptomatology, laboratory parameters and treatment of hyperprolactinemia;
- aetiopathogenesis, clinical symptomatology, laboratory parameters and treatment of diabetes insipidus ;
- Etiology, the pathogenesis, clinical picture, laboratory parameters and treatment of obesity;
- Peculiarities of the course of acute respiratory diseases COVID-19, caused by SARS-CoV-2 coronavirus in patients with hypothalamic-pituitary system diseases and obesity.

The student should be able to (α = 3)**:**

- evaluate hormone hypophysary function after carrying out the

corresponding laboratory tests;
- differentiate pituitary disorders;
- acromegaly and gigantism adequate treatment algorithm;
- Perform diagnosis and differential diagnosis of diabetes insipidus;
- Determine the approach to diabetes insipidus treatment;
- Peculiarities of diagnosis, differential diagnosis and treatment of patients with hyperprolactinemia;
- Determine the approach to the diagnosis, differential diagnosis and treatment of obesity in children and teenagers,
- Determine the approaches to the treatment of patients suffering from obesity,

3. Educational goal

Attract the students' attention to the differential diagnosis of acromegaly and gigantism, early detection and treatment of diabetes insipidus, синдрому hyperprolactinemia, obesity.

4. Interdisciplinary integration:

Subjects	To know	To be able to
I. Previously studied subjects Systemic Anatomy Hominal Physiology Histology, Pathoanatomy Pathophysiology, pharmacology II. Subjects that will be studied later: internal medicine, surgery, narrow specialization	adenohypophysis, neurohypophysis (organization, morphology, hormones and regulation of their synthesis) Main clinical scores of pituitary-hypothalamic functional abnormality, clinical picture, laboratory measurement, differential diagnoses .	Diagnose the pathology of the pituitary-hypothalamic area Prescribe adequate laboratory examinations to confirm the diagnosis Prescribe etiological pathogenetic and symptomatic treatment of the underlying diseases of the pituitary-hypothalamic system

III. Interdisciplinary integration	Modern diagnostic and treatment methods of the underlying diseases of pituitary-hypothalamic system.	Know how to perform the differential diagnosis of the underlying diseases of pituitary-hypothalamic system. Make the corresponding prescriptions

5. Training subjects:

Underlying diseases, caused by adenohypophysis functional abnormality and their classification.

Acromegaly, gigantism: etiology, the pathogenesis, clinical picture, laboratory diagnostics and treatment

Diabetes insipidus: etiology, pathophysiology, classification, clinical manifestations, differential diagnosis, treatment.

Hyperprolactinemia: etiology, the pathogenesis, clinical picture, diagnosis and differential diagnosis, treatment

Obesity: etiology, the pathogenesis, classification, clinical picture, diagnosis, treatment. Peculiarities of the course and treatment in children and teenagers.

6.Plan and organizational structure of the class

(see «Introduction»)

7. Materials and methodological support of the class

7.1. Materials of the preparatory stage of the class

Tests (α=2)

1.Which of the following medicinal products is not used in the treatment of obesity?

A. Insulin therapy

B. Metformin

C. Acarbose

D. Xenical

E. Sibutramine

2.What is the probable side effect of analogues of antidiuretic syndrome?

A.Depression

B. Hyperexcitability

C. Vision loss
D. Convulsive syndrome
E. Headache

3. According to what symptoms there may be suspected diabetes insipidus of central origin?
A. Low specific urine density, polyuria 1-2L/day, depression
B. High specific urine density, polyuria 5-10 L/day, hyperhidrosis
C. Normal specific urine density, swelling, arterial hypertension
D. Low specific urine density, polyuria 5-10L/day, dryness and poor skin turgor
E. Hypo-or isosthenuria, proteinuria, arterial hypertension, depression

7.2. Materials and methodological support of the class .

Acromegaly – a pathological increase of some parts of the body, related to the overproduction of somatotrophic hormone (growth hormone) by anterior pituitary as a result of its tumor involvement. It occurs in adults. Its symptoms include the enlarged face (nose, ears, lips, lower jaw bone) feet and hands, persistent headache and joint pain, sexual dysfunction and decrease in fertility in males and females. Secretion of somatotropic hormone (somatotropin, STH) is performed by the pituitary body. At an early age, somatotropic hormone conducts the process of formation of the musculo-skeletal system and linear growth, and in adults, it maintains control over carbohydrate, fat, water-salt metabolism. Secretion of somatotropic hormone is regulated by the hypothalamus, which produces special neurosecretion: somatoliberin (encourages the production of STH) and somatostatin (hold down production of STH). Within the normal limits, the content of somatotropin in blood ranges during the day, attaining its maximum at break of day. A patient with acromegaly is noticed not only the increase of STH concentration in the blood,but also the disorder of normal rhythm of its secretion. The cells of the anterior pituitary, because of various reasons, do not subordinate to regulating effect of the hypothalamus and start actively multiply. Enlargement of cells in the pituitary gland leads to the occurrence of benign glandular tumor – pituitary adenoma that intensively produces somatotropin. Adenoma size can reach several centimeters and exceed the size of the gland itself, compressing and destroying normal cells of the pituitary body.

