Ministry of Education and Science of Ukraine
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Sumy State University

O. Melekhovets

DIABETES MELLITUS MANAGEMENT.

Practical Guide with Elements of Augmented Reality

Study guide

Recommended by the Academic Council of Sumy State University

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Increased interest in the diabetes mellitus over the last 25 years has resulted in major advances in the care of diabetes. The study guide emphasizes a practical approach to understanding the basic problem of diabetes, diagnostic algorithms, making diagnosis and management with newly oral hypoglycaemic agents and insulin. This guide includes basic evidence information of international multicentral clinical trials. The elements of augmented reality involve students in the process of learning and provide visual access to practical skills understanding.

The study guide will be of use for medical students, internships, clinical ordinators.

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INTRODUCTION

Future health care professionals must have not only profound theoretical knowledge, but also skills to apply it in their clinical practice. All the fundamental and specific medical sciences make a basis for doctor`s clinical thinking and altogether with the accurate practical knowledge form not a student, but a professional, able to solve clinical problems and self-educate.

This guideline is built according to the algorithm, with is followed by a clinician at establishing the correct diagnosis and prescribing the proper treatment. It helps to precisely understand how to treat themanage the main disease, but also how to deal with the patient`s comorbidities and how to assess the patient`s risks for developing other diseases, and thus, prevent it.

To turn learning into an interactive and creating process, each chapter is accompanied by augmented reality elements, which is not only helpful for acquiring practical skills, but also for involving the education receiver into the atmosphere of doctor-patient communication.

The first part of the guideline is built in the way that turns a diagnosis into a step-by-step algorithm, in which every step is profoundly reasoned and clinically based. All the diagnosis criteria are contemporary and based on clinical trials and up-to-date international guidelines.

Establishing a clinical diagnosis is based on determining the signs, symptoms, and syndromes of a particular disease.

A sign is an indication of any objective evidence of a disease which is perceived by the physician, as opposed to the subjective sensations (symptoms) of the patient.

A syndrome is a group of signs with a common pathogenesis.

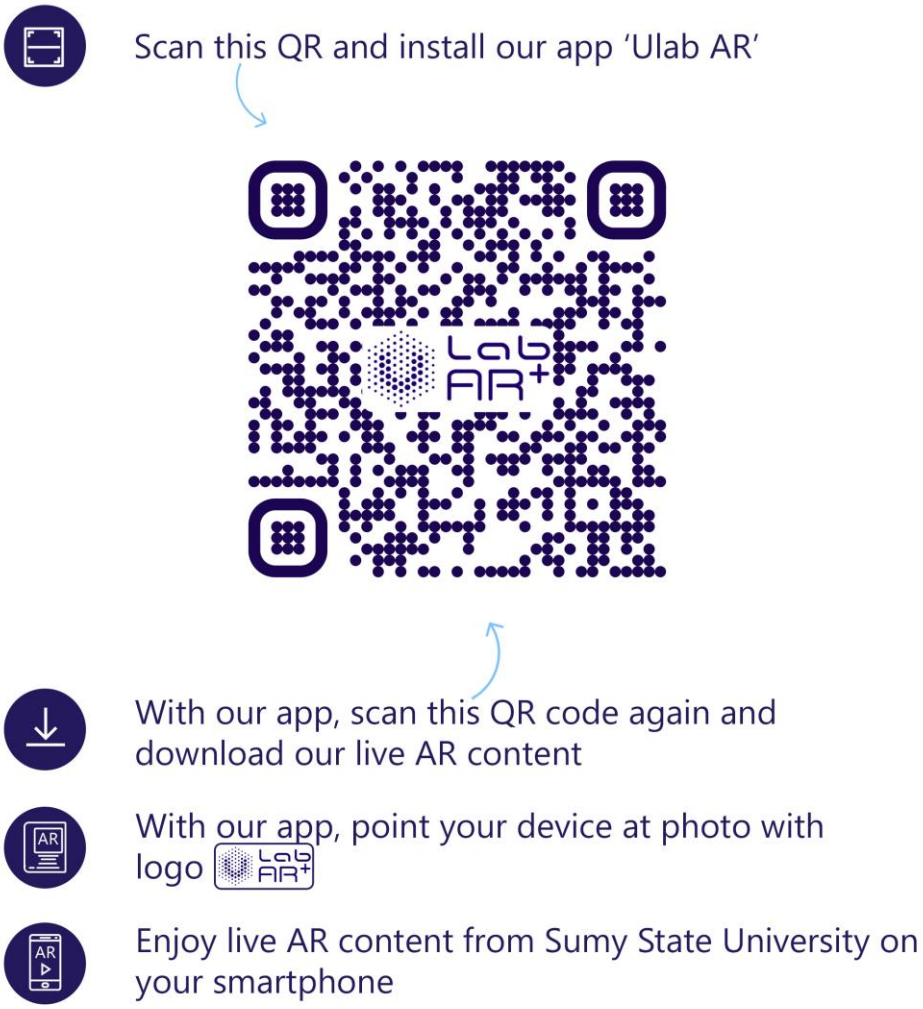
A disease is a combination of signs and/or syndromes with a common aetiology.

The milestone in clinical examination is making a diagnosis. The physician analyses all obtained information from interviewing the patient as well as objective examinations to establish a preliminary diagnosis. The next step involves using additional objective methods in substantiating the preliminary diagnosis.

Laboratory and instrumental investigations (additional diagnostic methods) must be *supporting evidence in establishing the basic diagnosis and the diagnoses of complications.* The choice of the volume of additional diagnostic methods requested by the physician should depend on the results of all obtained information. The requested investigations should be focused on confirming the preliminary diagnosis, basic diagnosis, and diagnoses of complication separately.

Individual examination of patients gives a real opportunity to arrange theoretical knowledge in order to form a proper clinical judgment.

Finally, it is important to note that clinical endocrinology characterizes a multidisciplinary approach in combining knowledge from different medical fields.



ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DF	Diabetic Foot
DKA	Diabetic ketoacidosis
DN	Diabetic Neuropathy
DM	Diabetes mellitus
DR	Diabetic Retinopathy
IGT	Impaired glucose tolerance
DPP-4	Dipeptidyl Peptidase-4
IAA	Autoantibodies to insulin
ICA	Autoantibodies to islet cell
IFG	Impaired fasting glucose
FPG	Fasting plasma glucose
GLP-1	Glucagon-Like Peptide-1
GFR	Glomerular filtration rate
GTT	Glucose Tolerance Test
HbA1c	Glycated haemoglobin
LADA	Latent autoimmune diabetes in adults
MODY	Maturity Onset Diabetes Mellitus in Young
OGLD	Oral Glucose-Lowering Drugs
OGTT	Oral Glucose Tolerance Test
PAD	Peripheral Artery Disease
PPG	Postprandial plasma glucose
SGLT-2	Sodium-Glucose Cotransporter- 2
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

1. DIAGNOSIS OF DIABETES MELLITUS AS THE BASIC DIAGNOSIS

1.1. Definition and Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a heterogeneous group of metabolic diseases characterized by chronic hyperglycaemia due to absolute/relative insulin insufficiency or peripheral insulin resistance.

DM can be classified as follows:

I. According to types by the World Health Organization (WHO), 1999:
   1. DM type 1 (results from β-cell destruction, leading to absolute insulin deficiency), including LADA-diabetes.
   2. DM type 2 (results from a progressive insulin secretory defect on the background of insulin resistance).
   3. Other specific types of diabetes (secondary diabetes):
      a. monogenetic defects in ß-cells function (MODY – maturity onset diabetes of the young);
      b. genetic defects in insulin action (leprechaunism, Rabson-Mendenhall syndrome);
      c. diseases of the exocrine pancreas (pancreatitis, cystic fibrosis, trauma, pancreactomy, etc.);
      d. endocrinopathies (e.g., thyrotoxicosis, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma);
      e. associated with other genetic syndromes: Klinefelter's syndrome, Down's syndrome, Turner's syndrome, etc.;
      f. drug- or chemical-induced DM due to their toxic effects on ß-cells.
   4. Gestational diabetes (found in pregnant women especially in the second and third trimesters of pregnancy).

II. According to degree of DM severity (based on the methods used to achieve DM compensation and the degree of chronic complications).
   1. Mild degree.
   2. Moderate degree.
   3. Severe degree.

III. According to the degree of compensation (based on the patient's clinical state and laboratory parameters).

1. Compensation state.
2. Subcompensation state.
3. Decompensation state.

IV. According to the complications of DM (hypoglycaemic and hyperglycaemic comas).

A. Acute complications.

1. Hypoglycaemic coma.
2. Diabetic ketoacidotic coma (DKA).
3. Hyperosmolar coma.
4. Lactacidemic coma.

B. Chronic complications (macroangiopathy and microangiopathy):

1. Microangiopathy complications.

1) diabetic retinopathy;
2) diabetic nephropathy;
3) diabetic neuropathy.

2. Macroangiopathy complications.

1) cardiovascular diseases;
2) cerebrovascular diseases;
3) diabetic angiopathy of the lower extremities.

NB: Detailed explanations of the various classifications are found in the respective sections below.

1.2. Algorithm in Making a Proper Diagnosis of Diabetes Mellitus

A proper understanding of DM and diagnosing is best done with the help of understanding the aetiology and pathogenesis of DM and hence following the algorithms in diagnosing diabetes mellitus as elaborated below.

DIAGNOSIS OF DIABETES MELLITUS

The preliminary diagnosis of DM is established based on the physician's primary evaluation of the patient's state, including patient's complaints, anamnesis and general objective clinical examination of the patient.

CLINICAL DIAGNOSIS OF DM

In order to establish a clinical diagnosis, the physician must substantiate the preliminary diagnosis with the help of objective additional investigative methods (laboratory and instrumental data).

1.3. Basic Diagnosis

The basic diagnosis of DM consists of 3 parts:

1. Type of DM.
2. Degree of DM severity.
3. State of DM compensation/decompensation.

The basic diagnosis of DM should be done based on the information gathered by the physician from the patient to support the presence of the *main triad of symptoms of DM* and by the lab verification. Clinical triad includes:

1. Polyuria (increased urination).
   This could either be *nocturnal polyuria*. Normal frequency of daily urination is 3 times (2 times in the day and 1 time at night).
2. Polydipsia (increased thirst thus requiring more fluid intake).
3. Loss of weight (for type 1 DM from normal body weight till cachexia, while for type 2 DM from one degree of obesity to the other).

NB: The main aim of establishing the basic diagnosis is:

1. *To confirm the preliminary diagnosis through information gathering (complaints and anamneses).*
2. *To set a base framework to perform additional diagnostic methods to confirm the basic diagnosis.*
3. *To establish a base for determining the type of DM, severity of DM and diagnoses of the chronic complications of DM.*

Verification of Diagnosis of DM

Verification of the basic diagnosis of DM involves performing laboratory diagnostic methods:

1. Fasting plasma glucose level determination (FPG).
2. Postprandial plasma glucose (PPG) level determination.
3. HbA1c.

Types of tests for determining blood glucose level in DM

1. *Fasting glucose* – blood glucose level in the morning before breakfast, after preliminary fasting > 8 h. It can sometimes be referred to as “preprandial”, which means “before meal”.
2. *Postprandial test* is performed at any time of the day.

Additional tests, recommended by ADA, 2020.

1. *Peak prandial glucose* – blood glucose level 1 h after meal. Sometimes it can be measured at 1-2 h after meal interval.
2. *Oral glucose tolerance test (OGTT)* is performed in the fasting state, after preliminary fasting > 8 h by administering an oral glucose load. It is done by measuring blood glucose level twice (before and 2 h after taking oral glucose load).
3. *HbA1c* – a test which reflects mean blood glucose level for the last 3 months before taking a blood sample. It measures the amount of haemoglobin attached to glucose (glycated haemoglobin).

The OGTT rules:

1. For adults 75 g of glucose are dissolved in 200 to 300 ml of water.
2. For kids: 1.75 g of glucose per kg (1.75 g/kg) of body weight, but not more than 75 g should be dissolved in 200 to 300 ml of water and drunk for 3 to 5 min).

However, in order to establish the basic diagnosis of DM, it is recommended to use two separate test samples.

NB: The OGTT is not recommended for routine clinical use, it is indicated for diagnosing:

1. *Impaired glucose states, i.e., impaired fasting glucose state (IFG) and impaired glucose tolerance (IGT), which are asymptomatic disorders of carbohydrate metabolism.*
2. *DM, when the available data for the verification of DM is not enough to establish the basic diagnosis of DM.*

Figure 1 – Types of glucometers

Table 1 – Diagnostic criteria for diabetes and other disorders of carbohydrate metabolism (WHO, 2006)

Diagnosis	Determination of glucose in blood	Capillary blood glucose parameter	Plasma venous blood glucose level
Normal	Fasting	3.3 to 5.5 mmol/l (< 100 mg/dl)	–
	After 2 h, after GTT	< 7.8 mmol/l (< 140 mg/dl)	–
Diabetes	Fasting	≥ 6.1 mmol/l (< 110 mg/dl)	≥ 7.0 (≥ 126 mg/dl)
	After 2 h, after GTT	≥ 11.1 mmol/l (< 200 mg/dl)	≥ 11.1 (≥ 200 mg/dl)
Impaired glucose tolerance	Fasting	5.6–6.1 mmol/l (100 to 110 mg/dl)	< 7.0 (< 126 mg/dl)
	After 2 hours after GTT	7.8 to 11.0 mmol/l (140 to 200 mg/dl)	≥ 7.8 (≥ 140 mg/dl) and < 11.1 (< 200 mg/dl)
Impaired fasting glucose	Fasting	5.6 to 6.1 mmol/l (100–110 mg/dl)	≥ 6.1 (≥ 110 mg/dl) and < 7.0 (< 126 mg/dl)
	After 2 hours (if defined)	< 7.8 mmol/l (< 140 mg/dl)	< 7.8 (< 140 mg/dl)

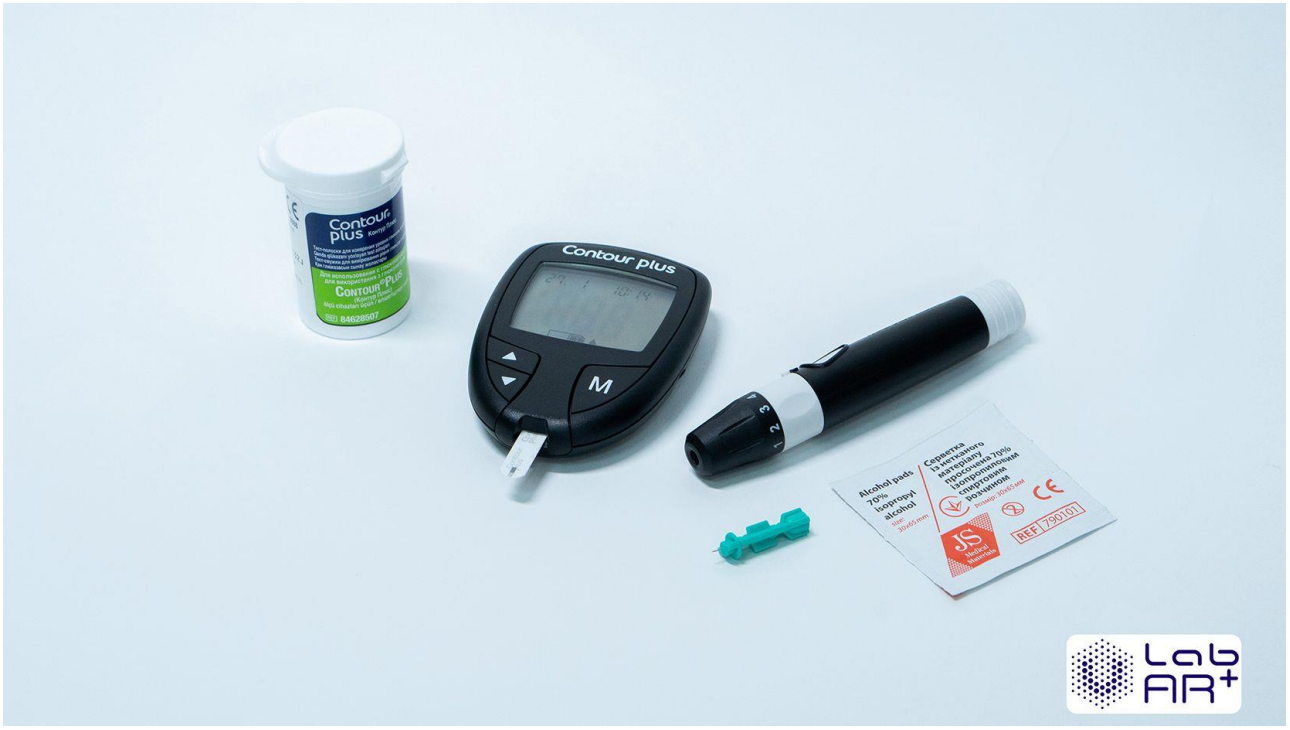


Figure 2 – How to use a glucometer

Rules of glucometer use:

1. *Glucometers work with the help of a plastic strip covered with glucose oxidase.*
2. *The strips are used only once and discarded.*
3. *0.2 to 1.1 µl of blood is sampled from the finger for testing using a lancing device, which is bought alongside the glucometer.*
4. *It takes about 30 seconds to get the desired result.*
5. *To convert mmol/l to mg/dl, multiply by 18.*

   NB: Note should be taken when reading glucometers based on their calibration because there exist capillary blood calibrated glucometers and plasma venous blood calibration. Glucose plasma levels are usually from 10 to 15% higher than capillary blood and even more after meals.

1.3.1. Determining the Type of Diabetes Mellitus

Determining the type of DM by WHO (1999) classification (see p. 8):

1. Anamnesis gathering to determine the conditions of DM onset (age, weight loss, DKA) and previous laboratory data.
2. Laboratory data:
   a) serum C-peptide and insulin;
   b) determination of autoantibodies to glutamic acid decarboxylase, insulin and islet cell autoantibodies.

The main task at this stage is differentiating between type 1 (about 5-10% of all diabetes cases) and T2DM (> 85 % of all diabetes cases).

Other specific types of DM

Late autoimmune diabetes of adults (LADA)

LADA is a subtype of type 1 DM, which is characterized by the following features:

- onset at > 30 years;
- presence of characteristic autoantibodies;
- patients do not require intensive basic-bolus insulin therapy;
- faster decline in C-peptide compared to type 2 DM;
- lower BMI than typical for type 2 DM.

The main differences from type 1 DM are slower progression and later onset. And the differences from type 2 diabetes are the absence of insulin resistance, autoimmunity and faster occurrence of insulin therapy necessity.

The diagnosis is confirmed via typical antibodies detection. Treatment should be aimed at preserving residual beta-cells` function, as well as at adequate glycaemic control. Patients need to be administered insulin therapy when the function of beta cells is lost. The period from LADA onset to absolute insulin deficiency is variable and can be prolonged by treatment, aimed at preserving beta-cells' function, decreasing insulitis and reducing hyperglycaemic stress. The options include insulin, DPP-4 inhibitors and GLP-1 agonists.

Maturity onset diabetes of the young (MODY)

Each MODY type is caused by single mutation in a gene, which is responsible for beta-cells function, development or regulation. This leads to impairment in glycemia regulation because of glucose-sensing or insulin release disturbances.

Signs to suspect MODY:

- strong family history of diabetes;
- onset at young age, especially at first 6 months of life;
- lack of insulin resistance evidence;
- absence of type 1 diabetes features (i.e., absence of GABA antibodies or normal C-peptide levels).

Diagnosis is confirmed via genetic testing. MODY 1 and 3 require sulfonylurea treatment. MODY 2 can usually be managed by regular exercises and diet.

Table 2 – Most common MODY types

MODY type	**Defected gene/protein**	**Prevalence**	**Description**
MODY 1	Hepatocyte nuclear factor 4α	5–10 %	HNF4α responds for the early development of the pancreas, liver and intestines. Responds to sulfonylurea treatment.
MODY 2	Glucokinase	30–70 %	Mild change in glucose tolerance test results. Can be easily managed through the diet and physical activity
MODY 3	Hepatocyte nuclear factor 1α	30–70 %	HNF1α is responsible for beta cells` differentiation. Disturbances in its function lead to reduction of beta cells` number and impairment of their function. Responds to sulfonylurea treatment.
MODY 4	PDX-1 homebox on chromosome 12	< 1 %	Pdx-1 is responsible for prenatal pancreas development. It also plays an important role in insulin and somatostatin regulation.

Table 3 – Differences between type 1 and type 2 DM

Parameter	**Type 1 DM**	**Type 2 DM**
Onset age	In childhood mostly	Mostly in adults
Percentage of total DM cases	About 5–10 % of all DM cases	> 85 % of all DM cases
Aetiology	Autoimmune attack on insulin and β-cells of the pancreas leading to an absolute decrease or absence of insulin	Increased resistance to insulin of target organs` receptors. Hence, insulin might be produced in normal quantities or in large amounts, but their effect is low
Association with obesity	Absent	Present (even though relative weight loss after overweight has been noted)
Ketoacidosis and ketonuria	Present	Absent
Treatment	Mainly by insulin replacement therapy	Using anti-diabetic drugs but occasionally insulin replacement therapy is used in case of severe state or high resistance to oral hypoglycaemic drugs
C-peptide and insulin in blood test	Low	High or normal (low in later stages)
Autoimmune antibodies to insulin	Present	Absent

Metabolic syndrome

Metabolic syndrome is a combination of metabolic disturbances, that provoke and accelerate each other. It is composed of the following criteria.

1. Abdominal obesity (>102 cm in men, >88 cm in women).
2. TAG > 1.7 mmol/l.
3. HDL < 1.03 in men, <1.3 in women.
4. The level of fasting glucose > 5.5 mmol/l.
5. SBP $\geq$ 130 mmHg, or DBP $\geq$ 85 mmHg.

If 3 or more of the mentioned are present, the patient is at a high risk of cardiovascular or cerebrovascular accident.

Body mass index (BMI) is an indicator, that shows relation between the patient`s weight and height. It is used for determining the grade of obesity.

BMI = weight, kg / (height, m)^2

The normal range is 18.5-24 kg/m^2

Homeostatic model assessment of insulin resistance (HOMA-IR) – is a method for evaluating beta-cells` function and insulin sensitivity.

HOMA-IR = (fasting insulin, mcU/ml * fasting glucose, mmol/l) / 22.5

The normal range is < 3.

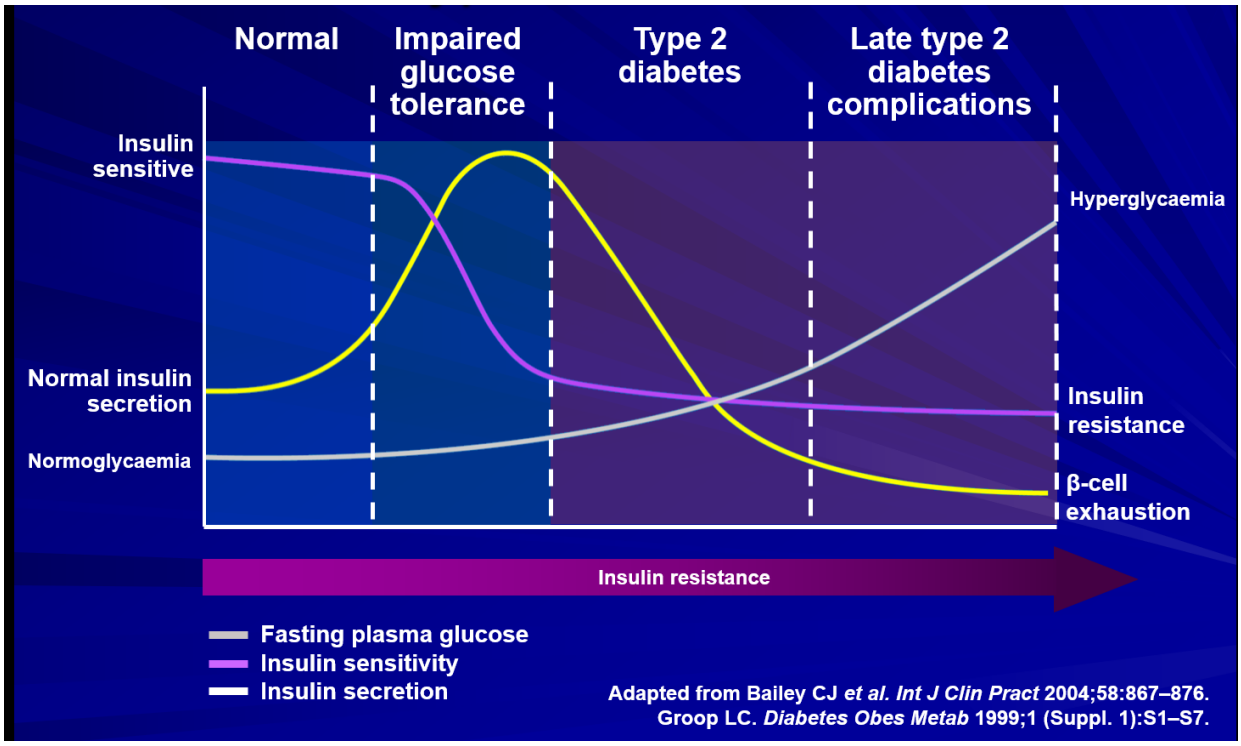


Figure 3 – Insulin resistance progression it type 2 DM

1.3.2. Determining Degree of DM Severity

The degree of severity of DM is determined by the following parameters:

1. Presence or absence of chronic complications and which stage of severity of these chronic complications (retinopathy, nephropathy, neuropathy, macroangiopathy) determines the degree of severity of DM determined by laboratory and instrumental methods of investigation.
2. Treatment scheme adopted to manage DM (diet, exercise, oral hypoglycaemic drugs and/or insulin therapy).

I. Mild severity:

Absence or presence of early stages of chronic complications of DM.

Treatment scheme: diet, physical exercises and lifestyle modification to normalize the condition.

NB: Mild severity of DM is seen only in Type 2 DM since insulin nor are oral hypoglycaemic drugs required for management purposes.

II. Moderate severity:

Chronic complications from 1st–3rd stages.

Treatment scheme: compensation reached only after insulin therapy for T1DM or after oral anti-diabetic medications for T2DM.

III. Severe state:

Any chronic complications of the 3rd and 4th stages. Insulin is for treatment:

1. Increased dose of administered insulin in T1DM.
2. Start administration of insulin replacement therapy in T2DM due to resistance to sulfonylureas.

Figure 4 – Glucose monitoring alarm points

1.3.3. Determining the State of DM Compensation/Decompensation

There are three states of compensation in DM:

1. Compensation.
2. Subcompensation.
3. Decompensation.

The state of compensation is determined by two major parameters:

1. Presence or absence of main triad of DM. If present, then state is said to be decompensation. If absent, then compensation.
2. According to laboratory data obtained from fasting and postprandial glycaemic levels, and level of glycated haemoglobin in blood (HbA1c). See summary in the table below.

Table 4 – Criteria of compensation of carbohydrate metabolism in type 1 and type 2 diabetes mellitus

Indicator		**Compensation**	**Subcompensation**	**Decompensation**
HBA1c*		< 7.0	7.1 – 7.5	> 7.5
Capillary blood glucose, mmol/l	Fasting glucose test	5.0 – 6.0	6.0 – 6.5	> 6.5
	Postprandial glycaemia (2 h after meals	7.5 – 8.0	8.1 – 9.0	> 9.0
	Glycaemia bedtime	6.0 – 7.0	7.1–7.5	7.5

** Normal HBA1c from 4 to 6%*

Figure 5 – One strip test for HbA1c evaluation

2. DIAGNOSIS OF CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Classification of chronic complications of diabetes mellitus:

1. Microangiopathic complications:

1) diabetic neuropathy;
2) diabetic retinopathy;
3) diabetic nephropathy.

2. Macroangiopathic complications:

1) macroangiopathy of lower extremities;
2) cerebrovascular angiopathy;
3) cardiovascular diseases:
   - ischaemic coronary heart diseases (myocardial infarction).

2.1. Microangiopathy

2.1.1. Diabetic Neuropathy

It should be understood, that diabetic neuropathy is the earliest (first) chronic complication of DM and it is seen in all patients but in varying degrees of clinical manifestations, hence the need for a better classification occurs in order to properly observe the clinical changes.

Pathogenesis

DN is mostly caused by microangiopathy of vasa nervorum. Another contributing mechanism of nerve damage is the direct nerve damage by disturbances of glycaemia levels. The process of nerve lesion can be described with the help of the term “primary axonopathy”. It refers to primary damage of the nerve axon, which is followed by demyelination. It then results into axonal current insufficiency and reduction of intracellular energy production. In the case of DN, most of the damage done can be successfully reversed by the proper therapy and adequate glycaemic control.

Classification of diabetic neuropathy

There exist different approaches to classification of diabetic neuropathy (DN): based on clinical manifestations, pathogenesis, location, onset and other features. Clinical classifications include up to 20 types of DN.

1) Symmetrical polyneuropathies:
    a. sensorimotor
    b. sensory
2) Autonomic neuropathy
    a. cardiovascular autonomic neuropathy
        i. tachycardia at rest
        ii. postural hypotension
        iii. silent myocardial infarction/ischaemia
    b. gastrointestinal autonomic neuropathy
        i. gastroparesis
        ii. diabetic diarrhoea
        iii. constipation
    c. genitourinary autonomic neuropathy
        i. urinary retention
        ii. impotence
    d. decreased hypoglycaemia perception
3) Focal and multifocal neuropathies
    a. radiculoplexus neuropathies
        i. lumbosacral
        ii. thoracic
        iii. cervical
    b. mononeuropathies
        i. Median neuropathy at the wrist
        ii. Ulnar neuropathy at the elbow
        iii. Peroneal neuropathy at the fibular head
    c. cranial
        i. Oculomotor palsy
        ii. Abducens palsy
    d. proximal motor (amyotrophy)

Clinical presentation

Typical DN is described as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates.

Sensorimotor DN

Sensorimotor DN usually has an insidious onset with paraesthesia or numbness. It is more likely to be found on screening, than to be a main complaint. It starts from the soles and toes, and then spreads upside symmetrically. In severe cases it may also affect fingers and hands. It affects all sensory modalities and results in reduced vibration perception threshold, pinprick, fine touch and temperature sensation. Loss or reduction of vibration sensation and/or absent ankle reflexes are the first signs found. An inability to fill 10g monofilament is a risk factor for ulceration. Less often, allodynia is a presenting sign – skin is tender and sensitive to touch.

Mononeuropathies

Diabetic mononeuropathies may be spontaneous or occur because of nerve entrapment or external pressure. Most commonly carpal tunnel syndrome is found. Symptoms include pain, numbness, paraesthesia beginning in fingers. The pain can irradiate to elbow and shoulder. Motor component of neuropathy presents as troubles taking small objects and clenching a fist. The disease progresses to partial or total loss of control over the hand.

Cranial mononeuropathies tend to occur suddenly and have a good prognosis. Most commonly seen (but still infrequent) are the palsies of III and VI nerves. Spontaneous recovery is slow over several months.

Autonomic neuropathy

Cardiovascular autonomic DN

1) *Tachycardia at rest* can be the first sign of autonomic cardiovascular DN. It is characterized as resting heart rate of up to 140 bpm, which becomes fixed as the disease progresses. This means, that, following the heart denervation, heart rate loses ability to increase or decrease in response to stimuli.

2) *Postural hypotension* is caused by absence of compensatory vasoconstriction in response to moving the body to upward position. When any person stands up, a significant part of circulating blood volume moves downwards, affected by gravity. Peripheral vasoconstriction is a normal compensatory response to that, and if it doesn`t occur, patient experiences hypotension up to collapse.

3) *Silent myocardial ischaemia* occurs in more than 60% of all patients with diabetes. Autonomic neuropathy can mask ischaemic pain, thus removing the limiting factor for physical or stress activity. Patients don`t feel the need to rest and take nitrates which can lead to myocardial infarction. Myocardial infarction is the main cause of deaths in patient with diabetes. It is accompanied by atypical pain or is painless (silent) in more

than 30% of all cases associated with diabetes. Atypical pain syndrome leads to late diagnostic and delays the necessary treatment.

Gastrointestinal autonomic DN

1) *Gastric motility disorders*, as well as oesophagus motility disorders, result from vagus nerve impairment. Symptoms include nausea, dysphagia, postprandial fullness, recurrent vomiting and electrolyte disbalance in severe cases.

2) *Diabetic diarrhoea* can be explained both by disturbances of intestine innervation and overgrowth of gastrointestinal flora. Characteristic features include imperative urges to defecate and nocturnal diarrhoea. Patients suffer from 15-20 stools daily, which can lead to hypoglycaemia.

3) *Constipation.* Gastrointestinal DN can result into hyper- or hypomobility of the affected gastrointestinal segment. Diminished colon peristalsis can lead to decrease in stool regularity up to 1-2 times a week.

Genitourinary autonomic DN

1) *Urinary retention* is clinically noticeable in advanced stages. Initial symptoms include the enlargement of the bladder and increased postvoiding residual volume. Urinary retention may promote urinary infections perceptivity.

2) *Impotence* occurs in response to disorganization between parasympathetic innervation, which promotes erection, and sympathetic innervation, which promotes ejaculation.

Decreased hypoglycaemia perception can be associated with autonomic neuropathy. It is characterized as a state, when the patients doesn`t experience typical symptoms of hypoglycaemia. The other causes for this state include hypoglycaemia during sleep or physical exercises and administration of non-selective beta-blockers.

Rare DN

Insulin neuritis (Ellenberg syndrome)

It occurs in patients who overwent rapid glycaemia reduction with high doses of insulin after a long period of inadequate glycaemic control. The main symptom is acute onset of intensive pain 6-8 weeks after rapid decrease of glycaemia. It is accompanied by rapid weight loss (diabetic cachexia) which can be misinterpreted as a result of proper glycaemic control. Pain is often described as 10/10 by patients. Pain-provoking factors are touching, non-painful irritants, bedsheets, clothes. Components of autonomic neuropathy may also be present.

Diabetic amyotrophy

Symmetrical proximal motor neuropathy is one of the rare variants of DN. It has a subacute onset (several weeks or months). Symptoms include progressive weakness and atrophy of proximal leg muscles, sometimes – brachial muscles. Another presenting symptom is severe deep burning pain, which can keep patients awake at night and cause cachexia. Sensitivity disturbances are minimal or absent. This state may be misdiagnosed as a primary muscle damage or myelopathy.

Instrumental diagnosis of diabetic neuropathy

The diagnosis of diabetic motor neuropathy can be established by visual observation (signs of hyperkeratosis, skin dryness, ulcer formations, bone deformations of hands and/or feet), objective evaluation as well as instrumental diagnostic methods, e.g., ultrasound, electromyography; for osteoarthropathy X-ray, CT-densimetry, etc.

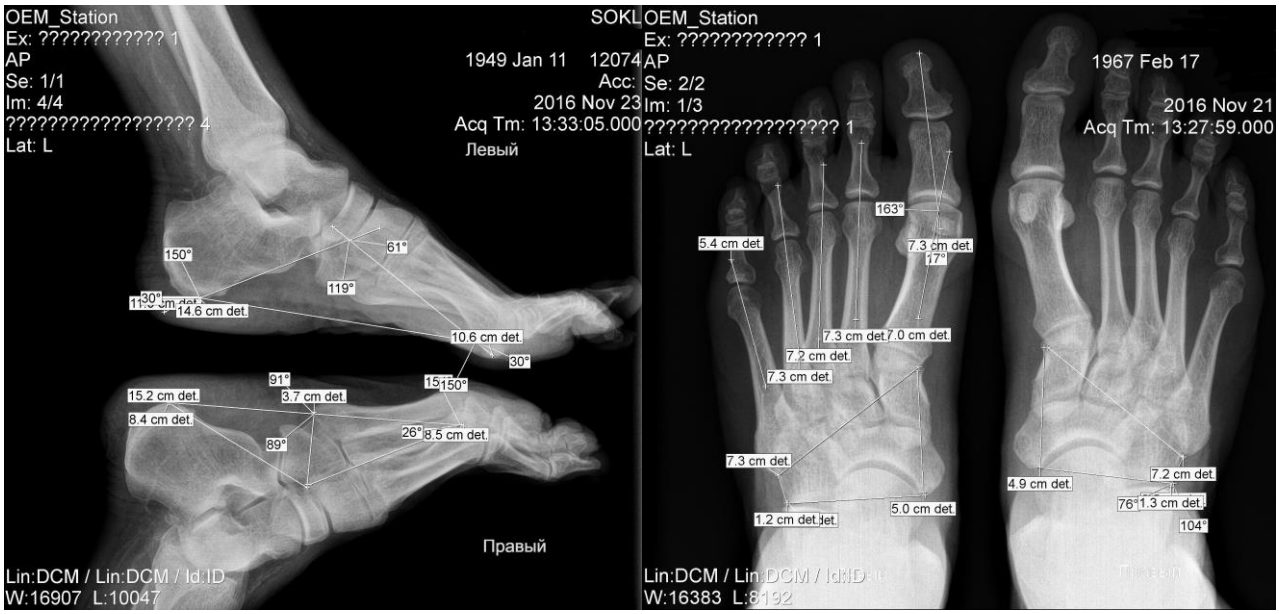


Figure 6 – Lateral (left) and anteroposterior (right) radiograph views of feet deformations caused by diabetic osteoarthropathy

Evaluation of sensory diabetic neuropathy includes the use of diagnostic instruments which are indicated below.

I. General recommendations.

1. Explain each test before you do it.
2. Unless otherwise specified, the patient's eyes should be closed during the actual testing.
3. Compare symmetrical areas on the two sides of the body.

4. Also compare distal and proximal areas of the extremities.
5. When you detect an area of sensory loss map out its boundaries in detail.

II. Vibration perception.

1. Use a low-pitched tuning fork (128 Hz). It usually has a 0-8 scale and the result of test is percepted by the examiner via optical illusion, which appears on a scale due to vibration. A normal vibration sense is > 6 points, while < refers to high ulceration risk.

a) Perform a test with a non-vibrating tuning fork first to ensure that the patient is responding to the correct stimulus. You may also demonstrate which feeling should a patient respond to on a probably unaffected region.

b) Place the stem of the fork over the distal interphalangeal joint of the patient's index fingers and big toes.

c) Ask the patient to tell you when he stops feeling vibration and note the result.

2. If vibration sense is impaired proceed proximally. Suggested regions to perform the test: wrists, elbows, medial malleoli, patellas.

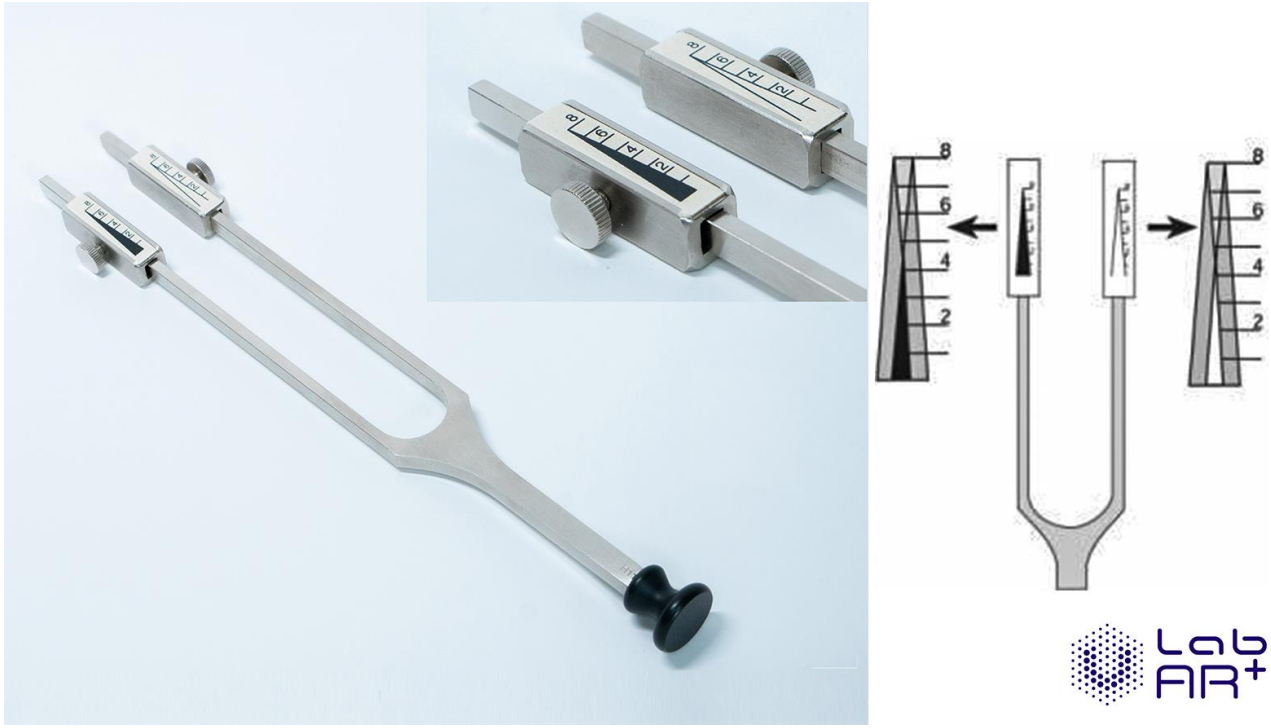


Figure 7 – Neurological low-pitched tuning fork

3. Electronical devices can also be used to measure vibration perception threshold: neurothesiometer and biothesiometer. They send vibration of different intensities applied to the big toe. The threshold is measured in volts per micrometre (VPT), and the normal sensation refers to $\leq$ 25 V.

Figure 8 – Electronical devices for vibration perception measurement

III. Subjective light touch.

1. Use your fingers to touch the skin lightly on both sides simultaneously.
2. Test several areas on both the upper and lower extremities.
3. Ask the patient to tell you if there is difference from side to side or other "strange" sensations.

IV. Position sense.

1. Grasp the patient's big toe and hold it away from the other toes to avoid friction. Move the finger up and down with the patient's eyes closed and ask the patient to identify the direction you move the toe.
2. If position sense is impaired move proximally to test the ankle joint.
3. Test the fingers in a similar fashion.
4. If indicated, move proximally to the metacarpophalangeal joints, wrists, and elbows.

V. Dermatomal testing.

It is performed to evaluate focal or multifocal neuropathy. With the use of all mentioned methods (most commonly, pinprick and light touch sensation) symmetrical dermatomes are tested and compared.

VI. Tactile and pain sensation.

Use Semmes-Weinstein monofilament for touch sensation threshold evaluation and a sharp sterile object (pin) to test pain sensation. The monofilament is applied perpendicular to the skin until it bends or buckles from the pressure, left in place for approximately one second and then moved away.

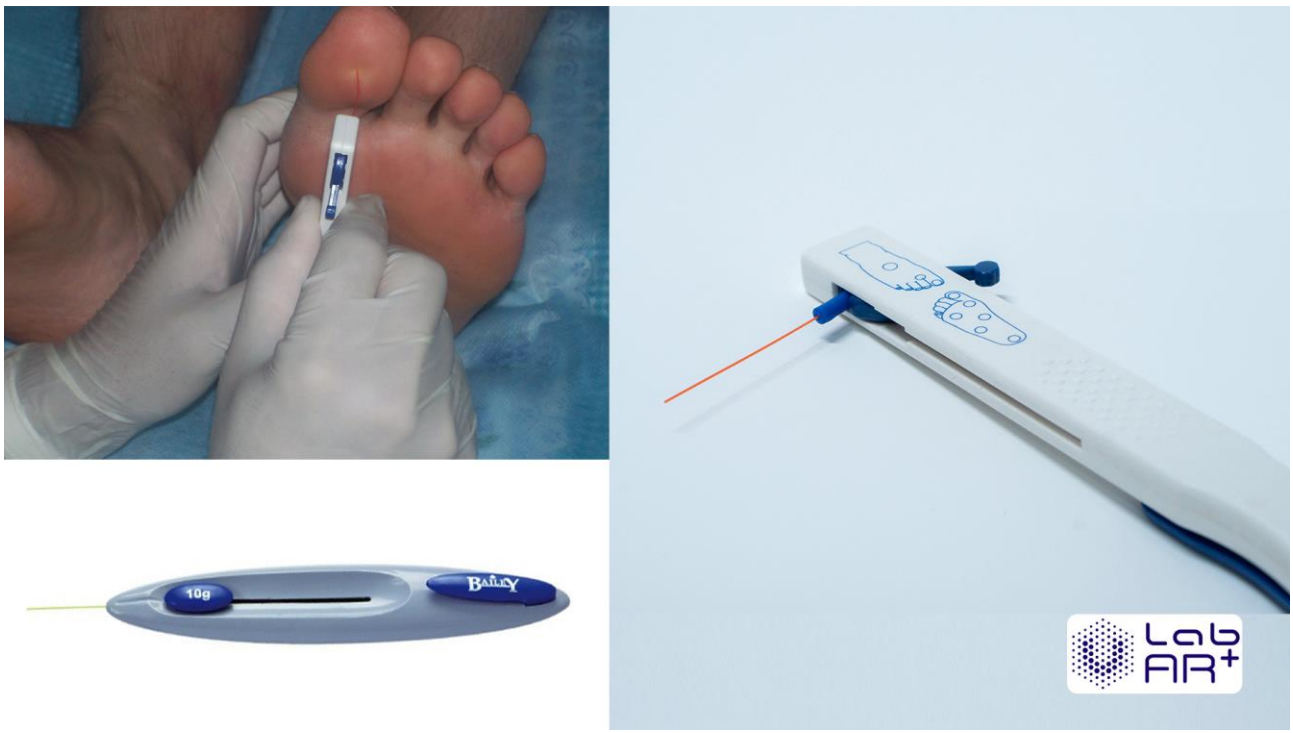


Figure 9 – Testing tactile sensation with Semmes-Weinstein monofilament

Semmes-Weinstein monofilament instructions

Semmes-Weinstein monofilament helps to evaluate A-beta fibers, measuring the patient`s sensation to light touch.

1. Explain the procedure to the patient and instruct him/her how to respond to the stimuli.
2. Take note of areas with corns, calluses, burns or other types of defects.
3. Support the patient's extremity on a flat, stable surface. The test should be done in a comfortable atmosphere with the patient`s eyes closed.
4. Press the monofilament on the skin at an angle of 90^0 until it bends. Hold it in this position for 2 seconds and remove it. The stimulus is applied once, and the reaction indicates positively.

   Register the results using a circle to indicate sensitive zones and a cross to indicate lack of sensation

NB: Before and after usage, the filament should be gently cleaned with a disinfectant. Do not use if it is bent or twisted.

VII. Temperature sensation.

Often omitted if pain sensation is normal.

Use Tip Therm instrument with different properties of plastic and metal to generate sensations of different temperatures on the skin's surface.

Apply both tips of the stick in turn at the dorsum of the feet and legs and ask the patient (with the eyes closed) to identify whether the stick is cold or hot.

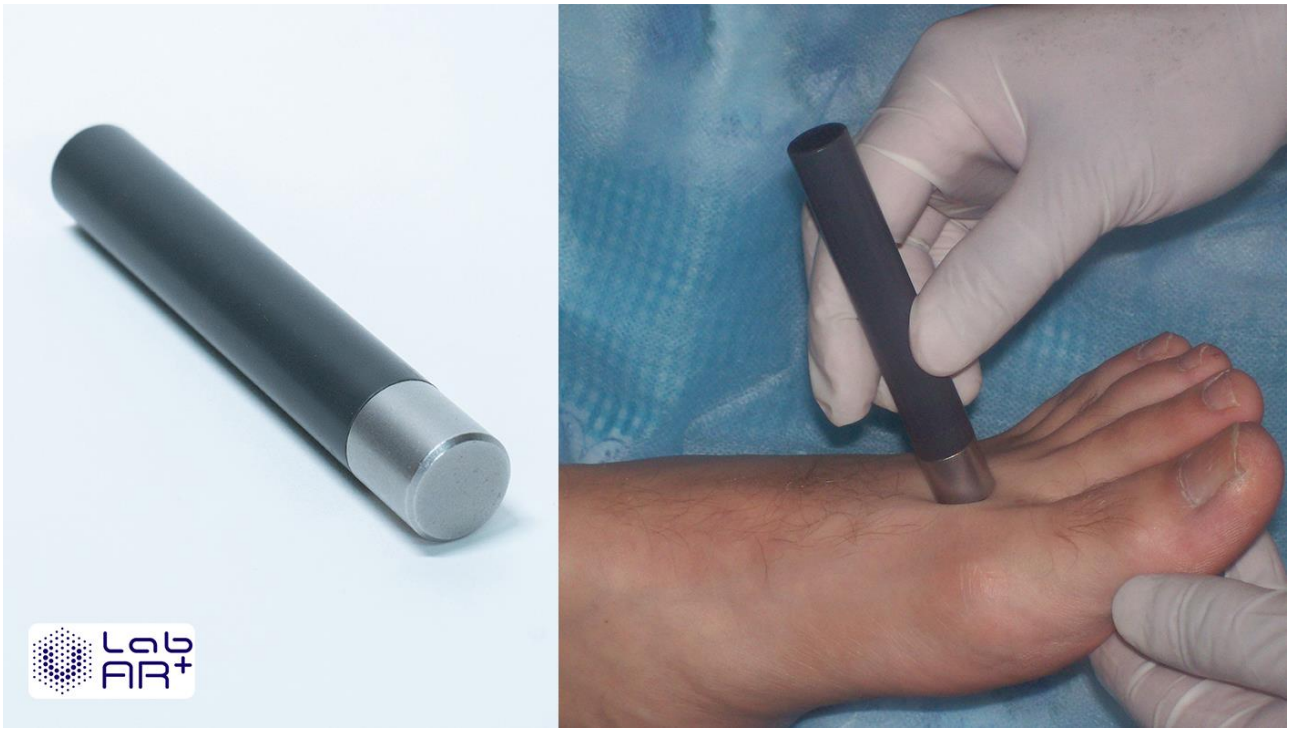


Figure 10 – Temperature sensory testing with Tip Therm

VIII. Pulsation.

This is to rule out vascular damage. Normal pulse with other symptoms indicates more of neuropathic effect, whereas decreased or absent pulse points to vascular damage.