In the event of acromegaly, there occurs hypertrophy of parenchymatous tissue and stroma of internal organs: heart, lungs, pancreas gland, liver, spleen, intestinal tract. Enlargement of the connective tissue leads to a sclerotic change of such organs, increases the risk of benign and malignant tumor development including endocrine ones.

Stages of acromegaly development:

Acromegaly is characterized by a long-term course. Depending on the acuteness of symptomatology the development of acromegaly is divided into several stages:

- pre-acromegaly stage – there appear initial, mild symptoms of the disease. At this stage, acromegaly is seldom diagnosed, exclusively according to the indications of somatotropic hormone level in blood and findings of CT scan of the brain.
- Hypertrophic stage – there is observed full-blown symptomatology of acromegaly.
- Tumor stage – the centre stage play the symptoms of compression of the neighbouring brain divisions (an increase of abdominal pressure, nervous system and ophthalmic disorders).
- cachexy stage – cachexia caused by acromegaly.

Manifestations of acromegaly may be caused by an excess of somatotropin or the influence of pituitary adenoma on optic nerves and neighbouring brain structures. The excess of growth hormone causes peculiar changes in the appearance of patients with acromegaly: increase of lower jaw bone, jugal bones, superciliary arches, hypertrophy of lips, nose, ears, which leads to coarse face. The increase of lower jaw bone causes spacing of teeth and change of occlusion of teeth. The tongue is enlarged (macroglossia) and has a tooth mark. Because of hypertrophy of the tongue, larynx and vocal ligaments, the voice becomes deep and hoarse. Changes in the appearance of a patient with acromegaly take place gradually, silently.

Acromegaly causes deformation of the skeleton: spinal curvature, enlarged breast in A-P diameter, taking on barrel-like shape, widening of intervertebral spaces. There develops hypertrophy of connective and cartilaginous tissues, which causes deformation and restriction of joint movement, arthralgia.

In the event of acromegaly, there is observed excessive sweating and sebaceous excretion, caused by the increase in the number and increment in the activity of perspiratory and sabeceous glands. The skin of patients with acromegaly indurates, thickens, folds, especially on the hairy part of the head. Acromegaly causes the enlargement of muscles and internal organs (heart, liver, kidney) with gradual worsening dystrophy of muscle fibre. Acromegaly causes genital function disorder. In the majority of women with an excess of prolactin and gonadotropin deficiency there develops menstrual disorder and infertility, there occurs galactorrhea – a milky nipple discharge, unrelated to the normal milk production of breast-feeding. In 30% of cases, males suffer from lowering of sexual potency. Hyposecretion of antidiuretic hormone in patients with acromegaly causes the development of diabetes insipidus.

Hyperproduction of growth factor, in patients with acromegaly causes the development of tumors (both benign and malignant) effecting different organs. Acromegaly often accompanies diffuse or nodular goiter, chronic cystic masticatory,

adrenal adenomatous hyperplasia, polycystic ovary syndrome, uterine fibroids, intestinal polyposis. There develops pituitary failure caused by compression and destruction of hypophysis tumors.

Diagnosis of acromegaly. In late stages (in 5-6 years after the incursion of disease) acromegaly may be suspected based on enlargement of parts of the body and other external evidence, visible during the examination. In such cases, a patient is referred to the endocrinologist and delivery of medical tests for laboratory diagnostics procedures.

The main laboratory criteria for the diagnosing of acromegaly is the determining of blood count:

- the somatotropic hormone in the morning and after glucose test;
- IGF I – insulin-like growth factor.

Somatotropic hormone effects on the body via insulin-like growth factor (IGF).The concentration of IGF I in the blood plasma reflects the total discharge of IGF dor a day. The increase of IGF I in blood of an adult explicitly specifies the development of acromegaly.

During the ophthalmic examination a patient with acromegaly suffers from a narrowing of visual fields, as long as anatomically visual pathways are located in brain close to hypophysis.

In the event of craniography, there is detected the enlargement of the Turkish saddle where the hypophysis is. To visualize pituitary tumor there is conducted computer-assisted diagnosis and head MRI.