Assess the pulse symmetry and artery amplitude of each leg.

The Dorsalis Pedis Artery pulse is palpable on the dorsum of the foot in the first intermetatarsal laterally to the extensor tendon of the great toe.

The Posterior Tibial Artery pulse can be examined behind and below the medial malleolus.

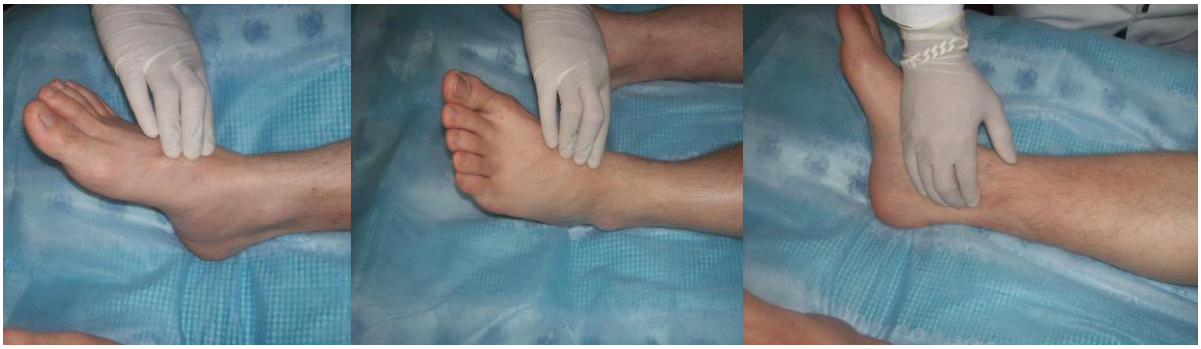


Figure 11 – Palpation of the pulse on the Dorsalis Pedis Artery and Posterior Tibial Artery

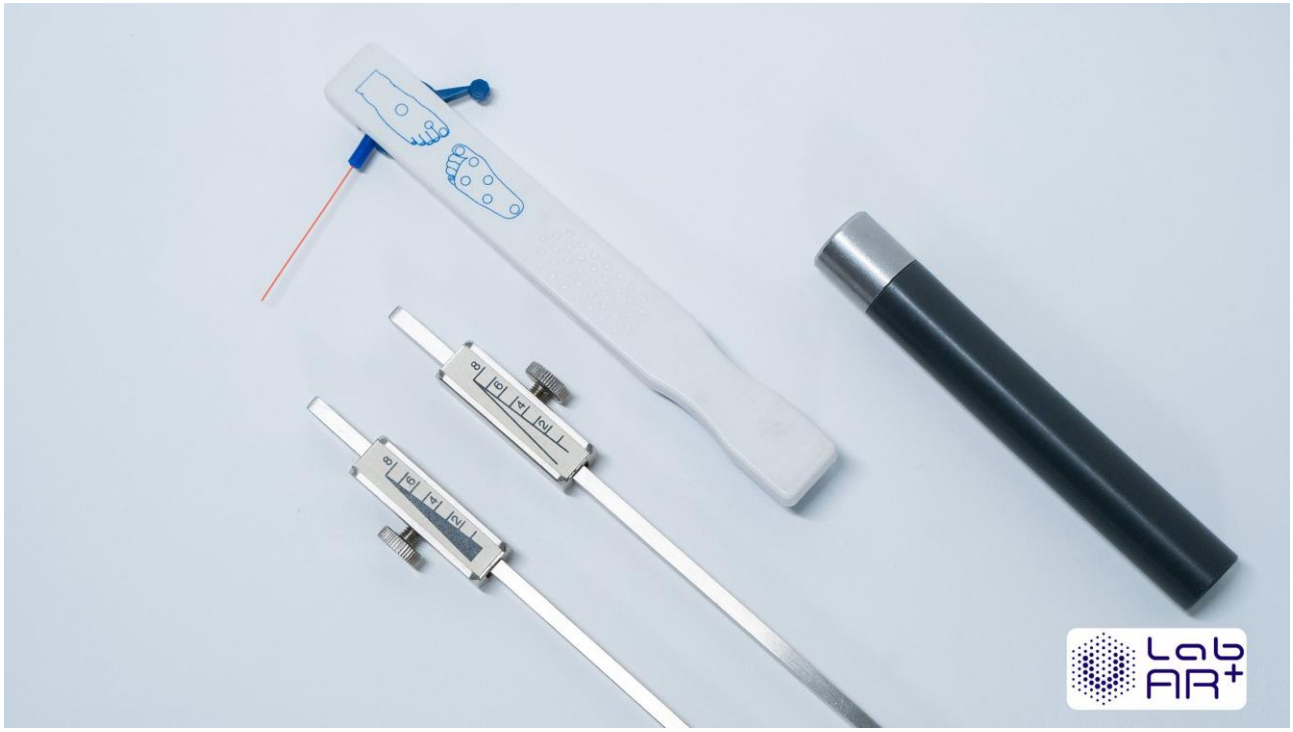


Figure 12 – Objective neurological examination

Evaluation of diabetic neuropathy severity

Diabetic polyneuropathy is commonly staged as follows (Neuropathy Symptom Score)

1. NO – no neuropathy
2. N1 – positive objective signs without symptoms
3. N2a – symptomatic mild diabetic polyneuropathy: sensory, motor or autonomic symptoms. Patient can heel-walk.
4. N2b – severe symptomatic diabetic polyneuropathy. Patient is unable to heel-walk.
5. N3 – disabling diabetic polyneuropathy.

Table 5 – Neuropathy Disability Score (NDS)

	Right side	**Left side**	**Summary**
Reflexes (0 – normal, 1 – decreased, 2 – absent)			
Knee reflex			
Ahillian reflex			
Sensitivity (0 – normal, 1 – impaired within toes, 2 – impaired from toes to the middle of the foot, 3 – impairment reaches ankles, 4 – impairment reaches knees)			
Pain			
Tactile			
Temperature			
Vibration sensitivity threshold			
1st finger			
Ankle			
Result: 0–4 points – normal, 5–13 – mild neuropathy, 14–28 – severe neuropathy			

Table 6 – Total Neuropathy Score (TNS)

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	Absent	Limited to fingers and toes	Symptoms extend to ankle or wrist	Symptoms extend to knees or elbows	Symptoms extend above knees or elbows / symptoms lead to disabling
Motor symptoms	Absent	Slight symptoms	Moderate symptoms	Patient requires help or assistance moving	Paralysis
Pain sensibility	Within normal range	Low in fingers or toes	Low up to wrists or ankles	Low up to elbows or knees	Low in regions above elbows and knees
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent

Severity grade for TNS:	asymptomatic	0–1 – none (grade 0)
		2–8 – minor (grade 1)
	symptomatic	9–16 – moderate (grade 2)
		17–24 – moderately severe (grade 3)
		25–28 – severe (grade 4)

Example of diabetic neuropathy diagnosis

1. Acute bilateral lower extremity diabetic neuropathy sensory form.
2. Chronic bilateral lower extremity diabetic neuropathy sensory form.

NB: Regarding the other forms of neuropathy, they are important too for clinical knowledge but are not very important in establishing the diagnosis of diabetic neuropathy. To establish the diagnosis of diabetic neuropathy, pay more attention to the peripheral distal neuropathy and autonomic neuropathy as explained above.

Treatment of diabetic neuropathy

1. Vitamin therapy (Vit B-group complex).

Thiamine (Vitamin B1) is a co-enzyme in several metabolic pathways of carbohydrates and branched-chain amino acids. Neurons receive chemical respiratory activity from the oxidation of carbohydrates, which is used to produce energy and maintain the correct structure of neurons.

Pyridoxine (Vitamin B6) is a co-enzyme in several metabolic pathways of amino acid, carbohydrate and sphingoid bases. In addition, it is involved in the formation of haemoglobin. Cobalamin`s (Vitamin B12) main functions are the cellular replication and growth, as he is a cofactor in DNA synthesis, and in both fatty acid and amino acid metabolism. It regulates the maturation of red blood cells in the bone marrow and the normal functioning of the nervous system

B-vitamins take part in the process of anaesthesia through effects on impaired axons impulse transmission, synthesis of inhibitory neurotransmitters and reduce oedematous neuronal processes. They can influence a broad range of neurological signs and symptoms like paraesthesia, diminished sensation of vibration and position, reluctant unsteadiness, depressed tendon reflexes, loss of memory, confusion, moodiness and loss of central vision (retinopathy).

Neurorubine combines three vitamins in high doses which are indispensable in the nervous system.

Each ampoule contains:

Vitamin Bl	(USP)	200 mg
Vitamin B6	(USP)	50 mg
Vitamin B12	(USP)	1000 mcg
Lidocaine HCl		10 mg

Each Lactab contains:

Vitamin Bl	(USP)	200 mg
Vitamin B6	(USP)	50mg
Vitamin B12	(USP)	1000 mcg

Figure 13 – Neurorubine

Each ***Milgamma*** ampoule contains 2 ml:

Cyancobalaminum	1 mg
Pyridoxinum chloratim	100 mg
Thiaminium chloratum	100 mg
Lidocainium chloratum	20 mg

Each Milgamma Dragee contains**:**

Cyancobalaminum	250 mcg
Benfotiaminum	50 mg

Figure 14 – Milgamma vials

2. Antioxidants. *Alpha lipoic, Thioctic Acid*

Oxidative stress resulting from enhanced free-radical formation and/or defects in antioxidant defence is implicated in the pathogenesis of diabetic neuropathy. Markers of oxidative stress such as superoxide anion and peroxynitrite production are increased in diabetic patients in relation to the severity of polyneuropathy. Thioctic (α-lipoic) acid favourably influences the vascular abnormalities of diabetic polyneuropathy such as impaired microcirculation, increased indices of oxidative stress, and increased levels of markers for vascular dysfunction, such as thrombomodulin, albuminuria. Treatment using intravenous or per os form of thioctic acid 600 mg/day reduces the chief symptoms of diabetic polyneuropathy to a clinically meaningful degree, reduces neuropathic deficits and improves cardiac autonomic neuropathy.

Figure 15 – Alpha lipoic acid medications

3. Laser therapy in the treatment of neuropathic pain syndrome.

The improvement of microcirculation and utilisation of oxygen in tissues as a result of low intensity laser therapy is intimately linked with positive influence on metabolism: higher level of oxidation of energy-carrying molecules of glucose, pyruvate, and other substances.

Laser procedures have analgesics effect, show reliable rising tolerance of patients towards physical tolerance test, elongation of the period of painless remission.

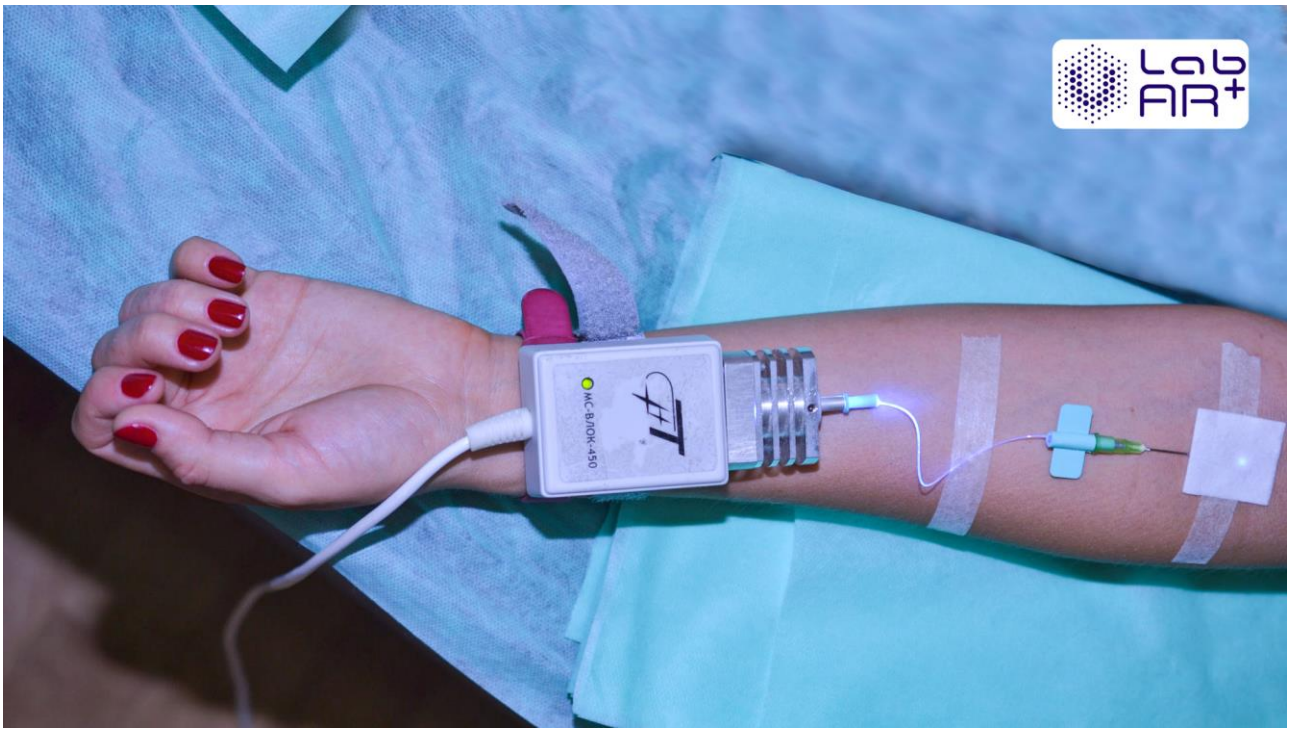


Figure 16 – Low intensity intravenous laser therapy

4. Pain reduction.

According to ADA, pregabalin, duloxetine and gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. Pregabalin is an antiepileptic drug. Treatment is initiated at 150 mg/day; maximal dose is 600 mg/day. Diabetic patients taking pregabalin may experience weight gain and it also causes a dose-dependent withdrawal syndrome. Gabapentin is initiated at 300 mg once a day and standard dose is 300 mg 3 times a day. Duloxetine is a serotonin and norepinephrine reuptake inhibitor. Initial dose is 60 mg/day.

Figure 17 – Pain reduction medications: duloxetine 30 mg, pregabalin 75 mg

2.1.2. Diabetic Nephropathy

Diabetic nephropathy is one of the chronic complications of DM. It is diagnosed by clinical manifestations (signs and symptoms), objective examination of patient, laboratory diagnosis and instrumental diagnosis.

Complaints and objective examination of diabetic nephropathy include:

1. Hypertension (secondary to kidney damage).
2. Generalized oedema starting from the face (during objective observation and palpation of the patient).
3. Polyuria (usually nocturnal polyuria) at initial stages of the disease which gradually decreases to oliguria/anuria in the 4^{th} and 5^{th} stages of diabetic nephropathy leading to chronic kidney disease (CKD).
4. Pollakiuria (increased frequency of daily urination > 3 times).

NB: *Pain during lumbar percussion (positive Pasternatsky sign) is not specific for diabetic nephropathy.*

Laboratory diagnosis of chronic diabetic nephropathy:

1. General urine analysis and 24 h urine control (to determine pollakiuria and polyuria).
2. Nechiporenko test (to rule out infections probably causing pyelonephritis as well as other infections of the urinary system).
3. Complete blood count and biochemical profile (to determine the blood levels of urea and creatinine in order to determine the staging of diabetic nephropathy).

Biopsy: it helps establishing the early morphological structure changes in the kidney (see classification of nephropathy by Mogensen C. E.).

Instrumental methods:

1. Ultrasound investigation.
2. Computer tomography.

Classification of diabetic nephropathy

1. *According to the stages of development of diabetic nephropathy (according to C. E. Mogensen).*
   Criteria for classification:
   a) glomerular filtration rate (GFR) by Roberg's probe (Normal GFR = 80 to 120 ml/min);
   b) proteinuria (24 h protein analysis of urine).

Figure 18 – Fast microalbuminuria assessment test

Table 7 – Classification of diabetic nephropathy by C. E. Mogensen

Stage of diabetic nephropathy		**GFR**	**Albuminuria**	**Other findings**
Preclinical stages (compensation stages)	Stage 1 Hyperfunction of kidneys	**Increased** >140 ml/min	Normoalbuminuria (< 30 mg/day)	1. Increasing of renal blood flow. 2. Hypertrophy of kidneys
	Stage 2 Initial structural changes of kidneys tissue	The **high** level of GFR is kept 120–140 ml/min	Normoalbuminuria (< 30 mg/day)	1. Thickening of the basal membranes of capillaries glomeruli. 2. Dilation of mesangium
Clinical stage (subcompensation)	Stage 3 Initial nephropathy (Start of kidney dysfunction with slight calibrations to normal function)	GFR decreases to **normal value** 90–120 ml/min	Microalbuminuria (from 30 to 300 mg a day)	1. Transient arterial hypertension. 2. Transient oedema
Stage of nephrotic syndrome* (decompensation)	Stage 4 High grade nephropathy	GFR is **decreased** $\leq$ 90 ml/min	Proteinuria (> 300 mg/day)	1. Nephrotic syndrome present. 2. Arterial hypertension
Stage of kidney failure (decompensation)	Stage 5 Uraemia	**Severe decreasing** of GFR < 10 ml/min	Proteinuria (> 300 mg/day)	1. Arterial hypertension. 2. Symptoms of intoxication

***** Nephrotic syndrome criteria: massive proteinuria > 3.5 g/day; hypercholesterolaemia, hypertension and generalized oedema, hypalbuminaemia < 25 g/l.

2. According to albuminuria.

Criteria of classification:

a) 24 h analysis of albumin in urine;

b) clinical urinalysis.

Table 8 – Classification of diabetic nephropathy by albuminuria

Parameter	**Clinical urine analysis**	**24 h urine analysis**	**Albumin (urine) to creatinine (urine) ratio, mg/mmol**	
			Male	**Female**
Normal albuminuria	< 20 mg/min	< 30 mg	< 2.5	< 3.5
Microalbuminuria	From 20 to 200 mg/min	From 30 to 300 mg	2.5–25	3.5–35
Macroalbuminuria	> 200 mg/min	> 300 mg	> 25	> 35

N.B. GFR has different standards for diabetic nephropathy staging, than for chronic kidney disease. I.e., GFR of 90 ml/min refers to normal kidney function in patient without diabetes, and to stage 4 of diabetic nephropathy.

Table 9 – Chronic kidney disease classification (according to Kidney Disease Quality Initiative

Stage	**GFR,** ml/min
1 – Kidney damage with normal kidney function	**≥ 90**
2 – Kidney damage with mild loss of kidney function	**89–60**
3a – Mild to moderate loss of kidney function	**59–45**
3b – Moderate to severe loss of kidney function	**44–30**
4 – Severe loss of kidney function	**29–15**
5 – Kidney failure	**< 15**

GFR calculations

Glomerular filtration rate (GFR) is considered as the best way to assess global renal function. Nowadays GFR estimations (based on creatinine equations) are most often used but measuring "true" GFR is still important in clinical practice, especially in particular patients.

1. Test of Reberg

GFR =(Cu/Cp) *V

Cu – urine creatinine; Cp – plasma creatinine; V – urine volume, ml/min

N.B.: the Danish physiologist, Paul Brandt Reberg was the first to use and define the concept of clearance. Reberg studied the urea and creatinine clearances on himself to prove that kidney has a filtrating and not only a secreting action (Reberg, 1926).

NB: *It should be noted that a normal Reberg's probe (from 80 to 120 ml/min) in healthy individuals is equivalent to 3rd stage of nephropathy in diabetic patients.*

2. Creatinine-based equations:

Estimated GFR (GFRe) using Cockroft-Gault formula:

$$\text{GFRe (ml/min)} = 1.228 \text{ X } \frac{(140 - \text{Age}) \text{ X Body Weight (kg)}}{\text{Plasma creatinine level (µmol/L)}} \text{ X } 0.85 \text{ (for women) or } 1.00 \text{ (for Men)}$$

Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula

eGFR = 186 x (Plasma creatinine, mg/dl) – 1,154 x (Age, years)–0.203

3. **CKD-EPI** formula is the most useful, as it helps to avoid analytical mistakes.

*GFR = 141 * min (Scr/κ,1)$^{\alpha}$ * max(Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 [if female] * 1.159 [if black];*

where

κ – 0.7 for female, 0.9 for male;

α – (-0.329) for females, (-0.411) for males

GFR can otherwise be calculated with the use of broadly available online calculators.

Treatment of diabetic nephropathy

To treat hypertension caused by diabetic nephropathy, **angiotensin converting enzyme (ACE) inhibitors** and/or **angiotensin receptor blockers** (ARB) are used.

B-blockers and calcium channel blockers are not recommended in treating hypertension caused by diabetic nephropathy.

NB: For detailed medications and doses for treating arterial hypertension of different aetiologies, see appendix B below.

Table 10 – Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors	
Captopril	12.5–50 mg once daily
Enalapril	5–40 mg once daily or in two equally divided doses
Fosinopril	10–40 mg once daily
Lisinopril	5–40 mg once daily
Peridopril erbumine	4–8 mg once daily
Peridopril arginine	5–10 mg once daily
Quinapril	5–40 mg once daily or in two equally divided doses
Ramipril	2.5–10 mg once daily or in two equally divided doses
Trandolapril	2–4 mg once daily

Table 11 – Angiotensin receptor blockers (ARB)

Angiotensin II receptor antagonists	
Candesartan	8–16 mg once daily
Eprosartan	600–800 mg once daily
Irbesartan	150–300 mg once daily
Losartan	50–100 mg once daily
Telmisartan	20–80 mg once daily
Olmesartan	20–40 mg once daily

Sodium-glucose cotransporter 2 inhibitors might also be used but consider side effects and cost. Dietary daily intake of protein should be approximately 0.8g/kg body weight in non-dialysis-dependent patients.

Treatment choice

Diabetes complications compromise the kidneys' filtration system, requiring the use of one of two techniques to purify the blood:

- haemodialysis
- peritoneal dialysis

Haemodialysis

Haemodialysis treatment does not cure kidney disease; it acts as a substitute kidney. Haemodialysis (cleaning the blood) uses a dialyzer (artificial kidney) to purify the blood of people suffering from severe renal (kidney) failure. The dialysis machine consists of a filter in which your blood circulates. The blood is mixed with a liquid called dialysate. The exchange between the two fluids (blood and dialysate) lets the blood eliminate certain substances (urea, creatinine, potassium, etc.) that were not filtered out by impaired kidneys. A system of tubing returns the blood to the body. At each treatment, a needle is inserted in the vein to allow the blood to flow through the tubes into the filter. Another needle is inserted to allow the blood to flow back into your body. The needles are removed at the end of each treatment run.

The treatment usually takes 4 hours. Dialysis must be done 3 times per week to both purify the blood and remove excess liquid. Haemodialysis requires adhering to a fixed schedule and living close to a dialysis centre.

Peritoneal dialysis

Peritoneal dialysis is another way to purify the blood. Peritoneal dialysis requires self-care, which need a medical visit once a month. Peritoneal dialysis demands a strict aseptic technique, because any contamination can cause intra-abdominal infections. The principle behind this treatment method is to use the peritoneal membrane (the membrane surrounding the abdominal organs) as a filter. A small tube (catheter) is inserted into the abdomen, with one end extending outside the body. A liquid (usually 2 litres) resembling the dialysate used in haemodialysis is infused into the abdominal cavity, exposing the blood vessels in the peritoneum to the fluid. The peritoneum functions like the artificial membrane in a dialyzer. Excess water and waste (urea, creatinine, potassium, etc.) pass from the blood through the peritoneum into the dialysis fluid. Usually, the liquid is left in the abdomen for 4 hours and is then drained away using the catheter. It usually takes 30-45 minutes four times per day, 7 days per week. The choice between the two forms of treatment depends on several factors: medical, personal and social. In both cases, adaptation to this new way of life, which disrupts people`s lives because of its frequency and necessary time.

Example of diagnosis of diabetic nephropathy: ***Diabetic nephropathy 4th degree.***

2.1.3. Diabetic Retinopathy

Pathogenesis

Diabetic retinopathy (DR) development is caused by several factors, the most contributive of which is chronic hyperglycaemia, which results into tissue damage via multiple mechanisms. The two main changes in retinal structure are increased vessels` permeability and their occlusion. Occlusion of blood vessels leads to ischaemia, thus causing chronic retinal hypoxia. It stimulates production of growth factors, including vascular endothelial growth factor (VEGF). VEGF acts via protein kinase C to stimulate endothelial cell growth (causing new vessel formation) and increases vascular permeability (causing exudative damage).

DR symptoms (based on complaints and objective examination) are characterized by:

1. Blurred vision/double vision.
2. Blindness in the late stages as a result of cataract caused by DR.
3. Excessive tearing (due to dryness of the eye).
4. Scotomas (presence of shapes or figures in the visual field due to oedema and exudates of the retina).
5. Pain in the eyes (caused by occlusion of the retinal artery supplying the optic nerve).
6. Oculomotor nerve palsy (rarely occurs).
7. Glaucoma (due to increased intraocular pressure).

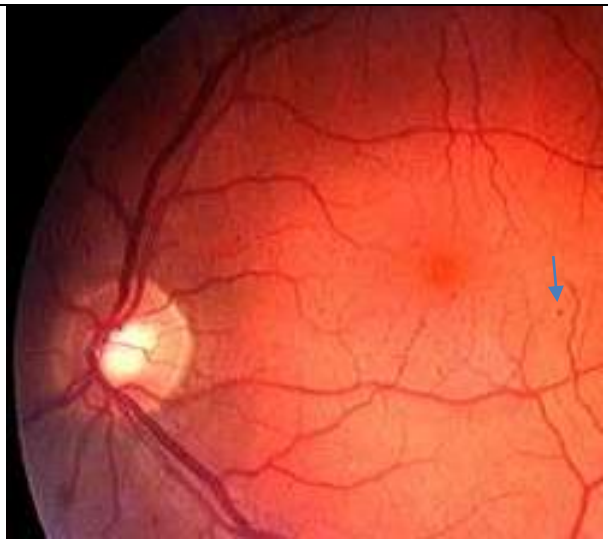
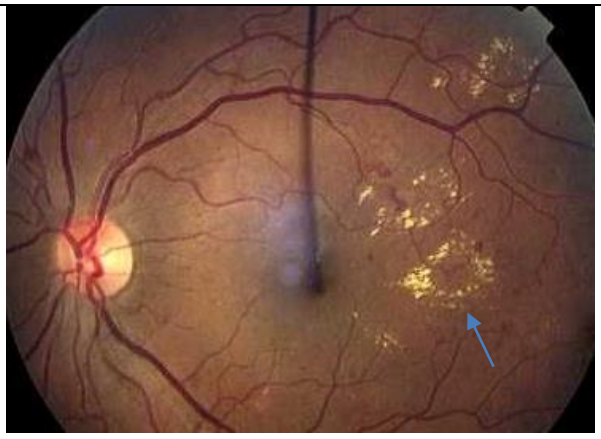
NB: *Usually DR is asymptomatic in the early stages. Signs of blindness or decreased vision are seen only in the late stages when macular oedema and vitreous haemorrhage takes place. All DM patients need eye check-ups every year and frequently depending on severity of DR.*

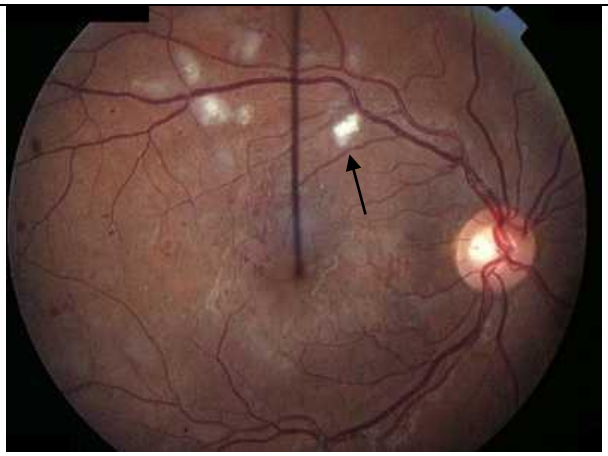
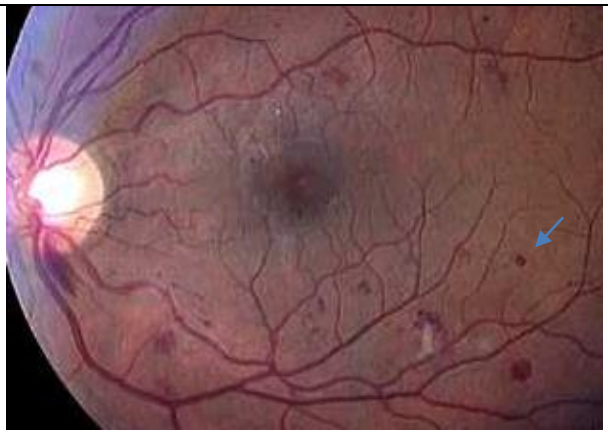
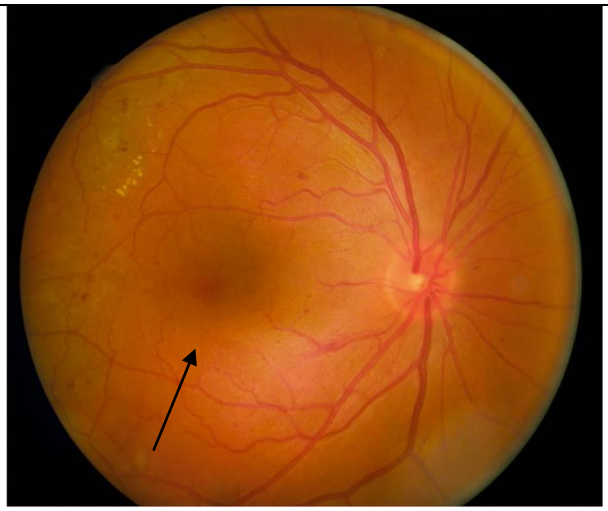
Diagnosing diabetic retinopathy student should pay attention to following signs:

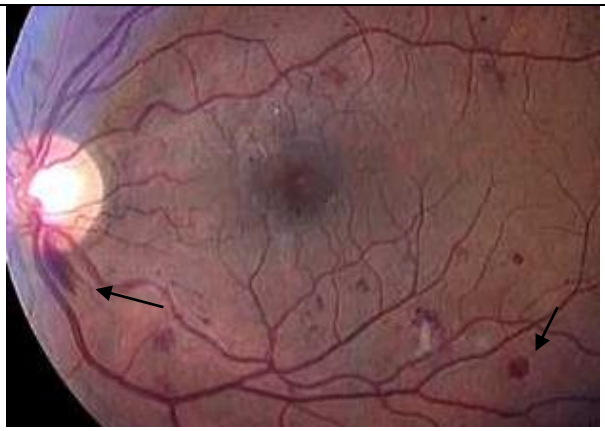
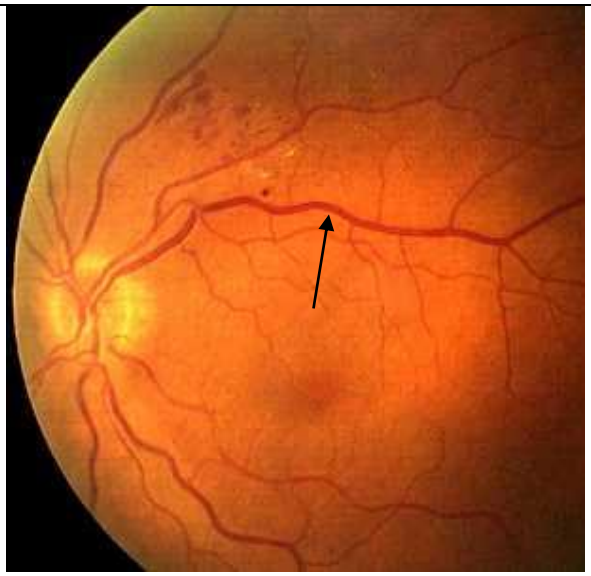
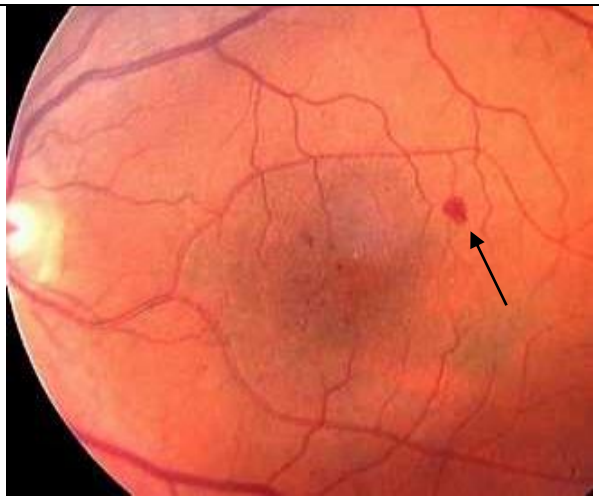
1. *aneurysms* or small *haemorrhages*, which appear as “dots&blots” signs;
2. *soft or hard exudates*;
3. *IRMA*s – abnormal branching of existing blood vessels;
4. state of venules - their shape, size, presence of *tortuosity*;
5. *neovascularisation* or abnormal new vessels;
6. state of *macula*;
7. *retinal detachment*;
8. *massive haemorrhages* and their localisation.

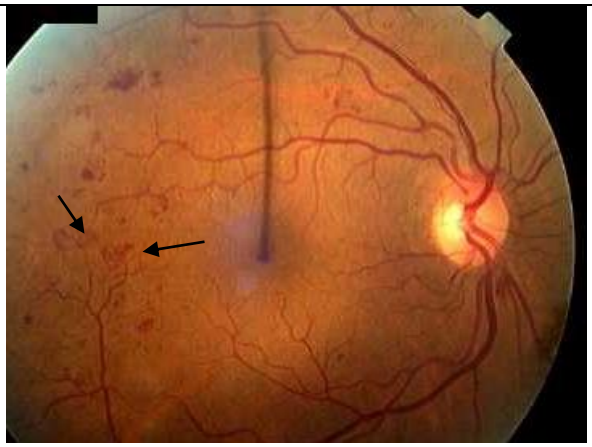
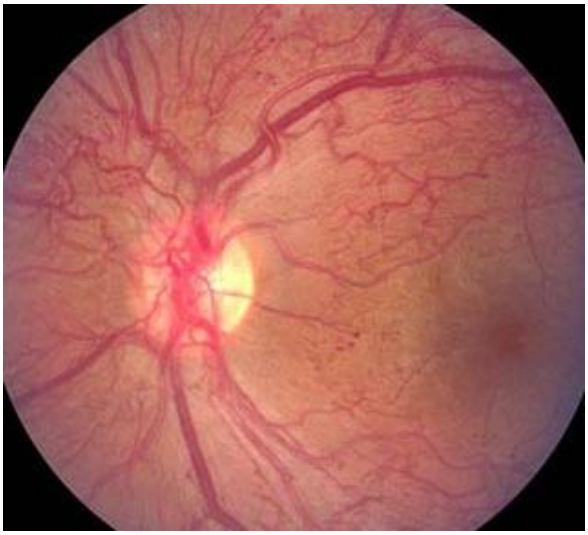
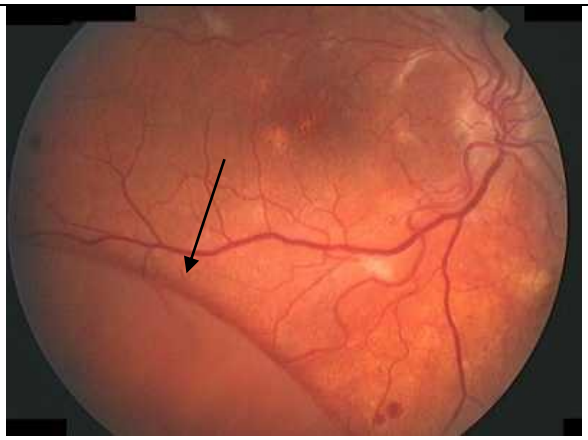
Classification. A classification of diabetic retinopathy is based on prognosis for vision and indications for specialist referral. Microaneurysms, abnormalities of the veins, and small blot haemorrhages and exudates situated in the periphery will not interfere with vision unless they are associated with macular oedema in the perimacular or macular area.

Table 12 – Diabetic retinopathy classification

Findings	**Image**	**Pathogenesis**
1. Nonproliferative stage		
Retinal microaneurysms		Asymmetrical dilatation of weakened capillary wall primary to partial/total occlusion site. In most cases these are the earliest clinical abnormalities detected. They appear as tiny, discrete, circular, dark red spots near to, but apparently separate from, the retinal vessels.
Hard exudates		These are characteristic of DR. They vary in size from tiny specks to large confluent patches and tend to occur particularly in the perimacular area. They result from leakage of plasma and proteins from abnormal retinal capillaries and overlie areas of neuronal degeneration.

Soft exudates or cotton wool spots		These are similar to those seen in hypertension, and occur particularly within five-disc diameters of the optic disc. They represent arteriolar occlusions causing retinal ischaemia and hence are a feature of pre-proliferative diabetic retinopathy.
Haemorrhages		Occur in the deeper layers of the retina and hence are round and regular in shape and described as 'blot' haemorrhages. May be difficult to differentiate from microaneurysms and the two are often grouped together as 'dots and blots'. Superficial flame-shaped haemorrhages may also occur, particularly if the patient is hypertensive.
2. Preproliferative stage is characterised by the findings described above and:		
Macular oedema		Focal or diffuse capillary leakage sometimes accompanied by cystoid macular changes. Ischaemic variant follows capillary closure and is associated with vision loss.

Blot haemorrhages		As the weakening of the vessels` walls progresses, haemorrhages appear to be larger in size.
Venous changes		These include venous dilatation (an early feature probably representing increased blood flow), 'beading' (sausage-like changes in calibre) and increased tortuosity including 'oxbow lakes' or loops. These latter changes indicate widespread capillary non-perfusion and are a feature of advanced pre-proliferative retinopathy.
IRMAs		Intraretinal microvascular abnormalities (IRMA) are dilated, tortuous capillaries which represent the remaining patent capillaries in an area where most have been occluded.

3. Proliferative stage		
Neovascularisation	 	May arise from the venous circulation on the optic disc or the retina in response to areas of ischaemic retina. The earliest appearance is that of fine tufts of delicate vessels forming arcades on the surface of the retina. As they grow, they may extend forward to the vitreous. They are fragile and leaky and are liable to rupture, causing haemorrhage which may be intraretinal, pre-retinal (‘sub-hyaloid’) or into the vitreous. Serous products leaking from these new vessel systems stimulate a connective tissue reaction, retinitis proliferans.
Retinal detachment		Neovascularisation is followed by fibrosis. Fibrous tissue causes retinal traction, which may result into tractional retinal detachment.

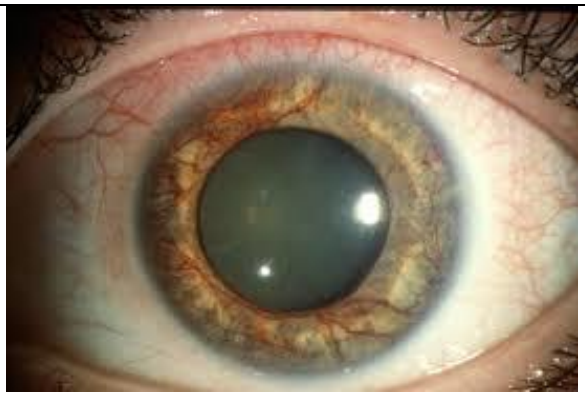
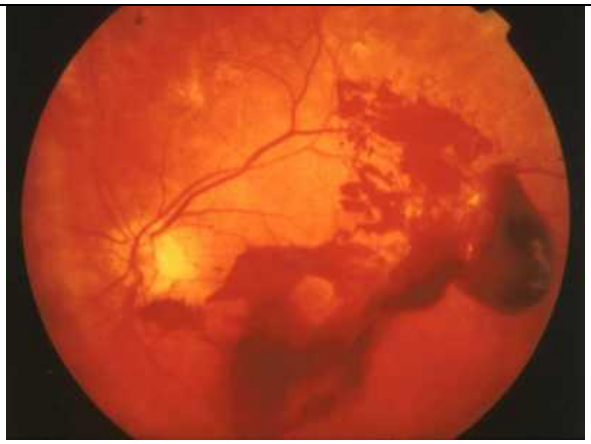
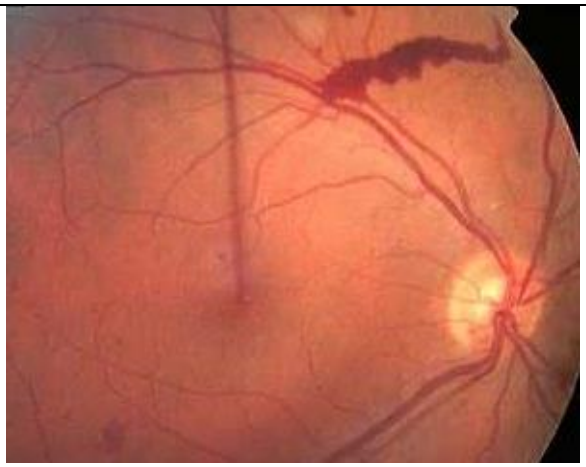
Rubeosis iridis		Neovascularisation on the surface of iris.
Vitreous haemorrhage		Vitreous haemorrhage is the extravasation of blood into one of the several potential spaces formed within and around the vitreous body.
Sub-hyaloid haemorrhage		Accumulation of blood in areas of localized detachment of retina.

Image source https://www.glycosmedia.com/education/diabetic-retinopathy/

Example of diabetic retinopathy diagnosis

1. Diabetic retinopathy, pre-proliferative stage.
2. Diabetic retinopathy, proliferative stage.

Treatment of diabetic retinopathy

1. Control of blood glucose level (diet, exercise, medications and/or insulin) in the early stages of the non-proliferative stage of DR.
2. Photocoagulation is the process of sealing the leaking weak vessels in the macular area and retina. It also reduces the stimuli for neovascularisation and stops bleeding. The options are focal, grid and panretinal laser photocoagulation. Focal and grid photocoagulation is used to treat diabetic macular oedema. Indications for panretinal photocoagulation are proliferative DR and some cases of non-proliferative DR. The potential complications of the procedure are reduced night vision and loss of peripheral sight.
3. Glaucoma (abnormal intraocular pressure) and secondary cataract are the most common cause of blindness in patients with diabetes. OptoYag Slt&M Laser ophthalmic system appropriately generates a beam at 1064 nm Nd: YAG for performing selective laser trabeculoplasty (for the treatment of glaucoma) and 532 nm for performing secondary cataract surgery.
4. ADA considers intravitreous injection of anti-vascular endothelial growth factor (anti-VEGF) to be as effective, as laser photocoagulation. Following drugs are currently used:
    a. Ranibizumab (Lucentis);
    b. Bevacizumab (Avastin);
    c. Aflibercept (Ailia).

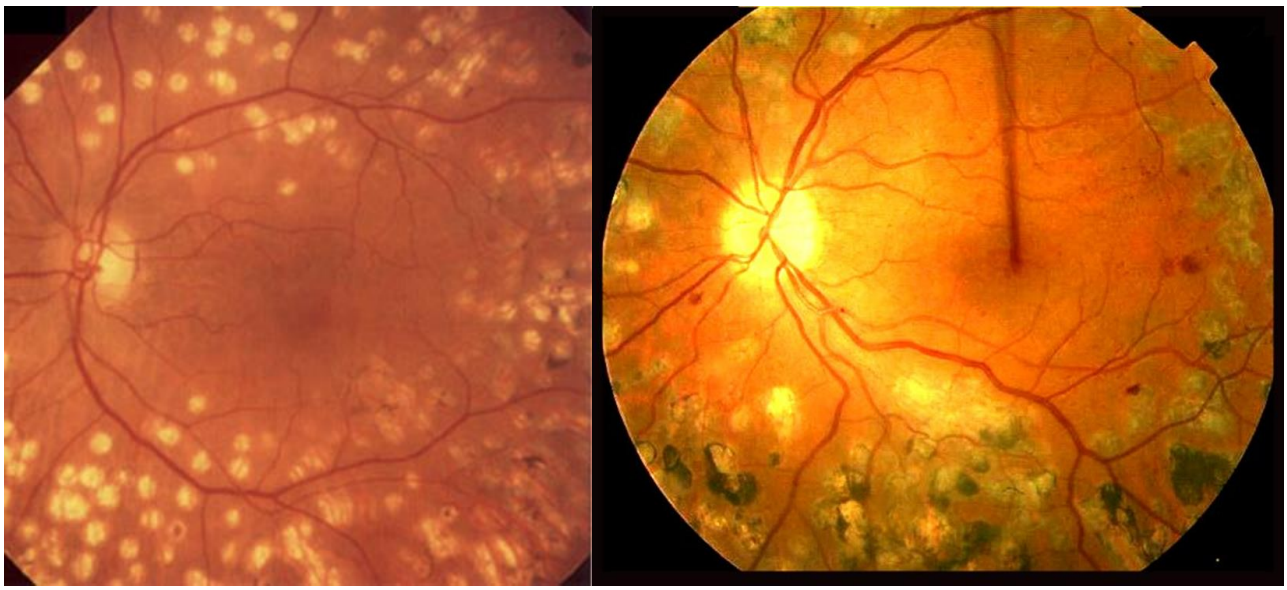


Figure 19 – Treatment with panretinal laser photocoagulation

Figure 20 – OptoYag&Slt M Laser

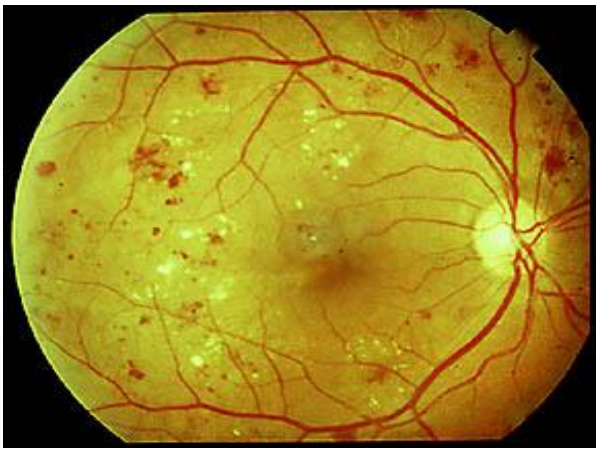


Figure 21 – After photocoagulation

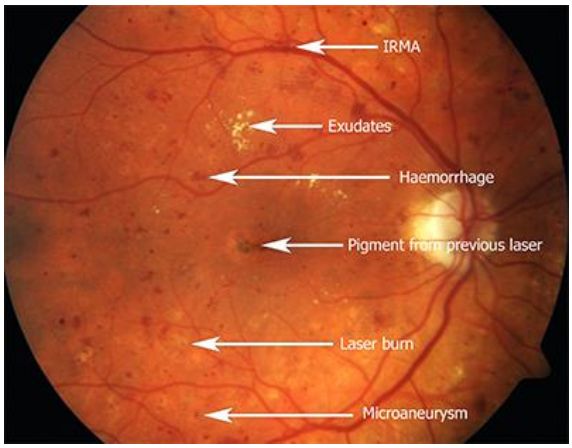


Figure 22 – Preproliferative stage after laser photocoagulation

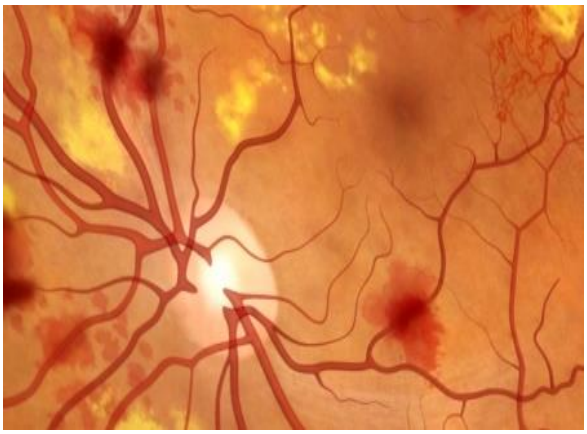


Figure 23 – Proliferative stage with retinal bleeding and neovascularization

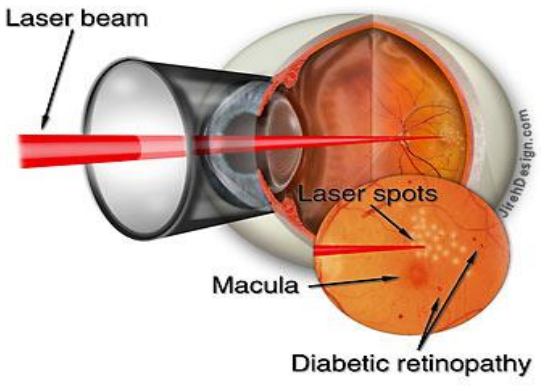


Figure 24 – Treatment by Laser photocoagulation

Figure 25 – Secondary cataract surgery procedures with ophthalmic laser system

2.2. Macroangiopathy

Diabetic macroangiopathy could be all or either of the following:

1. Cerebrovascular diseases.
2. Cardiovascular diseases.
3. Diabetic angiopathy of lower extremities.

Risk factors of macroangiopathy

Table 13 – Cardiovascular risk factors and target organ damage

MAJOR RISK FACTORS
Hypertension* Age (older than 55 years for men, 65 years for women). Diabetes Mellitus * Elevated LDL (or total) cholesterol, or low HDL cholesterol. Estimated GFR < 60ml/min. Family history of premature CVD (men < 55 years of age or women < 65 years of age). Microalbuminuria. Obesity * (BMI $\geq$ 30 kg/m^2). Physical inactivity. Tobacco usage, particularly cigarettes.
TARGET ORGAN DAMAGE
Heart Left ventricular hypertrophy Angina or prior myocardial infarction Prior coronary revasculation Heart failure
Brain Stroke or transient ischaemic attack Dementia
Peripheral arterial disease
Chronic kidney disease
Retinopathy

BMI – body mass index, CKD – chronic kidney disease, CVD – cardiovascular disease, GFR – glomerular filtration rate, HDL – high density lipoproteins, LDL – low density lipoproteins.