Besides, patients with acromegaly are examined for the detection of various complications: intestinal polyposis, diabetes mellitus, multinodular goiter etc.

Treatment of acromegaly is directed to the induction of remission of the disease by the liquidation of somatropin hypersecretion and normalization of IGF I concentration. To treat acromegaly, modern endocrinology applies medicamentous, surgical, radiological and combined methods.

To normalize hormone level in blood there are prescribed equivalents of somatostatin – hypothalamic neurosecretion that inhibits the secretion of growth hormone (sandostatin, octreotide, lanreotide). In the event of acromegaly there is indicated the prescription of reproductive hormones, Dopamine agonists (parlodel, cabergoline, abergin).

Further, there is usually performed single time gamma or beam-therapy in the pituitary region. In the event of acromegaly, the most effective is surgical removal of tumor at the base of the skull through sphenoid bone. If adenoma is small then after the surgical intervention 85% of patients report normalization of somatotropin level and sustained remission of the disease. If the tumor is large the percentage of recovery after the first surgical intervention reaches 30%. The death rate from acromegaly in the event of surgical treatment is from 0,2 to 5%.

GIGANTISM In children and teenagers against the background of long-term increase of chronic hypertension STH causes gigantism, which is characterized by excessive, however, relatively proportional increases of bones, organs and soft tissues. With the termination of physiologic growth and ossification in the skeletal system there develop disorders similar to acromegaly – disproportional bone production, enlargement of internal organs and specific metabolic disorders. In the event of gigantism the child growth rate and its indicators far exceed anatomico-physiological norm and until the end of adolescence reach more than 1,9 m in females and 2 m in males with the preservation of body balance. The frequency of gigantism cases ranges from 1 to 3 per thousand people. Parents of patients suffering from this pathology are usually people of average height. Gigantism must be differentiate with respect to familial (constitutional) tall stature

Classification of gigantism:

Modern endocrinology distinguishes the following types of gigantism development:

- Acromegal – gigantism with symptoms of acromegaly;
- Splanchnomegaly or gigantism of the viscera – it is accompanied by the enlargement of size and weight of the viscera;
- eunuchoid – gigantism in patients with hypogenitalism (hypofunction or complete cessation of genital gland function), it is manifested by nonproportional elongated limbs, open growth zones in joints, absence of secondary sexual characters;
- true - gigantism is characterized by proportional increase of the body size and absence of deviance on the part of physiological and psychical functions;
    - Partial – gigantism, which manifests by the increase of separate parts of the body;
    - localized – gigantism which is accompanied by the enlargement of a half of the body;
- cerebral – gigantism is caused by organic brain lesion and is accompanied by derangement.

Gigantism and acromegaly are two age-related variations of one and the same pathological processes: hyperplasia and hyperactivity of pituitary cells, producing somatotrophic hormone (growth hormone). Hypersecretion of growth hormone may be observed in the event of affected hypophysis which is the result of gland tumor (pituitary adenoma), intoxication, neuroinfections (encephalitis, brain fever, meningocephalitis), traumatic brain injuries.

A sudden increase of body length in the event of gigantism occurs at the age of 10-15 years old. Patients with gigantism suffer from hormonal diseases, psychical and genital function disorders (infantilismi). In females with gigantism there

develops primary amenorrhea or early termination of menstrual function, infertility, and in males – hypogenitalism.

Diagnosis of gigantism.

The diagnosis of gigantism is established based on simple examination of a patient, results of laboratory, X-ray, neurologic and ophthalmological examinations. In the event of gigantism, there is defined in the laboratory high content of STH in blood. To detect the pituitary tumor there is conducted craniography, computed tomography, head MRI. In the event of adenoma there is reported the increased Turkish saddle. Hands X-ray images point at inconsistency between skeletal maturity and age. In the event of ophthalmological examination of patients with gigantism there is detected narrowing or loss of visual field, congestive phenomena in fundus of eye.

Gigantism treatment principles are the same as acromegaly treatment principles. To normalize STH level there are applied the equivalents of somatostatin, for more rapid closure of the growth plate – reproductive hormones. Etiotropic treatment includes the application of radiation therapy or surgical removal in combination with Dopamine agonists therapy. In the event of eunuchoid gigantism treatment is directed to the removal of sex infantilism, acceleration of ossification of skeleton, termination of its further growth. Treatment of partial gigantism includes orthopedic alignment carried out by means of corrective surgery. Combination therapy for gigantism combines hormonal and beam-therapy. It allows to achieve positive results in substantial number of patients.