∗ Components of the metabolic syndrome. Reduced HDL and elevated triglycerides are components of the metabolic syndrome. Abdominal obesity is a component of metabolic syndrome.

Ɨ Increased risk begins at approximately 55 and 65 years of age for men and women respectively. Adult treatment panel used earlier age cut points to suggest the need for earlier action.

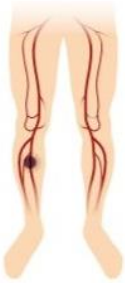
Pathogenesis

The main link of pathogenesis of macrovascular complications of DM is a promotion of atherosclerosis formation, which happens because of insulin resistance, obesity and hyperglycaemia. Excessive adipose tissue releases free fatty acids and mediators of inflammation. Increase in free fatty acids downregulates GLUT-4 expression, which leads to increased insulin resistance. It also leads to reduction in NO production, which can cause endothelial dysfunction.

Normal levels of insulin in the blood create antithrombotic state. Decrease in insulin levels or increasing insulin resistance lead to prothrombotic state, which also is a risk factor for macroangiopathy.

Another mechanism of organ damage is Möckerberg`s arteriosclerosis, which refers to mediacalcinosis of the vessels. Its origin is not fully understood, it can be a result of excessive calcium accumulation due to impaired protein synthesis.

Table 14 – The main types of macroangiopathies

STROKE	CORONARY ARTERY DISEASE	PERIPHERAL ARTERY DISEASE
		
AFFECTS THE BLOOD VESSELS SUPPLYING BLOOD TO THE BRAIN	AFFECTS THE BLOOD VESSELS SUPPLYING BLOOD TO THE HEART	AFFECTS THE BLOOD VESSELS SUPPLYING BLOOD TO THE LEGS AND FEET
includes: cerebrovascular disease, cerebral arterial disease, intracerebral hemorrhage, cerebral infarction	includes: ischaemic heart disease, atherosclerotic heart disease, coronary heart disease, angina pectoris, heart attack (myocardial infarction), sudden coronary death	includes: lower-extremity arterial disease, limb threatening ischaemia, intermittent claudication, critical limb ischaemia

2.2.1. Cerebrovascular Diseases Caused by DM

Mainly, it manifests as *discirculatory encephalopathy* with non-specific symptoms such as deterioration (gradual loss) of memory, dizziness, headaches, etc.

Note that discirculatory encephalopathy is caused due to neuropathy as a result of microangiopathy.

Patients with DM are also more likely to develop Alzheimer`s disease.

Later clinical manifestations include *ischaemic cerebral stroke,* caused by atherosclerotic blockage of cerebral arteries. It results in brain infarction.

2.2.2. Cardiovascular Diabetes Macroangiopathy

Cardiovascular changes tend to occur earlier in patients with DM when compared with individuals of the same age. Frequency of myocardial infarction (MI) and mortality is higher in diabetics than that in nondiabetics of the same age. The prognosis is even worse if ketoacidosis or other complications of DM are present. Diabetic patients have more complications of MI (arrhythmias, cardiogenic shock and others) than nondiabetic ones. Often atypical (painless) forms can observe).

Table 15 – Cardiovascular risk assessment in patients with diabetes according to ECS 2019 guidelines

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

b – Proteinuria, renal impairment (eGFR < 30 mL/min), left ventricular hypertrophy, or retinopathy.
c – Age > 65 years, hypertension, dyslipidaemia, smoking, obesity.

Very high risk refers to 10-year risk of CVD ≥ 10 %.

High risk – 10-year risk of CVD 5–10 %.

Moderate risk – 10-year risk of CVD ≤ 5 %.

Classification of arterial hypertension:

1. According to aetiology:
   a) primary arterial hypertension (cause is usually unknown);
   b) secondary arterial hypertension (resulting from other secondary diseases like cardiovascular diseases, diabetes mellitus-nephropathy, chronic kidney diseases, etc.).
2. According to clinical grades:
   a) grade 1 hypertension;
   b) grade 2 hypertension;
   c) grade 3 hypertension.

Table 16 – Classification of arterial hypertension according to clinical grades

Category	**SBP, mmHg**	**DBP, mmHg**
Optimal	< 120	**And < 80***
Normal	**120–129***	And/or 80–84
High normal	130–139	And/or 85–89
Grade 1 hypertension *(Start antihypertensive drugs)*	140–159	And/or 90–99
Grade 2 hypertension	160–179	And/or 100–109
Grade 3 hypertension	≥ 180	And/or ≥ 110
Isolated systolic hypertension	≥ 140	And < 90

***Target for patient with diabetes

3. According to clinical stages (by joint national committee for the prevention, detection and treatment of arterial hypertension – 2009). JNC 7 category classification helps in determining treatment protocol:
   a) uncomplicated hypertension;
   b) asymptomatic hypertension;
   c) established hypertension.

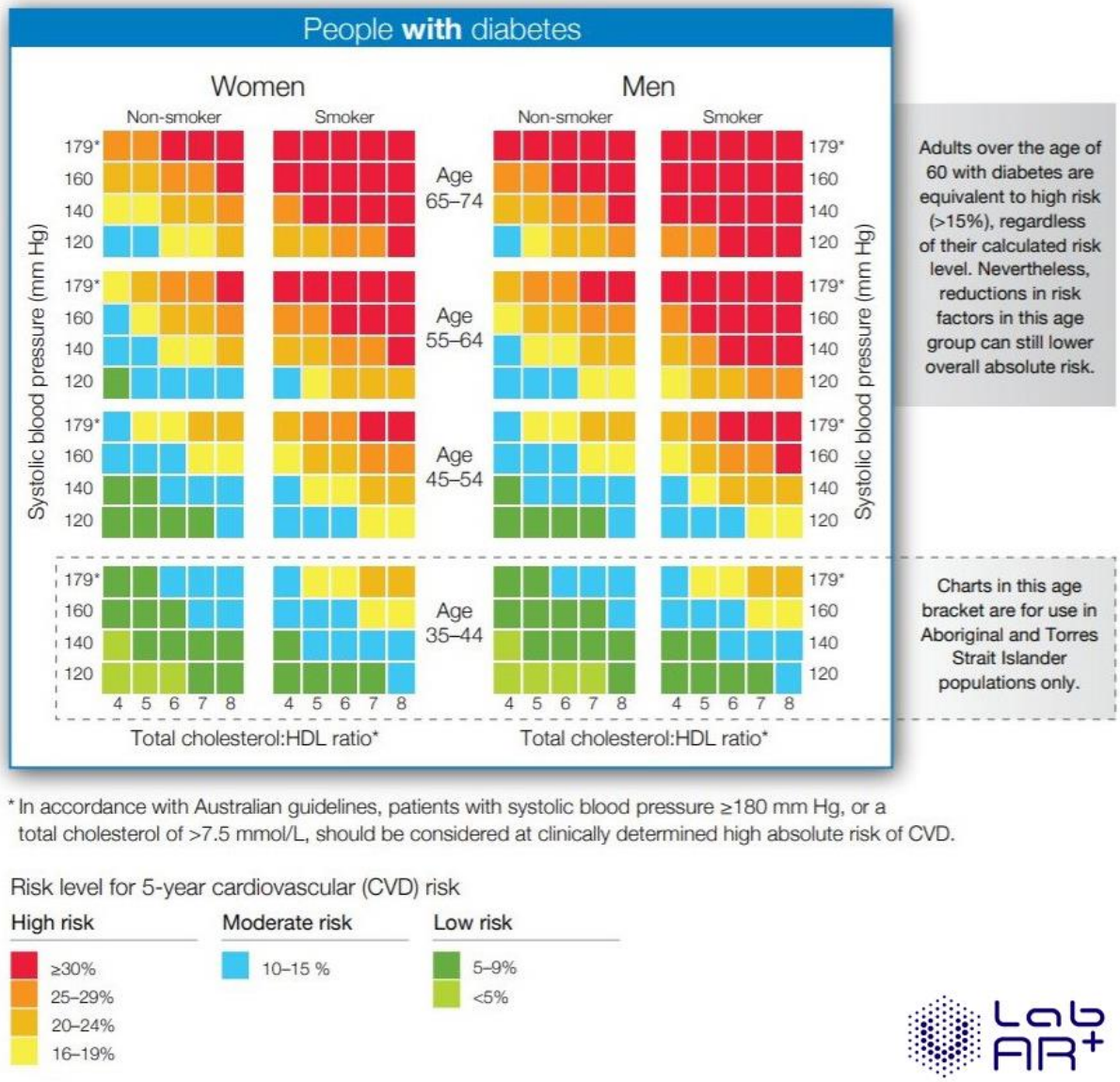


Figure 26 – Australian cardiovascular risk charts

Strategy of treatment of arterial hypertension in patient with diabetes

1. Start antihypertensive drugs at ≥ 140/90 mmHg.
2. Target systolic blood pressure is 120–129 mmHg and 130–139 mmHg in older people (> 65 years).
3. Target diastolic blood pressure is 70–79 mmHg.
4. Start with ACE-inhibitor/ARB + CCB/thiazide diuretic (or thiazide-like diuretic).
5. Do not combine ACE-inhibitors with ARB.

See appendix D for preferred drugs and dosing.

2.2.3. Diabetic Angiopathy of Lower Extremities

Diabetic angiopathy of lower extremities is diagnosed based on the *clinical picture* and *instrumental methods*.

Clinical symptoms include:

1. *Decreased skin temperature of distal part of extremities* in comparison to proximal part during palpation.
2. *Decreased or absent pulse* in lower extremity arteries (Posterior tibial and Dorsalis Pedis arteries).
3. *Cyanotic or pale skin colour*.
4. *Pain*: manifested as intermittent claudication (pain when walking, causing patient to rest a little while to relief pain before continuing walking, due to vascular insufficiency).
5. *Trophic ulcers:* located in areas not in contact with shoe pressure areas as well as at the terminal extremities of toes (because arterial insufficiency starts at the capillary levels which supply toes.)
6. *Gangrene of toes and extremities* due to chronic untreated vascular insufficiency.

Instrumental methods:

- *X-ray* for bony destruction (Charcot or osteomyelitis; Menceberg' arteriites).
- *Ankle-Brachial (ABI) and Toe-Brachial Indices, Segmental Pressure Examination*. The ABI should be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline.
- *Magnetic resonance angiography* of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD.
- *Contrast angiography* provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated.
- Rheovasography is a graphical recording of impedance in a local area of study between electrodes with low-flux electric current. The procedure allows to provide a qualitative and quantitative assessment of vascular disorders, which determines the following integral rheovasographic indicators:

1. Rheographic index (RI) indicates the relative value of pulse blood filling (N on foot=1,0 mom).

2. The dicrotic index contains data about the tonic indices of the venous and signs of the venous stasis.

3. Diastolic index (DI) is the relation of the value of the amplitude on the level of dicrotic cog (additional wave) to the maximum amplitude of the rheographic wave and reflects mostly the condition of blood outflow from arteries to veins and tonus of the veins.

4. The amplitude of the diastolic wave, which reflects the ratio of the arterial and venous component of the blood circulation.

5. The velocity of fast blood flow reflects the blood filling of the large arteries (om/s).

6. The rate of the slow blood flow characterizes the blood filling of the arteries of the medium and small diameter (om/s).

7. Diastolic-systolic index demonstrates venous outflow.

8. Asymmetry index (AI).

- Continuous-wave Doppler ultrasound blood flow measurements are useful to provide an accurate assessment of lower extremity PAD location and severity, to follow lower extremity PAD progression, and to provide quantitative follow-up after revascularization procedures.

Figure 27 – Continuous-wave Doppler ultrasound blood flow measurements

- Pulse oximetry measures the oxygen saturation of peripheral blood (SaO2) and is a screening tool to detect significant lower extremity arterial disease in patients with diabetes mellitus.

Figure 28 – Pulse oximeter

- The **Ankle Brachial Index** (ABI) is the systolic pressure at the ankle, divided by the systolic pressure at the arm. An ABI is calculated for each leg.

$$\text{Right ABI} = \frac{\text{Highest Pressure in Right Foot}}{\text{Highest Pressure in Both Arms}}$$

Interpreting the Ankle Brachial Index

1. Normal ABI ranges from 1.0–1.4.
   Pressure is normally higher in the ankle than the arm.
2. Values above 1.4 suggest a noncompressible calcified vessel.
3. In diabetic patients, the limb vessels may be fibrotic or calcified. In this case, the vessel may be resistant to collapse by the blood pressure cuff, and a signal may be heard at high cuff pressures. The persistence of a signal at a high pressure in these individuals results in an artifactually elevated blood pressure value.
4. A value below 0.9 is considered diagnostic of PAD.
5. A value 0.5–0.8 suggests moderate PAD.
6. Values less than 0.5 suggests severe PAD and should be considered for revascularization.

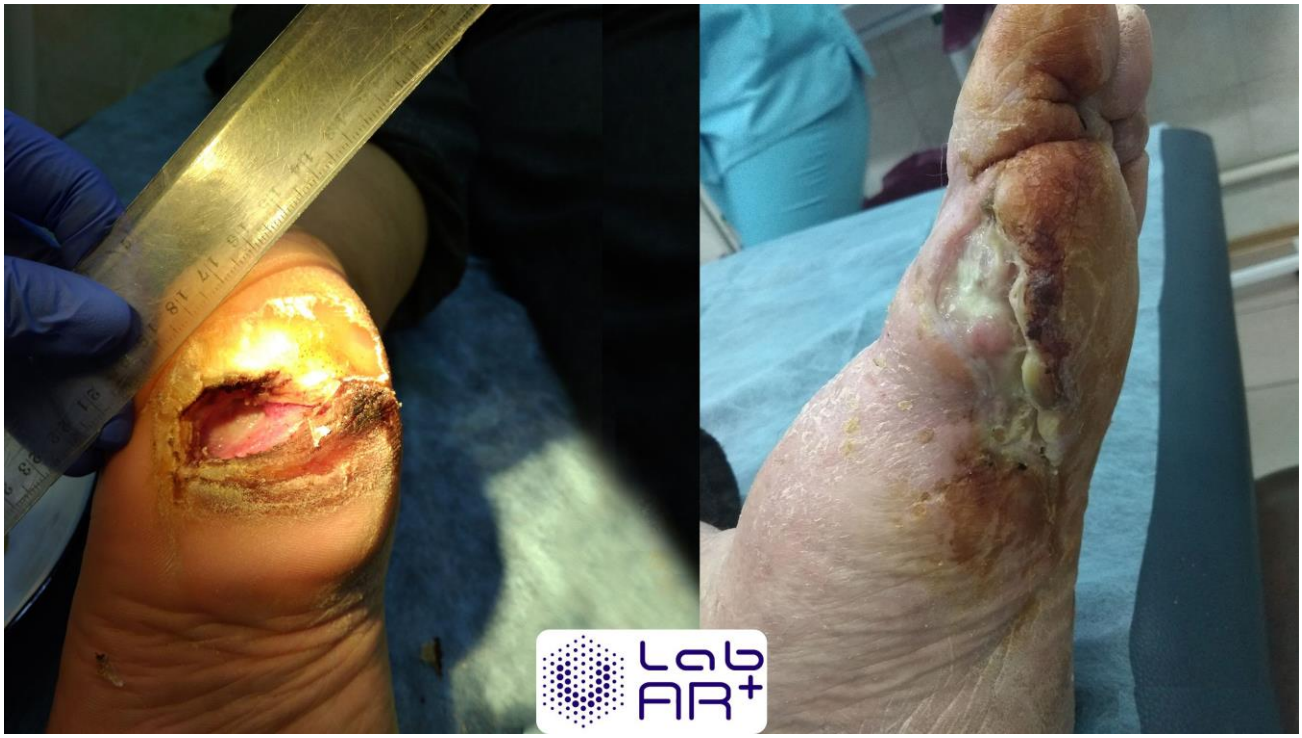


Figure 29 – Ischaemic foot examination

Definition of peripheral occlusive disease of extremities

According to the American College of Cardiology/American Heart Association (ACC/AHA) pathologies of the peripheral extremities fall under the following divisions:

1. Asymptomatic: Absence of intermittent claudication symptoms.
2. Claudication: Inadequate blood flow during exercise, causing pain during movement forcing patient to stop before continuing so that the limb is reperfused.
3. Critical limb ischaemia: Compromise of blood flow to extremity, causing limb pain at rest. Patients often have ulcers or gangrene.
4. Acute limb ischaemia: A sudden decrease in limb perfusion that threatens limb viability. Associated with the "5 Ps": Pain, Paralysis, Paraesthesia, Pulselessness, Pallor.

NB: The pulse is usually determined by feeling the dorsalis pedis artery and the posterior tibial artery.

The classification of lower extremity macroangiopathy is based on the degree of progression of chronic peripheral ischemia to critical limb ischemia with intermittent claudication.

Table 17 – Classification of PAD after Fontane and Rutherford (comparison chart)

Fontane		*Rutherford*		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
II a	Mild claudication	I	1	Mild claudication
II b	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
		III	5	Minor tissue loss
IV	Ulceration or gangrene	IV	6	Ulceration or gangrene

Table 18 – Classification of peripheral artery diseases by Leriche-Fontane-Pokrovsky

Stage			**Explanation**
1st degree	Pre-clinical stage		Present all symptoms of vascularization disturbances (dry, scaly, cold, hyperkeratinized skin and absent pulse of feet) and chronic pain only during movement. Critical ischaemia is absent
2nd degree. Intermittent claudication	2A	Claudication at a distance *greater* than 200 metres	Present intermittent claudication (intensified pain during walking due to ischaemia forcing patient to stop and rest before continuing to walk to revascularize the leg)
	2B	Claudication distance *less* than 200 metres	
3rd degree	Nocturnal and / or resting pain		Pain present throughout the day and at night due to the development of severe critical ischaemia. *NB: Need to differentiate this with polyneuropathic pain because the latter lacks prior intermittent claudication in history of the patient*
4th degree	Necrosis (death of tissue) and/ or Gangrene in the limb		Localized and/or spreading gangrene

** Source: Am Fam Phys 2001; 61:1027–1032, 1034.*

2.3. Diabetic Foot Syndrome

Diabetic foot syndrome is a polysymptomatic chronic complication of DM, characterized by both functional and organic damage of the lower extremities of diabetic patients due to both the disturbances of *vascular* and *neurological properties* of the lower extremities and infection complications.

Classification of diabetic foot syndrome

I. *According to aetiopathogenesis:*

1. *Neuropathic* (neuropathic pain, paraesthesia, vibration loss and neuropathic ulcer formations*).*

2. *Ischaemic form* (impairment of circulation).

Manifested as pain (intermittent claudication), cyanotic skin colour, trophic ulcers on ends of toes and areas of feet not subjected to pressure with shoes.

3. *Neuroischaemic form.*

II. *According to the depth of trophic ulcer (by Wagner).*

Table 19 – Classification of diabetic foot by Wagner

Stage 0	There is no trophic ulcer. This stage includes all signs of an increased risk of feet ulceration: cold and dry skin, pain with walking (claudication), paraesthesia (numbness), paralysis (weakness), pulselessness (of dorsalis pedis and posterior tibial pulsus), pallor or cyanosis of distal extremities
Stage 1	Presence superficial diabetic ulcer without infection
Stage 2	Ulcer extension, i.e., involving ligament, tendon, joint capsule or fascia. Osteomyelitis is absent
Stage 3	Deep ulcer with osteomyelitis
Stage 4	Localized gangrene to toes or distal part of feet
Stage 5	Extensive gangrene of foot (spreading gangrene)

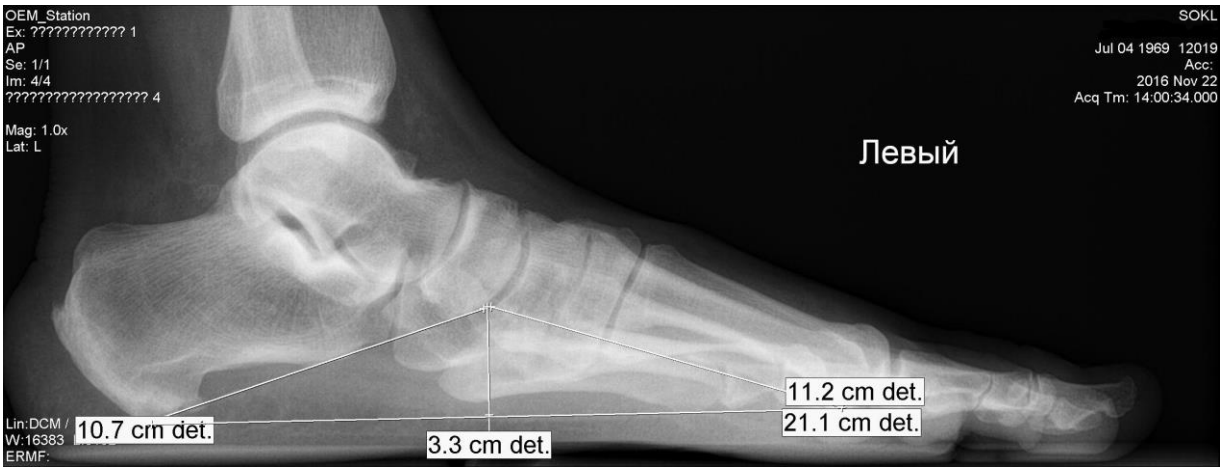


Figure 30 – Lateral view of foot radiograph

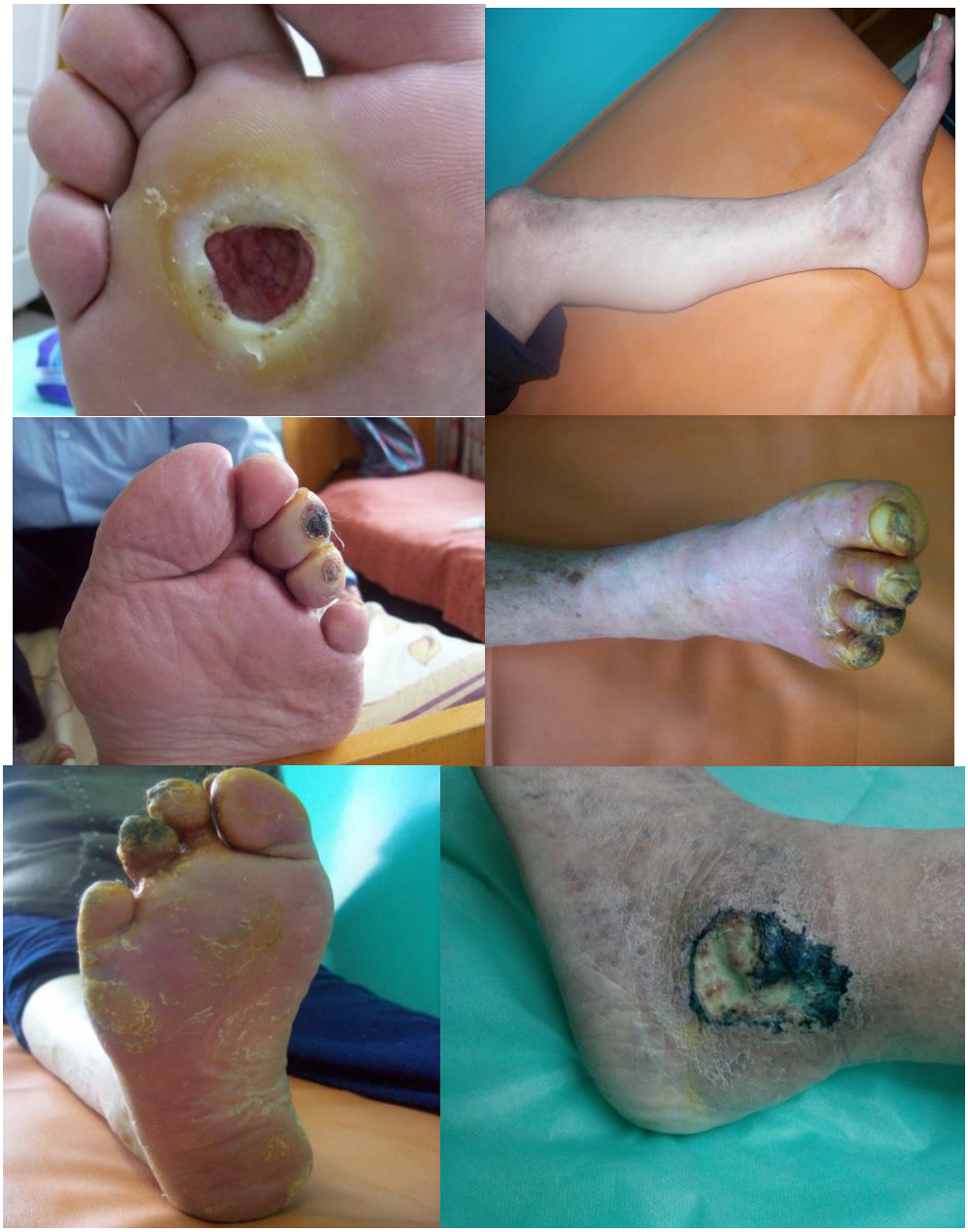


Figure 31 – Signs of diabetic foot syndrome at different stages of development

Table 20 – Differential diagnosis between neuropathic and ischaemic diabetic foot syndrome

Clinical sign	**Neuropathic DF**	**Ischaemic DF**
Foot deformities	Clawed toes, possible high arch, possible Charcot deformities	No specific deformities. Possible absent toes/forefoot from previous amputations
Foot temperature/ foot pulse	Warm, palpable pulse	Cold or decreased temperature, pulse may be absent or reduced
Skin colour	Normal or red	Pale or cyanotic. Pronounced redness when lowered (dependent rubor), blanching on elevation
Skin condition	Dry skin due to decreased sweating	Thin, fragile and dry
Ulcer location	On the plantar aspects (forefoot 80 %) of the foot/toes	Distal/tips of the toes, heel, or margins of the foot
Callus present	Commonly seen on the weight-bearing areas and is generally thick	Not usually. If present, distal eschar or necrosis
Ulcer characteristics	Usually painless, with a "punched out" appearance (granulation or deeper base) surrounded by callus	Painful, especially with necrosis or slough
Sensation	Reduced or absent sensation to touch, vibration, pain, and pressure	Sensation may be present but decreased if there is associated neuropathy
Ankle reflexes	Usually not present	Usually present

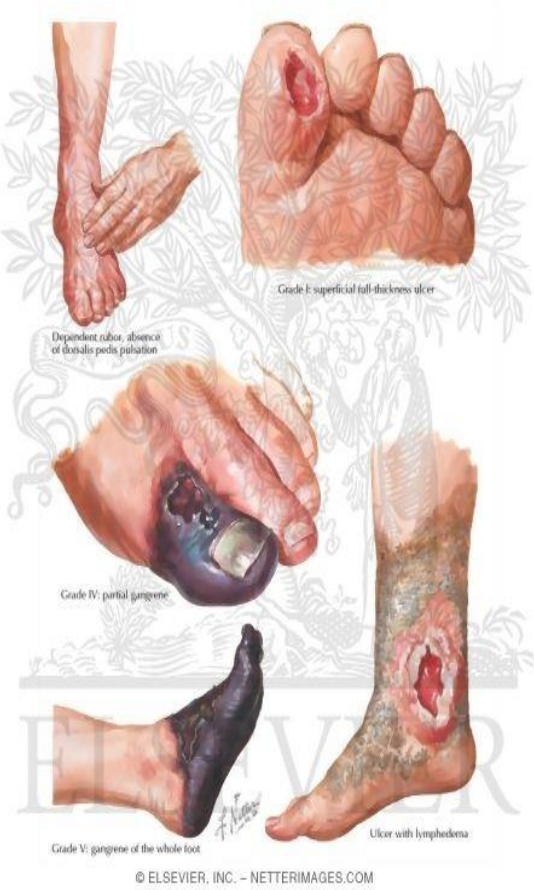


Figure 32 – Different stages of diabetic foot syndrome

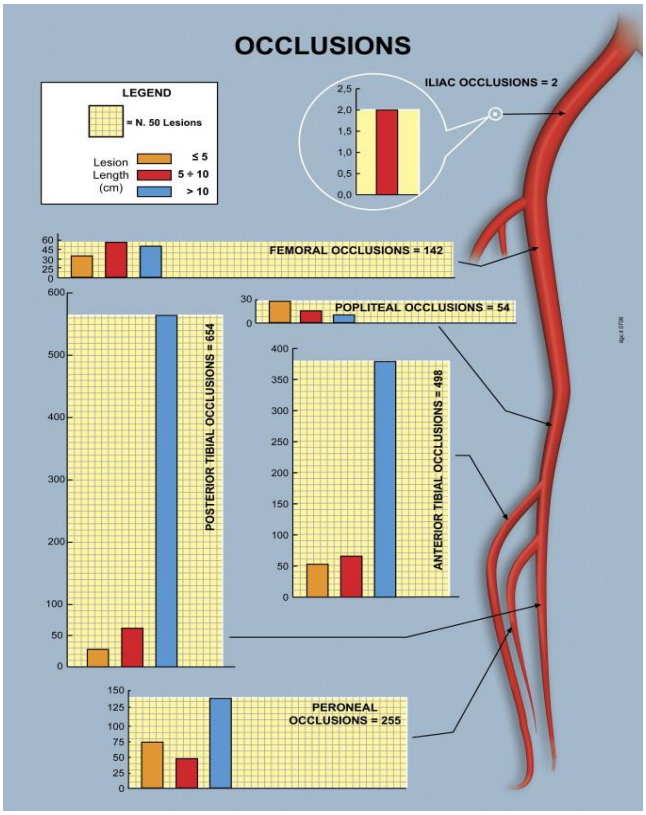


Figure 33 – Possible areas of vascular occlusion of the lower extremities in diabetes mellitus

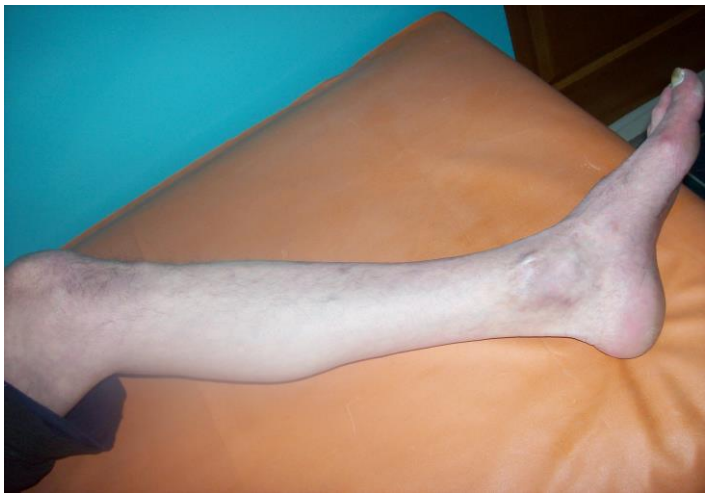


Figure 34 – Lower extremity cyanosis

EXAMPLE OF MAIKING DIAGNOSIS OF DIABETIC FOOT SYNDROME

1. Diabetic foot syndrome stage 4, mixed form, bilateral lower extremity angiopathy stage 4, bilateral lower extremity sensory motor neuropathy.

2. Diabetic foot syndrome stage 2, mixed form, bilateral distal lower extremity sensory neuropathy, bilateral lower extremity angiopathy stage 2b.

3. MANAGEMENT OF DIABETES MELLITUS

Treatment of DM is carried out based on the type and degree of severity taking into consideration the state of compensation as well. The average hospitalization period is 10–14 days to achieve a compensation state and the target values of the various diagnostic parameters as indicated in the tables below.

1. Diet, exercise, self-education are often started as first line treatment protocols in early diagnosed cases of DM.
2. Oral hypoglycaemic drugs are administered when diet control is ineffective in treating type 2 DM.
3. Insulin is administered for treating T1DM and gestational DM and in the treatment of severe decompensated T2DM which is not responsive to oral hypoglycaemic medications and severe stages of chronic complications.

Table 21 – Obesity stages and risk management

	BMI (kg/m^2)	Obesity Class	Disease Risk (Relative to Normal Weight and Waist Circumference)*	
			Men: ≤40 inches (≤102 cm) Women: ≤35 in (≤88 cm)	> 40 inches (>102 cm) > 35 inches (>88 cm)
Underweight	< 18.5		—	—
Normal weight‡	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	≥ 40	III	Extremely high	Extremely high

* Disease risk for type-2 diabetes, hypertension, and cardiovascular disease.
‡ Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Note:

1. Treatment of DM should be individualized per patient since the therapeutic goal parameters to be achieved by any adopted method of treatment should be individualized for every patient.
2. Determine therapeutic goal depending on the following parameters:

- age (older patients have higher standards because of risks of hypoglycaemia amongst others);
- patient's self-motivation and willingness to use the adopted therapeutic measures;
- cardiovascular risks (previous strokes, myocardial infarction, etc.);

- financial situation as well as social status of patient;
- other histories of chronic diseases (which may render treatment of DM more difficult).

3.1. Therapeutic Goals in Treating DM

The therapeutic goals in treating DM:

1. HbA1C goals:
   a) < 6 % – pregnant women;
   b) < 7 % (53 mmol/mol) – most nonpregnant adults and children;
   c) < 8 % (64 nmol/mol) – a history of severe hypoglycaemia, limited life expectancy, long-standing diabetes, refractive to adequate treatment);

2. Fasting* capillary plasma glucose, measured by patient with a glucometer (patient self-monitoring of blood glucose) – 4.4–7.2 mmol/l (80–130 mg/dl);

   5.0–7.2 mmol/l for older adults;

   < 5.3 mmol/l for pregnant women.

3. Peak postprandial capillary plasma glucose** – < 10 mmol/l (< 180 mg/dl)

   < 7.8 mmol/l for pregnant women.

4. Bedtime glucose – 5.0–8.3 mmol/l (90–150 mg/dl) for older adults.
5. Blood pressure:
   a) systolic – 120–129 mmHg and 130–139 mmHg in older people (> 65 years);
   b) diastolic – 70–79 mmHg.
6. Lipids:
   a) total cholesterol – < 4.4 mmol/l;
   b) LDL cholesterol – < 2.6 mmol/l;
   c) HDL cholesterol – > 1.02 mmol/l;
   d) TAG – < 1.7 mmol/l.

[American Diabetes Association Standards of medical care in diabetes – 2015. Diabetes Care. 2015; 38 Suppl1:S1–94.]

Table 22 – Lipid-lipoprotein goals in patients with DM

Risk factor	**ATP III**	**ADA**	**IDF**
LDL cholesterol	< 100 mg/dl (< 2.6 mmol/L) in individuals without overt CVD	< 100 mg/dl (< 2.6 mmol/L) in individuals without overt CVD	< 95 mg/dL
	< 70 mg/dl (1.8 mmol/L) optional or reasonable with overt CVD	< 70 mg/dl (1.8 mmol/L) in individuals with overt CVD	
Non-HDL cholesterol	< 130 mg/dl (< 2.6 mmol/L) if triglyceride ≥ 200 mg/dl	Not specified	Not specified
Triglycerides	Not specified	< 150 mg/dL	< 200 mg/dL
HDL cholesterol	Not specified	> 40 mg/dL in men > 50 mg/dl (1.3 mmol/L) in women	> 39 mg/dL

ADA – *American Diabetes Association,* ATP III – *Adult Treatment Panel III,* CVD – *Cardiovascular disease;* HDL – *High density lipoprotein,* IDF – *International Diabetes Foundation,* LDL – *Low Density Lipoprotein*

3.2. Treatment of Type 1 DM

Treatment of T1DM is by insulin therapy; however, diet, light aerobic physical and education of patient to be able to control signs of acute complications as well as managing DM are equally very important.

Diet

1. Exclude from daily diet foods with glycaemic index (GI) of 70 to 100 %. Limit to products with GI of 70 to 65 % carbohydrates (sugar, honey, sweet pastries, jams, soft drinks).

2. Daily caloric value of carbohydrates (55 to 60 %), proteins (15 to 20 %), and fat (20 to 25 %) should be maintained.
3. Restrict intake of saturated fatty acids to 10 % by substituting saturated fats with mono- and polyunsaturated fats (ratio 1:1:1), except for children of preschool age.
4. After calculating the number of calories attributable to carbohydrates, determine the amount of bread units (BU).

NB: *(10 to12 g of carbohydrate food taken equals 1 BU).*

Daily physical exercise

1. Physical activity increases insulin sensitivity and lowers blood glucose.
2. The risk of hypoglycaemia increases during exercise and in the next 12–40 hours after a period of prolonged and intense physical exertion.
3. For mild and moderate exercise lasting not more than 1 hour, it is required supplementation of carbohydrates before and after exercise (15 g of carbohydrate for every 40 minutes of sport).
4. At moderate exercise lasting more than 1 hour and intense sport, a low dose of insulin is needed, which acts during and subsequent to 6–12 hours after exercise at 20–50 %.
5. Blood glucose levels should be measured before, during and after exercise.
6. During decompensation of diabetes, especially in the stage of ketoacidosis, physical exercise is contraindicated.
7. Exercise should be regular but not traumatic.

Insulin therapy

It involves the use of either:

1. Semisynthetic human genetically engineered insulin.
2. Analogues of human insulin.

NB: Animal (pork) insulin is no longer used.

Figure 35 – Insulin pump

Figure 36 – Insulin pens

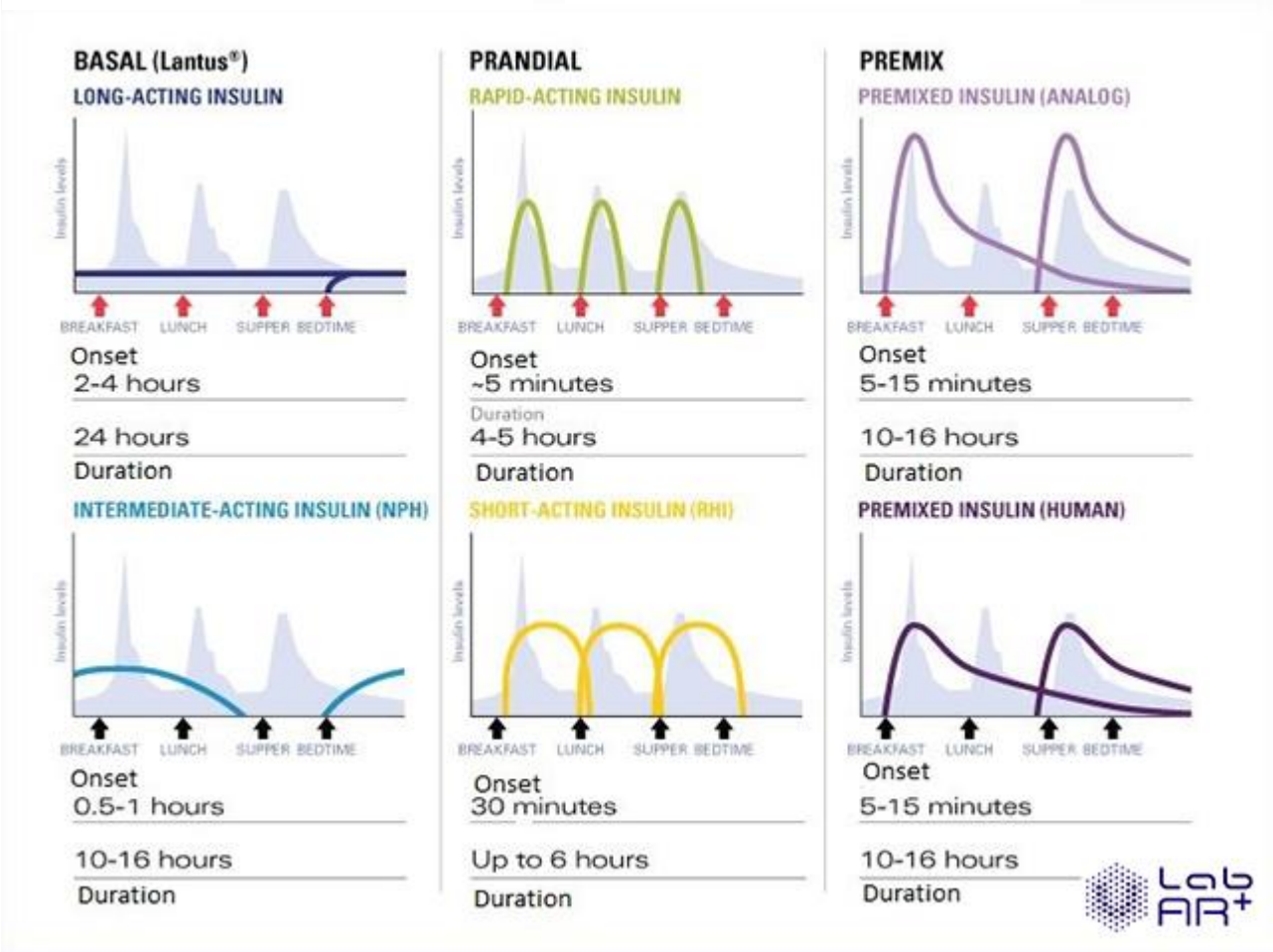


Figure 37 – Insulin therapy regimens

Figure 38 – Insulin injection

Mode of insulin administration

In general, patients with T1DM require 50 % of their daily insulin as basal and 50 % as prandial. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and illness. Typical starting dose is 0.5 units/kg/day for diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption.

Typical multidose regimens for patients with T1DM combine premeal use of shorter-acting insulins (3 times a day) with a longer-acting formulation (2 times a day for intermediate action and once a day for ultralong, usually at bedtime). The long-acting basal dose is titrated to

regulate overnight, fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation, the premeal blood glucose level, and carbohydrate consumption.

Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery. Exogenous-delivered insulin should be injected into subcutaneous tissue, not intramuscularly. IM injection being associated with frequent and unexplained hypoglycemia in several reports. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm.

Table 23 – Classification of insulin according to duration of action

Insulin	**Onset of action**	**Peak action**	**Duration**
Analogues of human insulin ultra-short action	After 10 to 20 min	Through 0.5 h	3 h
Short-acting	30 min	In 1.5 h	From 5 to 8 h (av. 6 h)
Intermediate duration	From 1 to 1.5 h	From 12 to 24 h	From 12 to 24 h
Pre-mixed	Through 0.5 to 1 h	Over 1.8 h	From 12 to 24 h
Pre-mixed human insulin analogue actions	After 10 to 20 min	In 1 to 4 h	15 to 24 h
Analogue of human insulin ultra-long-acting	After 1 h	From 18 to 24 h	Up to 24 h

Daily insulin requirements

The average daily requirement of insulin in patients with type 1 diabetes is *40 to 60 units*.

1. At onset of diabetes, from 0.5 to 0.6 IU/kg.
2. Remission (“honeymoon”) – < 0.4 IU/kg.
3. Prolonged diabetes with progressive chronic complications: from 0.7 to 0.8 IU/kg.
4. Decompensation (puberty period, ketoacidosis): from 1.0 to 2.0 IU/kg.
5. The dose for each patient depends on his individual needs and on the following parameters: body mass; diet, exercise; other comorbidities.

Correction of insulin dose should be made daily based on self-monitoring of blood glucose throughout the day.

Pregnant women with diabetes, patients with diabetes with proliferative retinopathy, with decreased vision, children and adolescents should be provided with syringe-pens for insulin.

Complications/side effects of insulin therapy

1. Weight gain since insulin is an anabolic hormone.
2. Risk of hypoglycaemia during course of treatment.
3. Insulin resistance.
4. Allergic reactions to insulin.

Figure 39 – Insulin therapy

Plan of future follow-up

Recommendations to patients should be indicated in the epicrisis of the case history upon discharge from the hospital (dispensary follow-up).

Table 24 – Plan of diagnostic tests and consultations

		INITIAL VISIT	EVERY FOLLOW-UP VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**		
	▪ Characteristics at onset (e.g., age, symptoms)	✓	
	▪ Review of previous treatment regimens and response	✓	
	▪ Assess frequency/cause/severity of past hospitalizations	✓	
	Family history		
	▪ Family history of diabetes in a first-degree relative	✓	
	▪ Family history of autoimmune disorder	✓	
	Personal history of complications and common comorbidities		
	▪ Macrovascular and microvascular	✓	
	▪ Common comorbidities (e.g., obesity, OSA)	✓	
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓	
	▪ High blood pressure or abnormal lipids	✓	
	▪ Last dental visit	✓	
	▪ Last dilated eye exam	✓	
	▪ Visits to specialists	✓	✓
	Interval history		
	▪ Changes in medical/family history since last visit		✓
LIFESTYLE FACTORS	▪ Eating patterns and weight history	✓	✓
	▪ Physical activity and sleep behaviors	✓	✓
	▪ Tobacco, alcohol, and substance use	✓	
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓
	▪ Medication-taking behavior	✓	✓
	▪ Medication intolerance or side effects	✓	✓
	▪ Complementary and alternative medicine use	✓	✓
	▪ Vaccination history and needs	✓	
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓	
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓
	▪ Review insulin pump settings and use	✓	✓
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**		
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓	
	▪ Identify existing social supports	✓	
	▪ Consider assessment for cognitive impairment*	✓	
	Diabetes self-management education and support		
	▪ History of dietician/diabetes educator visits/classes	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓	
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓	
	Pregnancy planning		
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓

3.3. Treatment of Type 2 DM

The main cause of carbohydrate metabolism dysfunction in T2DM is mostly due to:

1. Insulin resistance and relative insulin deficiency.
2. A primary defect in insulin secretion with insulin resistance.

The therapeutic goal in diabetes mellitus type 2 is preventing the risk of micro- and macrovascular complications.

T2DM treatment involves:

1. Diet.
2. Exercise.
3. Oral sugar decreasing drugs.
4. Insulin therapy.
5. Learning self-control and psychological support.
6. Early treatment of complications and comorbidities (adequate control blood pressure, blood lipids).