Diabetes insipidus (DI) – a quite rare endocrine pathology that occurs equally as often in females as in males, sometimes this disease slightly prevails in males (60:40), more often at the age of 20-40 years old, however, may occur at any other age, including in children. Congenital forms of DI occur in children during the first months of life.

Almost in 50% of children and 20% of adults the occurrence of diabetes insipidus is connected with the primary or secondary tumor in hypothalamus region or is the result of surgical treatment caused by the tumor. Supracellar pituitary tumor leads to compression of hypothalamus and may become a reason for the occurrence of diabetes insipidus. Among primary hypothalamus tumors the most often occur craniopharyngioma, meningioma, glioma. In adults in 6-7% of cases there is detected metastatic lung cancer or breast cancer in hypothalamus region that controls vasopressin secretion.

Traumatic injuries of the central nervous system cause the occurrence of diabetes insipidus in 17% of cases in adults and in 2% of cases in children. Diabetes insipidus in the event of basal skull fracture and other traumas manifest during acute period and in 50% of cases symptoms disappear within 7-14 days.

In other cases diabetes insipidus remains for a long time and usually has three stages of development: 1) sudden occurrence of polyuria that lasts from some hours

to 5-6 days; 2) antidiuresis period that lasts from some hours to 7-12 days (it is related to vasopressin discharge from effected axis cylinders of pituitary-hypothalamic); 3) persistent diabetes insipidus.

Diabetes insipidus caused by pituitary-hypothalamic system disorder, usually developms immediately or during 2-4 weeks after the effect of disease-producing factor (trauma, acute infection etc). In the event of persistent infection the disease may develop during 1-2 years.

Vasopressin-Resistant Diabetes Insipidus – familial form, sex-linked; maternally inherited and occur only in boys. In this case, vasopressin is produced in sufficient quantity, however, kidneys do not respond to the increase of hormone in the blood. Pathogenesis of nephrogenic diabetes insipidus is related to the pathology of sense bodies reacting to vasopressin .

The severity of the course of diabetes insipidus depends on the degree of vasopressin insufficiency. The onset of a disease is usually acute. Basic clinical manifestations of the disease are as follows: excessive thirst, frequent urination, nocturnal urinary incontinence, general weakness, headache, bad appetite. The patient may drink 10 L of fluid and more during a day. It is worth mentioning that in the event of polyuria urine specific gravity usually does not exceed 1000-1005. The relative density of urine during a day does not change. In the event of restriction of fluid consumption there develops hyper dehydratation of the body. Skin and mucous membranes are extremely dry, sweat is not produced even when the loss of fluid loss with urine is compensated with the drinking of fluid. Because of reduced salivation (hyposalivation) patients suffer from persistent dry mouth. Appetite is also reduced, which leads to chronic undernutrition, in children it may cause the arrest of physical and sexual development. Patients complain about frequent painful joints, there is reported a disposition toward coprostasia, digestive system disorders, there occurs hypoacid gastritis, colitis, biligenesis disorders. There is often observed gastric distention and gastroptosia (overloaded with water). If the disease has been badly compensated for a long time, there occurs urethral dilation, including ureters and renal pelvis.

Patients show a disposition toward arterial blood pressure decrease. Reduced body weight. Very seldom there is observed body weight gain, related to hypothalamic polyphagy. With the increase of dehydratation symptoms there appear lightheadedness, tachycardia, hypotonia, collapse, headache, nausea, vomiting, fever, twitch, psychomotor agitation. There are reported clots of blood, sodium, erythrocytes, hemoglobin, residual nitrogen level increase. Even in the event of extremely severe dehydratation polyuria preserves, urine concentration and its osmolarity almost do not increase. Severe polyuria (20-40 L a day) may cause fluid overload in the kidney, then nephrogenic diabetes insipidus can join the Central Diabetes Insipidus.

In women, there may be observed menstrual disorders and decrease in fertility

and in men - decrease in libido and low potency. Fatal cases are usually related to convulsions and comatose state.

Diagnosis of diabetes insipidus is based on clinical picture (polyuria, dipsesis, low urine specific gravity). There is detected plasma hyperosmolarity (over 290 mOsm/L), urine hyposmolarity (less than 300 mOsm/L), low relative density of urine (1000-1010).

To determine the reasons of the disease there is made a make a thorough examination of past medical history, there is performed neurologic, ophthalmological, X-ray examination, computed tomography and head MRI.

Differential diagnosis.

Diabetes insipidus should be differentiated with respect to diabetes mellitus, kidney pathology, psychogenic polydipsia etc. Diabetes insipidus of central origin should be differentiated with respect to the following diseases: psychogenic polydipsia, nephrogenic diabetes insipidus (vasopressin resistance), high output renal failure, diabetes mellitus, primary aldosteronism, hyperparathyroidism.