Note: Oral hypoglycaemic medications are used only in cases where:

1. Diet and physical exercises have not attained the therapeutic goal for a long period of time.
2. Laboratory parameters at diagnosis show high levels of HBA1c (> 7.5 %).
3. Metformin is preferred drug of choice, but it is usually used in combination with other oral hypoglycaemic agents to achieve desired therapeutic goal.

Diet

Principles of feeding includes:

1. Respecting of normal energy value (for obesity – foods with low energy value).
2. Diet with restriction of saturated fats, cholesterol and carbohydrate (not more than one third of total carbohydrates).

Diet № 9 and basic therapy for patients with type 2 DM is indicated with the main goal dedicated to weight loss in obese patients.

NB: Compliance with the diet often leads to normalization of metabolic disorders. When overweight, a low-caloric diet (< 1800 kilo calories) is recommended, which involves limiting the carbohydrate (candy, honey, sweet drinks) composition of food (% of energy value) as follows:

1. *Complex carbohydrates (pasta, cereals, potatoes, vegetables, fruits) 60 %.*
2. *Saturated fats (milk, cheese, and animal fat) – 10 %.*
3. *Polyunsaturated (margarine, vegetable oil) – 10 %;*
4. *Proteins (meat, fish, eggs, milk, cheese) – up to 20 %.*
5. *Inclusion in the diet foods rich in dietary fibers.*
6. *Moderate use of non-caloric sweeteners.*
7. *Limiting salt intake to 3 g/day in patients with arterial hypertension.*
8. *Not more than 20 g/day intake of alcohol (in terms of pure alcohol) is indicated only in cases of absence of pancreatitis, severe neuropathy, and hypertriglyceridemia and alcohol dependence.*

NB: *Compliance with the diet is an essential part of the treatment of type 2 diabetes regardless of any version of hypoglycaemic therapy.*

Physical activity

Can improve the compensation of carbohydrate metabolism, reduce and maintain optimal body weight and reduce the risk of chronic heart disease (CHD).

An individual approach, given the age of the patient, complications of diabetes, comorbidities (especially coronary heart disease, hypertension, autonomic and peripheral neuropathy, DR) is followed.

NB: Except in cases of contraindications to sports, exercise of moderate intensity, a total of at least 2.5 hours per week, at least 3 times a week (with breaks to two consecutive days).

To control blood glucose, because exercise can lead to hypoglycaemia, additional admission carbohydrate is done, provided that blood glucose level < 5.6 mmol/L before exercise.

Prolonged or intense exercise may require dose adjustments of insulin or insulin secretion stimulators. During severe decompensation, exercise is not recommended.

Oral hypoglycaemic drugs

Assigned in cases where dietary measures and increasing physical activity cannot achieve the goal of treatment in individual patients.

Table 25 – Oral hypoglycaemic drugs effects

Mechanism of action	**Advantages**	**Disadvantages and potential side effects**
Biguanides		
- inhibit hepatic gluconeogenesis; - reduce insulin resistance of muscle and adipose tissues.	- first line therapy; - effective; - weight loss; - no hypoglycaemia; - long history of safe using.	- dyspepsia; - can`t be used at GFR <30 ml/min; - may cause B12-defficiancy.
Sulfonylureas		
- stimulate insulin secretion.	- effective; - long history of safe using.	- hypoglycaemia; - weight gain; - may speed up destruction of beta-cells.
Dipeptidyl peptidase-4 (DPP-4) inhibitors		
- suppress cleavage of endogenous incretins.	- no weight gain; - well-tolerated; - preserve beta-cells` function; - don`t cause hypoglycaemia.	- dyspepsia; - immune reactions; - dangerous if heart failure risk is present.
Glucagon-like peptide-1 (GLP-1) agonists		
- enhance glucose-dependent insulin secretion; - suppress glucagon secretion; - slow down gastric emptying.	- weight loss; - no hypoglycaemia; - decrease glucagon levels; - reduce post-prandial hyperglycaemia.	- dyspepsia; - allergic reactions; - subcutaneous injection; - tachycardia; - should be avoided in patients with the history of pancreatitis or medullary carcinoma.

Table 25 continuation

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
- increase glucose secretion with urine.	- weight loss; - reduce blood pressure; - no hypoglycaemia;	- genitourinary infections; - polyuria; - hypotension; - increase low-density lipids.
Acarbose		
- alpha-glucosidase inhibitor – reduce intestinal carbonate absorption.	- no hypoglycaemia; - reduce post-prandial hyperglycaemia.	- diarrhoea; - dyspepsia; - less effective glycaemia control.
Meglitinides		
- stimulate insulin secretion.	- reduce post-prandial hyperglycaemia.	- hypoglycaemia; - weight gain.
Thiazolidinediones (glitazones)		
- reduce insulin resistance of muscle and adipose tissue; - decrease glucose production by the liver.	- increase high-density lipids levels; - reduce triglycerides levels.	- water retention; - bone fractures; - weight gain.

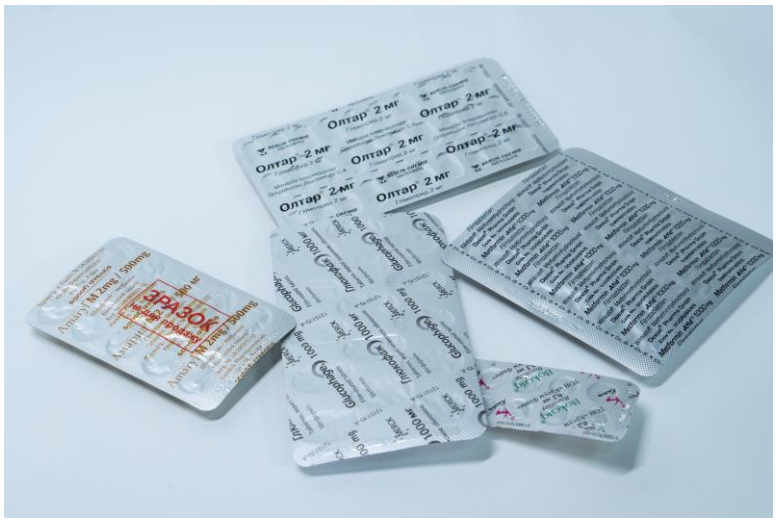


Figure 40 – Oral hypoglycaemic drugs

Table 26 – Groups of drugs and mechanism of action

Group of drugs	Action mechanisms
Sulfonylureas	Stimulation of insulin secretion and recovery
Biguanides	Reduced glucose production by the liver, reducing insulin resistance of muscle and adipose tissue
Meglitinides	Stimulation of insulin secretion
Thiazolidinedione (Glitazones)	Reducing insulin resistance of muscle and adipose tissue, decrease glucose production by the liver
Inhibitors of alpha glycosidase	Reduced absorption of carbohydrates in the intestine
Incretin analogues (GLP-1)	Enhances glucose-dependent insulin secretion, suppresses glucagon secretion and gastric emptying
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Suppresses cleavage of endogenous incretins by DPP-4, thus elevating endogenous incretin levels. Effects are same as for incretin analogues
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors	Inhibit glucose reabsorption, causing increased glucose excretion with urine

Table 27 – Oral hypoglycaemic agents

Preparation	Daily dose (mg)	Multiplicity Reception (times/ day)	Duration of action (h)	Evidence	Contraindication
1	2	3	4	5	6
SULFONYLUREAS				Type 2 diabetes with predominant insufficient secretion of insulin (without obesity) in inefficiency diet and physical loads	Type 1 diabetes ketoacidosis pregnancy and lactation; chronic renal insufficiency
Gliclazide MR	30 to 120	1	24		
Micronized glibenclamide	1.75 to 14	1.2	16 to 24		
Glibenclamide	2.5 to 20	1.2	16 to 24		
Glimepiride	1.8	1	24		
Glikvidon	30 to 120	1.3	8 to 12		

Table 27 continuation

1	2	3	4	5	6
Glipizide	2.5 to 30	1.2	16 to 24		
Gliclazide	80 to 240	1.3	8 to 12		
MEGLITINIDES				Type 2 DM predominant insufficient secretion of insulin (without obesity) and expressed hyperglycaemia after eating and at inefficiency diet and physical regimes	Type 1 DM ketoacidosis; pregnancy and lactation; chronic renal insufficiency
Repaglinide	0.5 to 16	3 to 4	3 to 4		
Nateglinide	120 to 480	3 to 4	3–4		
BIGUANIDES				Type 2 diabetes with predominant insulin secretion insufficiency (with obesity) and hyperglycaemia fasting during inefficient diet and physical regimes	1. Type 1 DM. 2. Ketoacidosis. 3. Pregnancy and lactation. 4. Chronic heart. 5. Hepatic and renal failure. 6. Anaemia. 7. Alcoholism. 8. Advanced age
Metformin	500 to 3000	3	8 to12		
THIAZOLIDINEDIONE				Type 2 DM prevalence of insulin secretion insufficiency after failure of diet and exercise	1. Type 1 DM 2. Ketoacidosis. 3. Pregnancy and lactation. 4. Pathologies of the liver 5. Severe Cardiac and renal insufficiency

Table 27 continuation

1	2	3	4	5	6
INHIBITORS OF ALPHA-GLUCOSIDASE				Type 2 DM with of hyperglycaemia prevalence ineffectiveness of diet and exercise	1. Type 1 DM. 2. Ketoacidosis. 3. Pregnancy and lactation. 4. Gastrointestinal tract pathology
Acarbose	150 to 300	3	6 to 8		
INCRETIN ANALOGUES (GLUCAGON-LIKE PEPTIDE – GLP-1)				1. Enhances glucose-dependent insulin secretion 2. Suppresses elevated glucagon secretion and slows gastric emptying. 3. Improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes	1. Hypoglycaemia, when taken in conjunction with a sulfonylurea. 2. GI disturbances nausea, vomiting, diarrhoea
Exenatide		2 (s/c)			

Table 27 continuation

DIPEPTIDYL PEPTIDASE – 4 (DPP-4) INHIBITORS				Blocks DPP-4 thus elevating the levels of endogenous incretins (endogenous GLP-1 and GIP). Effects similar to Exenatide	Respiratory disorders: headaches, nasopharyngitis, cold-like symptoms
Sitagliptin (Januvia®)	100mg	1			
SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT-2) INHIBITORS				Inhibit SGLT-2 in the proximal convoluted tube, therefore reducing glucose reabsorption and increasing glucose secretion with urine	1. Urinary tract infections. 2. Polyuria. 3. Hypotonia. 4. Increase in low-density lipids level
Canagliflozin	100–300	1	24		
Empagliflozin	10–25	1	24		
Dapagliflozin	5–10	1	24		

** Source: According to the recommendations of the International Diabetes Federation (IDF 19. Clinical Guidelines TasK Force. Global Guidelines for Type 2 Diabetes, 2019).*

1. Sulfonylureas are first line therapy is indicated for patients with a BMI of up to 30 kg/m^2.
2. Metformin is appointed as first line therapy in patients with type 2 diabetes with a BMI over 30 kg/m^{2,} given the contraindications (class I, level of evidence A). Among anti-hyperglycaemic drugs preference is given to those recommended drugs that can provide effective glycaemic control with minimal development hypoglycaemic conditions (class I, level of evidence A).
3. When monotherapy fails to achieve the targets, a combination oral therapy medication with different mechanisms of action is administered. According to the consensus of the American diabetes association (ADA) and the European Association for the Study of Diabetes (EASD 2008), it is not recommended to prescribe rosiglitazone given the

increased risk of congestive heart failure, myocardial infarction, oedema and bone fractures.

4. Recommended combinations of drugs (class PA, level of evidence B) sulfonylureas and meglitinides, sulfonylureas and thiazolidinediones (pioglitazone); meglitinides and biguanides, meglitinides and thiazolidinedione (pioglitazone), biguanides and thiazolidinedione (pioglitazone), acarbose combined with any hypoglycaemic drugs.

The purpose of insulin therapy

1. Fasting glucose < 6.5 mmol/l.
2. Glucose 2 hours after meals < 9.0 mmol/l.

NB: Before transfer to insulin therapy is necessary:

1. *To teach the patient self-monitoring techniques.*
2. *Warn about the possibility of hypoglycaemia and how to fix it.*
3. *See diet principles, variants of insulin therapy, combination therapy and adding insulin to oral glucose lowering drugs.*
4. *Monotherapy: monoinsulinoterapy for reversal of oral hypoglycaemic drugs.*

Table 28 – Combination of insulin and oral glucose lowering drugs (OGLD) dose estimated

Mode of insulin	**Starting dose**	**Time input**	**Dosage adjustment**
Insulin average duration	8 to 12 U	Bedtime	Correction insulin dose (+2 to +4 U) every 2 to 3 days to achieve the goal: fasting glucose < 6.5 mmol/l, postprandial glycaemia < 9 mmol/l
Insulin average duration	8 to 12 U	Before breakfast and before bedtime	
Insulin pre-mixed (30/70) once or twice a day	8 to I2 U	Before dinner or before breakfast and dinner	

Table 29 – Monotherapy with OGLD with insulin cancellation dose estimated

Scheme	Type of insulin	Starting out	Time input	Dosage adjustment
1	Insulin mixed (30/70)	8 to12 U	Before breakfast	Correction insulin dose (+2 to +4 U) every 2 to 3 days to achieve the goal: fasting glucose < 6.5 mmol/l, postprandial glycaemia < 9 mmol/l
		8 to 12 U	Before dinner	
2	Insulin average duration	8 to 12 U	Before breakfast and before bedtime	
	Short-acting insulin	6 to 8 U	Before meals	

For insulin patients type 2 diabetes drug of choice is genetically engineered human insulin (class PA, level of evidence B). Analogues of human insulin appointed in cases of intolerance to other insulin labile course DM with a penchant for severe hypoglycaemia.

The average dose of insulin in patients with diabetes type 2 diabetes who require insulin is 50 units (class PA, level C). The dose for each patient depends on his individual needs and depends on the body mass, diet, physical activity, degree of insulin resistance and other comorbidities.

Clinical observation of patients with type 2 diabetes without complications

Indications for hospitalization of patients with type 2 diabetes:

1. Acute decompensation of carbohydrate metabolism, requiring transfer to insulin.
2. Severe ketoacidosis or coma (ketoacidotic, hyperosmolar, hypoglycaemic).
3. Rapid progression of vascular complications of DM.

NB: If signs of chronic complications including comorbidities, appearance of additional risk factors and questions about the frequency of inspection is solved individually.

Table 30 – Plan of diagnostic tests and consultations for T2DM

Heading	Frequency of inspection
Self-monitoring of blood glucose (fasting and 2 hours after a meal)	In the onset of the disease and decompensation – daily. Future depends on the type of hypoglycaemic therapy: the insulin – daily, on a diet and OGLD several times a week at different times of day
HbA1c	And once every 6 months (more often if indicated)
Biochemical analysis of blood (total protein, cholesterol, triglycerides, bilirubin, AST, ALT, urea, creatinine, potassium, sodium, calcium)	Once per year (no change)
Total blood	Once every year
Urinalysis	Once every year
Microalbuminuria	Twice a year since diagnosis of diabetes
Blood pressure control	Each time you visit the doctor
ECG	Once every year
ECG stress test for the presence of > 2 risk factors	Once every year
Review feet	Each time you visit the doctor
Family doctor	On a diet and OGLD in the direction of the family, on insulin monthly.
Endocrinologist	On a diet and OGLD in the direction of family
Fluorography	Once every year
Optometrist, cardiologist	Once every year
Neurologist, surgeon, diabetic foot room	Once a year. According to testimony – often

3.4 Treatment of acute complications of diabetes

Acute complications of diabetes include:

1. Hypoglycaemic coma.
2. Diabetic ketoacidotic coma.
3. Hyperosmolar coma.
4. Lactacidemic coma.

Table 31 – Glasgow coma scale

Score	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensive sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion/ withdrawal to painful stimuli	Localises painful stimuli	Obeys commands

Ketoacidotic coma

Pathogenesis

Diabetic ketoacidosis is a result of absolute insulin deficiency. Absence of insulin makes glucose transporting into insulin dependent tissues impossible. Cells reach a state of "energy hunger" as if there was no glucose in the blood. Endogenous glucose depots begin to be used under the action of stress hormones: glycogenolysis and gluconeogenesis are activated and lead to significant hyperglycaemia, but there is not enough insulin for glucose to reach the insulin-dependent cells. In these conditions lipolysis is activated, and lipids break down to higher fatty acids to provide energy for cells. As a result, absolute insulin deficiency leads to uncontrolled excessive ketones production, severe electrolyte disturbances (K^+, Na^+, Cl^-, Mg^{2+}, Ca^{2+}, PO_4^{3-}) osmotic diuresis and dehydration.

Ketoacidosis is more common among patients with type 1 diabetes, especially if it is not diagnosed in time. Provoking factors are: acute or chronic infectious diseases, treatment noncompliance, mistakes in insulin injection technique, expired date for insulin use, unsuitable conditions for insulin storage, malfunction of insulin injection systems, poorly controlled glycaemia, surgical interventions or traumas, pregnancy, chronic therapy by insulin antagonists (glucocorticoids, diuretics).

Clinical presentation

Comatose state develops slowly – about 2–3 days or longer. Symptoms include thirst, polyuria, dryness of skin and mucous membranes, weakness, adynamia, headache, tachycardia, absence of appetite, nausea, vomiting, odour of acetone, loss of consciousness, Kussmaul breathing, hypothermia, hypotension, tachycardia, reduced tone of the eyeballs, miosis, acute abdominal syndrome.

Laboratory findings include hyperglycaemia > 30 mmol/l, hyperketonaemia, decompensated metabolic acidosis pH < 7.3, SB < 15 mEq/l, glucosuria, ketonuria, leucocytosis, proteinuria, hyperazotaemia, hypercreatinaemia.

Treatment

- *Rehydration:*
  - 0.9 % NaCl (if plasma Na^+ level does not exceed 150 mmol/l); 500 ml/hour for children, 500–1 000 ml/hour for adults.
  - 0.45 % NaCl – if plasma Na^+ is $\geq$ 150 mmol/l.
  - 5 % glucose or 10% dextrose – if glycaemia is < 14 mmol/l; can be combined with 0.9 % NaCl.

    Volume of rehydration per hour must not exceed diuresis per hour by more than 500–1 000 ml. Infusion should be stopped when the patient is conscious and able to drink.

Table 32 – Rehydration

Time	Volume of intravenous liquids
1st hour	1 000 ml
2nd hour	500 ml
3rd hour	500 ml
4th hour and later	300–500 ml

- *Insulin:*
    - low-dose regime; rapid-acting insulin;
    - 0.1 U/kg IV bolus;
    - continuous 0.1 U/kg/hour IV (diluted by 0.9 % NaCl solution);
    - target glycaemia of the first treatment day is 14 mmol/l;
    - glycaemia must not be decreased faster, than 5.5 mmol/l/hour.

Table 33 – Hypokalemia correction

K^+ plasma level	Infusion rapidity
< 3.5 mmol/l	40 mmol/hour
3.5–5.5 mmol/l	20 mmol/hour
< 3.5 mmol/l	not administrated

- *Hypokalemia correction:*

    start simultaneously with insulin, if pH > 7.1.

7. *Acidosis correction:*
    - aetiotropic therapy is insulin;
    - administer $NaHCO_3$ ***only*** recommended if severe acidosis pH $\leq$ 6.9 or/and SB < 5 mmol/l in very limited quantities (1–1,5 mEq/kg) only after initial hydration, it must be diluted to avoid osmotic impact and slowly infused.
8. *Disseminated intravascular coagulation syndrome prophylaxis:*

    heparin 2500-5000 U 4 times a day if plasma osmolality > 320 mOsm/l.

9. *After stabilization*:
    - glycaemia $\leq$ 10–12 mmol/l;
    - normal consciousness;
    - normal BP;
    - normal pH;

    proceed to subcutaneous rapid-acting insulin injections every 4–5 hours.

Hyperosmolar coma

Pathogenesis

It is usually provoked by exogenous dehydration accompanied by relative insulin deficiency. Hyperosmolar state is more common among people with type 2 diabetes. Provoking factors include vomiting, diarrhoea, bleeding, burns, diabetes insipidus, concomitant diseases.

Clinical presentation

Comatose state develops very slowly – about 10–12 days. Signs include:

- dry skin and mucous membranes;
- polyuria (later oliguria and anuria possible);
- progressive weakness;
- adynamia;
- reduced skin turgor;
- reduced tone of the eyeballs;
- malaise;
- acetone odour is absent;
- Kussmaul breathing is absent;
- polymorphic neurological symptoms (speech disturbances, nystagmus, paresis, paralysis, convulsions, etc.).

It is important to carry out a differential diagnosis with brain oedema to avoid misdiagnosis and administration of diuretics instead of rehydration.

Laboratory findings include prominent hyperglycaemia, > 30–50 mmol/l; hyperosmolarity, > 310 mOsm/l; no ketonemia; hypernatremia; massive glucosuria; no acetonuria; no acidosis, pH > 7.3; SB > 15 mEq/l.

Treatment

1. *Rehydration:*

a. 0.45 % NaCl solution if plasma Na^+ 145–165 mmol/l;

b. 5 % glucose solution if plasma Na^+ > 165 mmol/l; Na-containing solutions are contraindicated;

c. 0.9 % NaCl solution if plasma Na^+ < 145 mmol/l.

2. *Insulin* – same principles, as in DKA treatment.

Lactacidemic coma

Pathogenesis

Provoking factors include:

- states, that promote lactate production: decompensated diabetes, DKA, biguanides;
- states, accompanied by reduced lactate clearance: liver parenchyma destruction, alcohol abuse;
- states, which combine increased production and reduced clearance of lactate;
- tissue hypoxia: chronic cardiovascular failure, ischemic heart disease;
- combination of several factors: acute stress, age >65 years, late stages of diabetes complications, oncological processes;

Table 34 – Classification of lactacidemic states

Associated with tissue hypoxia (type A)	Not associated with tissue hypoxia		
	Type B1	Type B2	Type B3
Cardiogenic shock	Protractedly and formidably decompensated diabetes	Biguanides	Type 1 glycogen storage disease (von Gierke disease, when the body cannot break down glycogen)
Endotoxic, hypovolemic shock, CO-poisoning	Renal or/and liver dysfunction	IV glucose, fructose, sorbitol, xylitol	Methylmalonic acidaemia
Anaemia	Oncological processes	Salicylates	
Pheochromocytoma	Haemoblastosis	Methanol, ethanol	
Epilepsy	Infectious diseases	Cyanides	

Clinical presentation:

- muscle pain;
- heartache, which does not reduce after antianginal medication administration;
- stomach-ache;
- headache;
- weakness, malaise;
- nausea, vomiting;
- low blood pressure;
- drowsiness, which proceeds into stupor and coma;
- dyspnoea, later – Kussmaul breathing.

Laboratory findings include: hyperlactataemia; decompensated metabolic acidosis; anion gap > 15 mEq/l ($Na^+ - (HCO_3^- + Cl^-)$); HCO_3^- < 18 mEq/l; mild hyperglycaemia; pH < 7.3; no ketonemia; plasma lactate > 5 mmol/l.

Treatment

1. *Lactate synthesis inhibition:*
   a) rapid-acting insulin 2–4 U/hour IV diluted by 5 % glucose 100–250 ml/hour.
2. *Lactate excess removing:*
   a) haemodialysis with a lactate-free dialyzer.
3. *Acid-base balance restoration:*
   a) artificial hyperventilation for excess CO_2 removal;
   b) IV $NaHCO_3$ solution, **not more,** then 50 ml 8,5 % once.
4. *Treatment of shock and hypovolemia.*

Hypoglycaemia

Pathogenesis

Excess amount of insulin in the organism relatively to carbohydrates intake.

Classification:

1. Mild hypoglycaemia – patient can self-diagnose and self-medicate with oral carbohydrates intake.
2. Moderate hypoglycaemia – patient can`t help himself, but oral carbohydrates intake can resolve this state.
3. Severe hypoglycaemia – patient is half-conscious, needs parenteral carbohydrate therapy.
4. Asymptomatic "biochemical hypoglycaemia".

Table 35 – Hypoglycaemia symptoms

Adrenergic symptoms	**Neuroglycopenic symptoms**
Tachycardia	Malaise
Mydriasis	Headache
Tremor	Dizziness
Pallor	Disorientation
Sweating	Fear
Nausea	Paraesthesia
Hunger	Speech, sight, coordination disturbances
Aggressive behaviour	Cramps
Anxiety	Amnesia

Clinical presentation and laboratory findings:

1) glycaemia < 2.8 mmol/l;
2) adrenergic symptoms;
3) neuroglycopenic symptoms.