To differentiate the diagnosis of central and nephrogenic diabetes insipidus there is used fluid restriction test (dry diet).

Fluid restriction test procedure.

A patient after overnight fast is determined body weight, sodium, nitrogen, urea levels in blood, urine specific density and content of sodium in urine, then the patient stops drinking fluids. Usually the test lasts from 6-8 hours (in young children and significant polyuria) to 24 hours, depending on the way the patient transmits a disease.Every hour the patient is measured body weight, sodium level in blood, urinary volume and urine specific density. Testing is ceased if the patient's body weight reduces by 5% and sodium level is more than 3,0 mmol/L. It confirms the presence of diabetes insipidus because of the absence of antidiuretic hormone. Within the normal limits or in the event of psychogenic polydipsia during a test there occurs the decrease of discharged urinary volume, there is no increase of sodium in the blood, there is not observed the decrease of body weight.

Determination of vasopressin level promotes differential diagnosis of central and nephrogenic diabetes insipidus. In the event of the central (hypothalamic) type of disease the vasopressin level in blood is significantly decreased and its content almost does not change when performing the fluid restriction test or during infusion of 5% hypertonic sodium chloride solution. At the same time in the event of nephrogenic diabetes insipidus the vasopressin level significantly exceeds the normal limits (2,0-2,5 pg/ml) and significantly increases (up to 15-17 pg/ml) in response to administration of 5% hypertonic solution or in response to dehydratation. In th event of high output renal failure the urine specific gravity is 1009-1010 and in the event of urine output not more than 3-4 L. There is reported the increase of urea and creatinine level in blood, albuminuria and pathologic urinary sediment.

In case of primary aldosteronism there is observed persistent hypertension,

brachycardia, junctional conductivity disorder, cardiac arrhythmia, hypokalemia, hypernatremia, hyponatremia, hyperpotassemia. Urine output is lower, urine specific gravity is higher than in the event of diabetes insipidus. Polyuria with prevailing night diuresis over daytime one. On computed tomography – symptoms of the increase of one or both adrenal glands.

Excessive thirst and polyuria are reported in patients with hyperparathyroidism, which is related to the excess of potassium in blood, which blocks the effect of antidiuretic hormone on channels in adrenal glands. In this case it is important to determine the increased level of parathormone in blood (5-8 mg/mL and more). There is reported hypercalcemia, alkaline urine, proteinuria, cylindruria, microhematuria, nephrocalculosis and nephrocalcinosis.

The main thing in **treatment** of central and idiopathic diabetes insipidus is the prescription of substitution therapy involving vasopressin (medication) (Minirin (tablets). Desmopressin tablet (Minirin) contains in one tablet 100 or 200 mcg.The daily dose is from 1 to 4 tablets, which must be taken 30-40 minutes before eating or in 2 hours after eating. Such Desmopressin form contains active ingredient dose which 10 times higher as long as there occurs its partial destruction under the influence of peptidase in the gastrointestinal tract. Treatment begins with minimum doses with a gradual increase of the medication dose depending on clinical symptoms of the disease (excessive thirst, urine output indices, urina specific density). Intranasal administration of the soluble drug in the form of drops. 2-8 drops are needed a day (10-40 mcg).

Before beginning the therapy with Desmopressin the patient should discontinue the use of other medication to determine the initial level of polyuria to be able to establish a dose and duration of the reaction to medication. Changes in nasal mucosa (rhinitis, swelling etc) may cause absorption disorder, therefore in such cases there should not be prescribed Desmopressin for intranasal administration. During diabetes insipidus treatment there should be used the least efficient doses. Effective dosing must be determined from time to time guiding the volume and urine osmolarity, and in some cases – plasma osmolarity.

Treatment of nephrogenic diabetes insipidus still remains a pretty challenging problem as long as it is really hard to renew sensibility of kidneys to vasopressin. There are made attempts to renew sensibility to antidiuretic hormone using thiazide diuretics,potassium preserving medication, nonsteroid anti-inflammatory drugs, medicines containing lithium, dimethyl chlorotetracycline.

Hyperprolactinemia — is the most widely spread endocrine pathology of the pituitary-hypothalamic system. In females, it occurs more often than in males. Clinical symptoms of hyperprolactinemia include amenorrhea, infertility, galactorrhea in females, decrease in libido and sexual debility in males. Traditionally, prolactin-secreting pituitary tumors (prolactinoma), idiopathic hyperprolactinemia or intake of medication, which compromises bioaminergic activity, predominantly

prolactin inhibitory activity of dopamine are the reasons for the occurrence of hyperprolactinemia. Other less frequent reasons include primary hypothyroidism, hypothalamic or hypophyseal tumors, which do not secret prolactin and cause compression of hypophysis.

This is a specific state of the organism which is characterized by extremely intensive production of prolactin. Thus, its level in the blood significantly increases. This disease more frequently occurs in females,however, it also occurs in males. The most frequently hyperprolactinemia is diagnosed in females at the age of 25 – 40 years old.

Prolactin triggers the production of colostrum at the beginning of breast-feeding, and then promots its transformation into mature milk. Prolactin also immediately affects the growth of mammary glands, as well as the increase of a number of ducts and particles. The effect of this hormone on women's organism manifests by the continuation of the existence of yellow body of ovaries and suppression of ovulation process. If this mechanism remains within the normal limits, prolactin, in its turn promotes the prevention of pregnancy and suppressed menstruation during breastfeeding. However, the pathologically increased content of prolactin in the female's organism threatens the occurrence sexual anesthesia**,** anorgasmia and infertility**.**

Besides the above-described functions prolactin is responsible for the regulation of water-salt metabolism in the human body: kidneys under its effect discharge water and salt more slowly.

Specialists highlight many different reasons, which finally lead to to the development of hyperprolactinemia. It is customary to distinguish physiologic and pathologic forms of disease. In healthy women, the increase of prolactin level in the body occurs under the effect of several physiological factors. For example, the content of prolactin may increase while sleeping, breastfeeding, as a result of severe stress or extreme physical exercise, during sex intercourse, across pregnancy and after childbearing.

Pathological hyperprolactinemia, in its turn, is subdivided into organic and functional. The organic disease develops as a result of occurance of pituitary tumor – so called microprolactinomas and macroprolactinomas**.** Such tumors are benign, however, they intensively produce prolactin. Some medication, prescribed at high dose cause the increase of prolactin level. The similar effect is peculiar to antidepressant medication**,** neuroleptic agents**,** drugs with hypotensive effect**,** estrogen**s,** prostaglandin**,** oral contraceptive**s.**

Clinical picture. If hyperprolactinemia develops in a woman, the symptoms of the state manifests by delay of menstruation, its total suppression or insufficiency of the second phase of menses cycle. There may be disrupted ovulation cycle, herewith colostrum or milk flows from mammary glands from time to time. Besides the above-mentioned manifestations in the event of hyperprolactinemia in women

there sometimes occurs the increase of the size of mammary glands, as well as the development of adenomas or lactocele. In due course, these benign diseases may transform in breast cancer.

At the same time, the increased amount of prolactin in the male's body affects the formation of testosterone, its content in blood decreases, which leads to decrease in libido**,** in other words, interest in sex. Because of progress of the disease in the men there is observed inhibition of spermatozoa maturation in ovaries, sometimes with manifestation of gynecomastia, as well as galactorrhea. Then there may develop sexual debility and infertility in males. About half of all the patients with prolactinemia suffer from obesity, one third of them suffer from bone thinning and osteoporosis.

Thus, the symptoms of hyperprolactinemia should become the reason for the immediate reference of the representatives of both sexes to medical specialists.

Diagnosis of hyperprolactinemia. *The most important method in the process of examination of patients with suspected hyperprolactinemia is hormones blood test, which allows to specify the content of prolactin in blood. Single-time increase of prolactin may not be indicative of the development of pathological state in the woman's body.*

While diagnosing organic hyperprolactinemia there is conducted the examination of the location of hypophysis. Craniography is used for this purpose – study of the skull using photographs and drawings made from measurements of the configuration of the skull and the relations of its angles and craniometric points. Besides, computer tomography and magnetic resonance imaging are the informative and precise method of examination in this particular case.

Treatment of idiopathic hyperprolactinemia includes the prescription of drugs, treatment of adenoma may be medicamentous,surgical and include radiation therapy.

For a long time, agonists of Dopamine were agents of choice. They not only inhibit synthesis and secretion of prolactin but also inhibit synthesis of DNA found in the cell and suppress the growth of tumor (bromocriptine). Medication of this generation have short half lifetime and numerous side effects, in particular, decrease of arterial blood pressure, faint, headache. Lately, there has been used Carbegoline (Dostinex) a new derivative of Ergotalum, which selectively join dopamine receptors D2, has prolonging effect (allowed to be used twice a week) and minimum side effects. Tests that were using Carbegoline proved the reduction of prolactinomas in size.

Obesity is an overaccumulation of fat in the body, which is accompanied by profound metabolic, neuroendocrinal changes, organs and systems dysfunction, the frequency of cases of obesity in children is 5-9 %: in preschool children - 12 %, during the first year of life - 13 %. It occurs more often in females.

Aetiopathogenesis. Energy disbalance is the reason for obesity in children:

overeating, presence of easily digestible carbohydrates in the diet, refined food products, eating of high energy food in late afternoon, slowdown of calorie expenditure.

An initiating agent may be the inherited fat tissue structure (increased number of adipositis), congenial overactivity of lipogenic enzymes, diseases of the endocrine system like hyperinsulinism, hypothyroidism, hypercorticalism, hypogonadism. The realization of original disposition cause external factors (overeating, forced feeding, hypodynamia). Pathogenesis of obesity depends on the reasons of its occurrence.

In the event of **constitution-exogenous obesity** the excess of carbohydrates causes hyperinsulinism. Insulin is the main lipogenetic hormone. It promotes synthesis of triglycerids in the fat tissue, as well as has anabolitical effect (speed up in growth, differentiation in bone tissue). Fat overaccumulation causes the variation of hypothalamus function – increase of adrenocorticotropic hormone secretion and hypercorticoidism, disorder of sensitivity of ventromedial and ventrolateral nucleus to hunger and bellyful signaling, transformation of other endocrine glands function, heat regulating centers, arterial blood pressure regulation etc. Thus, a long-term course of obesity leads to the development of secondary deincephalic syndrome, which, in its turn, promotes obesity.

Diencephalic or hypothalamic obesity **occurs as a result of primary functional or organic disbalance of** ventromedial nucleus of hypothalamus in the event of trauma (including birth injury), tumor, basilar meningitis, encephalitides, general anesthesia, central nervous system hypoxia. Bulimia that develops herewith causes hyperinsulinism and obesity. Secondary obesity in the event of endocrine disease may arise as a result of endogenous or exogenous hyperinsulinemia (insuloma, hypercorticoidism, chronic insulin overdosage in patients with diabetes mellitus), deficiency of hormones enhancing lipolysis (hypothyroidism, hypopituitarism, hypogonadism).

Clinical picture. In origin of constitution-exogenous obesity (CEO) a a decisive role plays a hereditary factor. A simple form is characterized by exceedance of body weight by no more than 50 %, homogeneous distribution of fat, satisfactory state of health, insignificant complaints in some patients: fatigue, inertness, faintness, thirst, sweatiness. Vegetative and cardiovascular systems disorders are characterized by functional aspect.

Simple form is easy to treat with a diet that in 100 % has a positive effect. Transition form is accompanied by the occurrence of non-persistent and moderate symptoms: transient hypertension, sweatiness, headache, nervousness, faint, thirst, marbled skin, pyodermia, furunculosis, hyperchromatism of skin folds.

Diencephal obesity is usually diagnosed at the age of 5-6-years old and may result from organic and functional injuries of hypothalamic centres. It is reported in the event of complicated course of perinatal period (intrauterine hypoxia, asphyxia, intracranial birth trauma, neonatal hypoglycemia). Heritability is overburdened.

Diencephal obesity may develop at any age in several months after traumatic brain injury, central nervous system infection, caused by tumor.

Diencephal obesity is characterized by the appearance of stretch marks on abdomen, lacteous glands, and hips. Cyanotic marbled skin with folliculosis on the outer surface of hips, shoulders, breeches, dermatomelasma on neck, in inguinal folds. There is reported labile pulse, increased arterial blood pressure, often asymmetrical, there is reported loop of thermal control. A patient is complaining about headache, inertness, sleepiness, chest pain, short breath in the event of physical exercise. arrested or accelerated growth, sexual development, functional abnormality of genital glands are possible. Obese adolescent is the variant of diencephal obesity. It is preceeded by angina, recrudescence of chronic tonsilitis, measles, scarlatina and other infections.

The patient is suffering from headache, fatigability, faint, decrease in memory, worsening of attainment in studies. There is reported menstrual disorder. Diencephal obesity without treatment always progresses. Hypothalamic obesity is characterized by the same symptoms as diencephal one, and bad neurologicas disorder. Rare types of disorders of obesity are caused by congenital hypothalamic dysfunction called Prader–Willi syndrome: it causes obesity in the early childhood, muscular hypotonia during the first years of life, mental retardation, hypogenitalism, insulin-dependent diabetes mellitus. Laurence–Moon syndrome (Bardet–Biedl syndrome): obesity, mental retardation, polydactyly, hypogenitalism, pigmented retinitis, diabetes insipidus, renal failure or Barraquer-Simons Syndrome - disproportionate obesity.

Diagnosis. During the laboratory examination of patients with obesity there are detected: hyperlipidemia, hypercholesterolemia, hyperinsulinemia, moderate increase of adrenocorticotropic hormone, cortisone in blood. Sometimes there are recorded impaired carbohydrates tolerance or insulin dependent diabetes mellitus.

Complications of obesity are the most probable in teenagers and adults that experienced the disease in childhood. In most cases it is atherosclerosis, which causes the occurrence of cardiovascular system diseases, myocardiodystrophy, hypertension, gallstone disease, insulin independent diabetes mellitus, muscle-skeleton disorder, muscular atrophy, kidney failure, decreases in fertility, infertility. It is mandatory for all the patients to evaluate carbohydrate metabolism parameters, including glucose tolerance test; carry out craniography, ophthalmic fundus and visual field examination because of probable tumor as a reson for obesity.

To specify the nature of central nervous system damage it is recommended to carry out electroencephalogram and diencephalic test version (thermography, the Shcherbak thermoregulational reflex etc.). For the differential diagnosis with Cusheng's syndrome it is necessary to determine urinary excretion of 17-oxycorticosteroids, the level and diurnal rhythm of adrenocorticotropic hormone and cortisone in blood, and to exclude hypogonadism – 17-oxycorticosteroids, gonadotropins, testosterone.

The treatment of obesity must be integrated. The major method of treatment is dietotherapy. At the beginning of treatment the patient is put on a diet that corresponds to the physiological age of the child. Then the patient is switched to a diet with calorie restriction by 20-30 % in the event of Class I – II obesity, Class III IV obesity - by45-50 %. Reduction of calorie intake is carried out by limiting easily digested carbohydrates and lessering the extent of fats. There are prescribed vitamins, especially liposoluble ones, sometimes low-ceiling diuretics. Therapeutic physical training and level of activity are extremely important.

In the event of hypothalamic obesity treatment includes antiinflammatory, desensitizing, dehydration, soluble and vitamin therapy. Sanitation in the sites of infection is necessary.

7.3. Control materials for the final stage of the class:
Assignment (α= 2)

Assignment 1.
A patient was referred to the endocrinologist complaining about frequent headache, visual impairment, periodic thirst, dry mouth, increase of shoe size from 42 to 45. The patient has been suffering from the disease for a year since he mentioned the increase lower extremities. Clinician-observed: hypersthenic type, height 186 cm, weight 106 kg, massive face with apparent lower jaw bone, diastema, large tongue, deep voice. The upper and lower extremities disproportionally increased in comparison with the trunk, arterial blood pressure - 150/95 ,mmHg, heart rate 66 beats per min. Fasting glycemia 6,7 mmol/L, cholesterol 5,8 mg/dL.

1. What diagnosis can be suspected in this patient?
2. What laboratory tests must be done to confirm the diagnosis?
3. What is your treatment policy?

Assignment 2.
A patient was referred to the physician complaining about body weight loss, excessive thirst, dry mouth, excessive urination, general weakness, headache. He relates the disease with a car accident he had months ago. Since then he started suffering from the above-mentioned symptoms. Clinician-observed: asthenic type, extremely dry skin, slightly decreased turgor. Arterial blood pressure - 115?) mmHg.,heart rate 88 beats per min. Daily urine 8 L. Glycemia – 4,8 mmol/L, urine glucose 0%, acetone – 0.

1.What pathology can be suspected in this patient?
2.What medication should be prescribed?

Assignment 3.
A patient, aged 27 years old, referred to the physician complaining about infertility,

periodic headache, menstrual disorder. Clinician-observed: normosthenic type, satisfactorily nourished, clear, watery skin, in the course of examination of lacteous glands there was reported colostrum discharge. arterial blood pressure - 110/70 mmHg, heart rate 68 beats per min. Thyroid gland T1., slightly indurated, sensitive on palpation.

1. What pathology can be suspected in this patient?
2. What tests must be done?
3. What diseases there must be carried out the differential diagnosis with ?\
4. What is the treatment policy for this patient?

References:

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4. Endocrinology: (electronic edition): a student textbook in Russian (P.N. Bodnar, H.P.Mykhalchyshyn, Yu.I. Komissarenko, A.M.Prystupiuk et al.) under the editorship of professor P.N. Bodnar. Second edition amended and supplemented. Vinnytsia. Nova Knyha, 2015. – 496p.
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Independent study

1. Studying of professional literature.
2. Preparation of the library-research paper on the subject of the class using journal articles:
   - Endocrinology.
   - Endocrine pathology disorders.
   - International Journal of Endocrinology.
   - Problems of endocrinology and endocrine surgery.
   - Journals of Therapeutics.
3. Doing tests and case problems for Krok 2.
4. Writing protocols of clinical considerations for patients.