Treatment

1. Mild hypoglycaemia:

simple carbohydrates intake: 1–2 bread units (4–5 sugar cubes, dissolved in water), honey, jam, 200 ml of fruit juice or 100 ml of lemonade (Pepsi, cola, Fanta) or 4–5 tablets of glucose.

2. Severe hypoglycaemia:

a) IV bolus 40 % glucose solution 20–100 ml;

b) 1,0 ml glucagon SC or IM;

c) if the patient is still unconscious – 5 % glucose solution IV continuous infusion, transportation to intensive care unit.

Education of patients with diabetes

1. Education and psychological support for patients with diabetes is the integrating component of the treatment process of DM that provides patients the knowledge, skills and motivation to achieve a specific therapeutic purpose.
2. Educational activities are carried out with all patients with diabetes since its discovery and during its course. The purpose and objectives of training should be specified in accordance with the actual condition of the patient.
3. Training is carried out both individually and in groups of patients (type 1 DM, type 2 DM without insulin; type 2 DM on insulin, etc.). Using the developed programs.
4. Base training is a hospital or clinic with the release of a separate room with the necessary equipment (school board, glucometers, test strips, drug samples and tools insulin, visual aids, etc.).
5. Education and psychological support to patients carried out by specially trained health care workers: endocrinologists, nurses, involving a dietician and a medical psychologist.

APPENDICES

APPENDIX A

(obligatory)

SUMMARY OF THE CLINICAL METHODOLOGY

1. Investigation of complaints through patient interviews and physical examination.
2. Establishment of preliminary diagnosis and diagnoses of complications.
3. Select an array of diagnostic tests (integrating clinical data with laboratory and instrumental data).
4. Differential diagnosis of the basic diagnosis.
5. Establishment of clinical diagnosis.
6. Patient management.
7. Epicrisis with further recommendations.

PLAN OF PATIENT CASE HISTORY

PASSPORT DETAILS:

Name _____

Surname _____

Date of birth _____, age _____

Home address _____

Education: _____

Marital status: _____

Work record: _____

Date of admission to the hospital _____

Institution which has directed patient to the hospital ____

Pre-admission diagnosis _____

Patient's department _____

- *Complaints.*
- *Anamnesis Morbi.*
- *Anamnesis Vitae.*

Appendix A continuation

- *Physical examination of patient.*
- *Preliminary diagnosis of patient.*

  (Based on the information obtained from complaints, anamnesis morbi, anamnesis vitae, and physical examination of the patient).
- *Additional methods of routine diagnostic investigations to confirm clinical diagnosis:*
  - laboratory (stool, glycaemic level, general urine analysis, biochemical urine analysis, general blood analysis, biochemical blood analysis);
  - instrumental methods (ECG, etc.).
- *Analysis* of all obtained data from the patient's complaints till the additional investigative diagnostic methods and *differential diagnosis*.
- *Clinical diagnosis* and its confirmation.
- *General management plan:*
  - lifestyle modifications;
  - diet;
  - principles of treatment (pharmacological, surgical, physiotherapeutic methods, etc.) and prescription of medications.
- Daily evaluation of patient (daily dairy). At least 2 daily evaluations.
- Epicrisis: indicate here concise (short and detailed) information of patient during time of hospitalization and during time of patient discharge.

APPENDIX B

(obligatory)

PHYSICAL EXAMINATION TECHNIQUES (PATIENT CASE HISTORY GUIDELINES)

Patient Interview Technique

The written history of an illness should embody all the facts of medical significance in the life of the patient. If the history is recorded in chronological order, recent events should be given the most attention. Likewise, if a problem-oriented approach is used, the problems that are clinically dominant should be listed first. Ideally, the narration of symptoms or problems should be in the patient's own words. The health professional must be alert to the possibility that any event related by the patient however trivial, or apparently remote, may be the key to the solution of the medical problem.

An informative history is more than orderly listing of symptoms. Something is always gained by listening to patients and noting the way in which they describe their symptoms. Disturbance of voice, facial expression and attitude betray important clues to the meaning of the symptoms to the patient. In listening to the history, the interviewer discovers not only something about the disease but also something about the patient. Listening is the key to proper clinical history.

Patients cannot be tied down to an orderly sequence of history taking. They must be allowed as far as possible, to tell their story in their own words and in their own way. Only when they have done this should they be asked to enlarge on what appear to be the more important aspects of the story and only after that should specific questions asked.

Make it clear from your stance, gestures and expressions that the patient has your whole attention and that you will not be shocked or angered by anything he/she says. Gazing out of the window or continually writing notes will put off the patient. Never underestimate the power of communication inherent in touching your patient. If a patient does make one angry or confused, it is best to recognize this and try starting the interview afresh by saying: "I haven't quite got this clear yet; let's go over it again so that I get it right." A patient goes to a health institution, perhaps for the first time in his life, on the other hand with apprehension and suspicion and with the intention of unfolding his life story to the health professional that he regards as his best confidant and whom he expects to respect his human dignity. Patients often want to talk and explain their problem and, by

doing so, get some peace of mind. It should also be remembered that the patient is a person not simply a case.

Avoid careless remarks that may hurt the feelings of your patient and thereby jeopardize the friendly communication you would like to establish between your patient and yourself. Besides, remember that any emotional upset may change the course of the illness of the patient. So, you should try to alleviate anxieties by repeated reassurance.

It is also important to note that the medical and paramedical personnel should respect the professional secrecy so much expected of them. Thus, a medical record is strictly the property of the medical staff looking after the patient and should not be exposed to anyone outside the staff, nor should the contents be told to others at any time.

SAMPLE QUESTIONS FOR PATIENTS

Anamnesis Morbi:

1. The onset of disease, what was his/her fasting and postprandial glycaemic level when first diagnosed DM?
2. The duration of the diseases.
3. What preceded the disease?
4. The development of disease.
5. The result of previous additional methods of investigation, his/her fasting and postprandial glycaemic level (if they were present).
6. The previous treatment (if it was present). Ask about the type of insulin being used, delivery system (pump vs. injections), dose, and frequency. Also ask about oral hypoglycaemic agents taken, doses and frequency.
7. The effect of previous treatment (if it was present): Is the patient's diabetes generally well controlled? Does the patient self-monitor his or her blood glucose levels? Does the patient have severe hypoglycaemic reactions? Has the patient had episodes of unexplained hypoglycaemia? If so, when, how often, and how does the patient treat these episodes?
8. Regarding microvascular complications: Microvascular complications, such as retinopathy and nephropathy, should be considered as well. Consider the following questions:
   - When lastly did the patient see an ophthalmologist? What were the results?
   - Does the patient have known kidney disease?

- What were the dates and results of the last measurements of urine protein and serum creatinine levels?

9. Regarding macrovascular complications: Macrovascular complications should be explored. Questions should include the following:
   - Does the patient have hypertension? What medications are taken?
   - Has the patient had a stroke or transient ischaemic attack?
   - What are the patient's most recent cholesterol levels?
   - Is the patient taking cholesterol-lowering medication?
10. Regarding Neuropathy complications: Potential neuropathy should be taken into account. Ask whether the patient has a history of neuropathy or symptoms of peripheral neuropathy or whether autonomic neuropathy is present (including impotence if the patient is male).
11. Regarding Foot disease complications:
    - The possibility of foot disease should be addressed. Inquire as to whether the patient has a history of foot ulcers or amputations or whether any foot ulcers are present and when (if it was presence)?
    - Are frequent infections a problem? At what site?
12. The reason for present hospitalization?

NB: Main points that should be noted in the section of Anamnesis Morbi (meaning the events during the clinical course of the disease) include:

1. *Patients with poorly controlled blood glucose levels heal more slowly and are at increased risk for infection and other complications.*
2. *Patients with type 1 DM are treated with insulin, type 2 DM are treated by oral hypoglycaemic agents and only in some indicated cases of treatment resistance with insulin.*
3. *If the patient has episodes of severe hypoglycaemia and therefore is at risk for losing consciousness, this possibility must be addressed.*
4. *Note the frequency and range of glucose level values at each time of day which was monitored by the patient.*

Appendix B continuation

Anamnesis Vitae:

1. *Allergic anamnesis* to any foods of foreign substances as well as medications including insulin.
2. *Family history* of DM, obesity, hypertension, cardiac disorders, strokes, hereditary diseases amongst immediate relatives whether alive or deceased.
3. *Social habits* which worsen DM complications (e.g., alcoholism and smoking).
4. *Professional hazards* or possible exposure to environmental factors that may cause or worsen DM.
5. Other pathologies or health related problems:
   - big foetus of weight > 4200 g;
   - history of vascular diseases (varicose veins, obliterating endarteritis, etc.);
   - cardiovascular disorders (hypertension, myocardial infarction, cerebrovascular stroke, etc.);
   - previous surgeries prior to admission (types and extend of surgeries).

Table 36 – Diagnostic algorithm

Suspected diabetes	- Presence of the main triad of symptoms: polyuria, polydipsia, weight loss at the onset of DM - The presence of diabetes in relatives. See page 9
Verification of the basic diagnosis of DM	1. FPG > 6.1 mmol/l 2. PPG > 11.1 mmol/l See page 11
Type of DM	1. Anamnesis gathering to determine the conditions of DM onset (age, weight loss, DKA) and previous laboratory data. Ex.: DM type 1 – in childhood, DM type 2 – in adults). 2. Laboratory data: - serum C-peptide and insulin determination (DM type 1 – Low, DM type 2 – High); - determination of GADA, IAA and ICA (DM type 1 – "+"). See page 13
Degree of DM severity	According to the chronic complication stages and the treatment needed for glycaemia compensation. See page 16
State of DM compensation/decompensation	1. Presence or absence of main triad of DM. If present, then state is said to be decompensation. If absent, then compensation. 2. According to laboratory data obtained from fasting and postprandial glycaemic levels, and level of glycated haemoglobin in blood (HbA1c). See page 18

Table 37 – Chronic complications of DM diagnosis algorithm

Diabetic retinopathy	Signs of blindness or decreased vision. The stage is evaluated by ophthalmologist via retinoscopy examination. See page 40
Diabetic neuropathy	Neuropathy in anamnesis or symptoms of peripheral neuropathy or whether autonomic neuropathy is present. Neurological examination of vibration, tactile, temperature, pain sensitivity. Presence of paraesthesias, abnormal sensations, pain in extremities. See page 19
Diabetic nephropathy	Stage is evaluated according to microalbuminuria values, eGFR, creatinine to albumin ratio. See page 33
Diabetic angiopathy of the lower extremities	She is based on the clinical complaints (decreased skin temperature, pulse, cyanotic skin colour, pain, trophic ulcers, gangrene) and instrumental methods. The stage is evaluated by according to the depth of trophic ulcer. The form is evaluated by according to aetiopathogenesis. See page 53
Cerebrovascular angiopathy	It manifests as discirculatory encephalopathy (deterioration of memory, dizziness, headaches, etc), ischaemic cerebral stroke. See page 50
Cardiovascular diseases	Evaluate patient`s risk for cardiovascular accidents, manage comorbid cardiovascular states. See page 50

APPENDIX C

(obligatory)

RESULTS OF ADDITIONAL METHODS OF EXAMINATION

Table 38 – Routine blood analysis (clinical blood analysis)

Test	Normal	Date	Remark
Hb	120 to 140 g/L for women 130 to 160 g/l for men		
Erythrocytes	3.5 to $5.5x10^{12}$/L for women 4.2 to $6.9x10^{12}$/L for men		
Leucocytes	3.5 to $9x10^{9}$/L		
Eosinophil	1 to 7 % of WBC		
Basophil	0 to 2 % of WBC		
Neutrophilic *band form*	3 to 5 % of WBC		
Juvenile			
Segmented	45 to 70 % of WBC		
Lymphocytes	16 to 40 % of WBC		
Monocytes	3 to 10 % of WBC		
Haemoglobin	120 to 140 g/l for woman 130 to 160 g/l for men		
Thrombocytes	150 to $320x10^{9}$ cells/l		
ESR	5 to 15 mm/h for women 3 to 12 mm/h for men		

Table 39 – Biochemical analysis of blood

Test		**Normal**	**Date**	**Remark**
Total Protein		60 to 80 g/L		
Albumin		35 to 55 g/L		
Bilirubin	Total	5 to 20 μmol/L		
	Direct	0 to 5 μmol/L		
Calcium		2.25 to 2.75 mmol/L		
Potassium		3.5 to 5.1 mmol/L		
Alanine aminotransaminase (ALT)		5 to 56 IU/L		
Aspartate aminotransaminase (AST)		Male: 8 to 40 IU/L Female: 6 to 34 IU/L		
Glucose (capillary plasma)		3.3 to 5.5 mmol/L. 80 to 100 mg/dL		
Urea		1.2 to 7.0 mmol/dL 7 to 21 mg/dL		
Creatinine		Male: 0.7 to 1.3 mg/dL (60 to 118 μmol/L). Female: 0.6 to 1.1 mg/dL (50 to 98 μmol/L)		
BUN ratio		5 to 35		
Osmolarity		290 to 320 mOsm/l		
LDL		2.0 to 5.1 mmol/L		
HDL		1.0 to 2.2 mmol/L		
Cholesterol		$\leq$ 5.17 mmol/L		
Atherogenic Index		2 to 4.5		
TAG		$\leq$ 2.3 mmol/L		
HbA1c		4 to 6		
C-peptide		1.1 to 4.4 ng/ml		

Appendix C continuation

Table 40 – Glycaemic profile

Time	**Glucose levels**			
	Date	**Date**	**Date**	**Date**
7:00 (fasting)				
10:00 (2 hours after meal)				
14:00 (2 hours after meal)				
16:00 (2 hours after meal)				
22:00 (2 hours after meal)				
4:00				

Table 41 – General urine analysis

Test	**Normal**	**Date**	**Remark**
Amount	100 ml		
Specific Gravity	1.003 to 1.030		
Osmolality	400 mOsm/l		
pH	5 to 7		
Protein	0 to 20 mg/dL		
Glucose	absent		
Potassium	40 to 90 mmol/24 h		
Ketone bodies	absent		
Epithelium	absent		
Leucocytes	0 to 2		
Erythrocytes	0 to 3 (male) 0 to 6 cells (female)		
Casts	0		
Crystals	0		
Mucous	0		

Appendix C continuation

Urinal examination by Nechiporenko

Leucocytes = $2x10^3$ /l

Erythrocytes = $1x10^3$/l

24-hour urine test

24-hour urine protein = _____mg/day.

Reberg`s test

Normal GFR, glomerular filtration rate = 80 to 120 ml/min.

GFR (ml/min) = {urine creatinine (mmol/24 hours) * (diuresis per min (ml/min))}/blood creatinine(mmol/l)

Estimated GFR is adjusted to the body area (m^2)

eGFR (ml/min/1.73m^2) = {1.73 * urine creatinine (mmol/24 hours) * (diuresis per min (ml/min))}/(blood creatinine(mmol/l)*body area (m^2))

Inulin clearance test

This is one of the tests to determine the patient`s GFR. A fluid containing inulin is administrated and then urine samples are collected over several hours. The volumes of samples are noted and the amount of inulin in each sample is calculated. It is not routinely ordered.

APPENDIX D

(obligatory)

ORAL ANTIHYPERTENSIVE DRUGS

Table 42 – Oral antihypertensive drugs

Class	**Drug (trade name)**	**Usual dose range (mg/day)**	**Usual daily frequency**
1	**2**	**3**	**4**
Alpha-1 blockers	Doxazosin (Cardura) Prazosin (Minipress Ɪ) Terazosin (Hetzin)	1–16 2–20 1–20	1 2–3 1–2
Central alpha-2 agonists and other centrally acting drugs	Clonidine (Catapres Ɪ) Clonidine patch (Catapres – TTS) Methyldopa (Aldormet Ɪ) Reserpine (generic) Guanfacine (Tenex Ɪ)	0.1–0.8 0.1–0.3 250–1000 0.1–0.25 0.5–2	2 1 weekly 2 1 1
Direct vasodilators	Hydralazine (Apresoline Ɪ) Minoxidil (Loniten Ɪ)	25–100 2.5–80	1 1–2
ACEIs	Benazepril (Lotensin Ɪ) Capropril (Capoten Ɪ) Enalapril (Vasotec Ɪ) Fosinopril (Monopril) Lisinopril (Prinivil, Zestril Ɪ) Moexipril (Univasc) Peridopril (Aceon) Ramipril (Altace) Trandolapril (Mavik)	10–40 25–100 5–40 10–40 10–40 7.5–30 4–8 2.5–20 1–4	1 2 1–2 1 1 1 1 1 1
Angiotensin II antagonists	Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Lorsartan (Cozaar) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan)	8 – 32 400 – 800 150 – 300 25 – 100 20 – 40 20 – 80 80 – 320	1 1–2 1 1–2 1 1 1–2
CCBs – non-dihydropyridines	Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac Ɪ) Diltiazem extended release (Cardizem LA) Verapamil immediate release (Calan, Isoptin Ɪ) Verapamil long acting (Calan SR, Isoptin SR Ɪ) Verapamil – (Coer, Covera HS, Verelan PM)	180 – 420 120 – 540 80 – 320 120–480 120–360	1 1 2 1–2 1

Appendix D continuation

Table 42 continuation

1	2	3	4
CCBs – Dihydropyridines	Amilodipine (Norvasc) Felodipine (Plendil) Isradipine (Dynacirc CR) Nicardipine sustained release (CArdene SR) Nifedipine long – acting (Adalat CC, Procardia XL) Nisoldipine (Sular)	2.5–10 2.5–20 2.5–10 60–120 30–60 10–40	1 1 2 2 1 1
Thiazide diuretics	Chlorothiazide (Diuril) Chlorothialidone (generic) Hydrochlorothiazide (Microzide, HydroDIURIL) Polythiazide (Renese) Indapamide (Lazol[I]) Metolazone (Mylorox) Metolazone (Zaroxolyn)	125–500 12.5–25 12.5–50 2–4 1.25–2.5 0.5–1.0 2.5–5	1–2 1 1 1 1 1 1
Loop diuretics	Bumetanide (Bumex[I]) Furosemide (Lasix[I]) Torsemide (Demadex[I])	0.5–2 20–80 2.5–10	2 2 1
Potassium sparing diuretics	Amiloride (Midamor[I]) Triamterene (Dyrenium)	5–10 50–100	1–2 1–2
Aldosterone receptor blockers	Epelerone (Inspra) Spironolactone (Aldactone[I])	50–100 25–50	1 1
BBs	Atenolol (Tenormin[I]) Etaxolol (Kerlone[I]) Bisoprolol (Zebeta[I]) Metoprolol (Lopressor[I]) Metoprolol extended release (Toprol XL) Nadolol (Corgard[I]) Propanolol (Inderal[I]) Propanolol long acting (Inderal LA[I]) Timolol (Blocardren[I])	25–100 5–20 2.5–10 50–100 50–100 40–120 40–160 60–180 20–40	1 1 1 1–2 1 1 2 1 2
BBs with intrinsic sympathomimetic activity	Acebutol (Sectral[I]) Penbutolol (Levatol) Pindolol (generic)	200 – 800 10 – 40 10 – 40	2 1 2

Appendix D continuation

Table 42 continuation

1	2	3	4
Alpha-1 blockers	Doxazosin (Cardura) Prazosin (Minipress Ł) Terazosin (Hetzin)	1–16 2–20 1–20	1 2–3 1–2
Central alpha-2 agonists and other centrally acting drugs	Clonidine (Catapres Ł) Clonidine patch (Catapres – TTS) Methyldopa (Aldormet Ł) Reserpine (generic) Guanfacine (Tenex Ł)	0.1–0.8 0.1–0.3 250–1000 0.1–0.25 0.5–2	2 1 weekly 2 1 1
Direct vasodilators	Hydralazine (Apresoline Ł) Minoxidil (Loniten Ł)	25–100 2.5–80	1 1–2
ACEIs	Benazepril (Lotensin Ł) Capropril (Capoten Ł) Enalapril (Vasotec Ł) Fosinopril (Monopril) Lisinopril (Prinivil, Zestril Ł) Moexipril (Univasc) Peridopril (Aceon) Quinapril (Accupril) Ramipril (Altace) Trandolapril (Mavik)	10–40 25–100 5–40 10–40 10–40 7.5–30 4–8 10–80 2.5–20 1–4	1 2 1–2 1 1 1 1 1 1 1
Angiotensin II antagonists	Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Lorsartan (Cozaar) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan)	8 – 32 400 – 800 150 – 300 25 – 100 20 – 40 20 – 80 80 – 320	1 1–2 1 1–2 1 1 1–2
CCBs – non-dihydropyridines	Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac Ł) Diltiazem extended release (Cardizem LA) Verapamil immediate release (Calan, Isoptin Ł) Verapamil long acting (Calan SR, Isoptin SR Ł) Verapamil – (Coer, Covera HS, Verelan PM)	180 – 420 120 – 540 80 – 320 120–480 120–360	1 1 2 1–2 1
CCBs – Dihydropyridines	Amilodipine (Norvasc) Felodipine (Plendil) Isradipine (Dynacirc CR) Nicardipine sustained release (CArdene SR) Nifedipine long – acting (Adalat CC, Procardia XL) Nisoldipine (Sular)	2.5–10 2.5–20 2.5–10 60–120 30–60 10–40	1 1 2 2 1 1

Appendix D continuation

Table 42 continuation

1	2	3	4
Thiazide diuretics	Chlorothiazide (Diuril) Chlorothialidone (generic) Hydrochlorothiazide (Microzide, HydroDIURIL) Polythiazide (Renese) Indapamide (Lazol[Ł]) Metolazone (Mylorox) Metolazone (Zaroxolyn)	125–500 12.5–25 12.5–50 2–4 1.25–2.5 0.5–1.0 2.5–5	1–2 1 1 1 1 1 1
Loop diuretics	Bumetanide (Bumex[Ł]) Furosemide (Lasix[Ł]) Torsemide (Demadex[Ł])	0.5–2 20–80 2.5–10	2 2 1
Potassium sparing diuretics	Amiloride (Midamor[Ł]) Triamterene (Dyrenium)	5–10 50–100	1–2 1–2
Aldosterone receptor blockers	Epelerone (Inspra) Spironolactone (Aldactone[Ł])	50–100 25–50	1 1
BBs	Atenolol (Tenormin[Ł]) Etaxolol (Kerlone[Ł]) Bisoprolol (Zebeta[Ł]) Metoprolol (Lopressor[Ł]) Metoprolol extended release (Toprol XL) Nadolol (Corgard[Ł]) Propanolol (Inderal[Ł]) Propanolol long acting (Inderal LA[Ł]) Timolol (Blocardren[Ł])	25–100 5–20 2.5–10 50–100 50–100 40–120 40–160 60–180 20–40	1 1 1 1–2 1 1 2 1 2
BBs with intrinsic sympathomimetic activity	Acebutol (Sectral[Ł]) Penbutolol (Levatol) Pindolol (generic)	200 – 800 10 – 40 10 – 40	2 1 2

APPENDIX E

(obligatory)

QUESTIONS AND CASES

CASE STUDY 1

A 48-year-old man with a five-years history of diabetes mellitus comes to the primary care clinic for a routine check-up. He has no current complaints. His medications include metformin and acetaminophen. He is a teacher, smokes two packs of cigarettes per day, and drinks “occasionally”. He eats large amounts of meat daily and consumes excessive "junk food". On physical examination, his temperature is 37.1 °C (98.8 °F), pulse 88 bpm, respiratory rate 12 per minute, and blood pressure 158/96 mm Hg. His height is 1,7 m, weight is 90 kg. The remainder of his physical examination is unremarkable. Laboratory studies reveal HbA1c of 6.5 percent. At his last check-up one month ago, his blood pressure was 152/92 mm Hg.

1. Make the proper diagnosis.

2. Determine the BMI and the degree of obesity.

3. Set the grade of arterial hypertension.

4. Which groups of antihypertensive drugs would be most effective in reducing blood pressure in this patient?

CASE STUDY 2

A 50-year-old man comes to the office for a review of his laboratory studies. He has a history of diabetes mellitus, and his current medications include glipizide and metformin. He says that he takes his medications regularly, but his wife is concerned about his diabetes control. His health maintenance labs show HbA1c of 9%, increased from 7% at his last visit.

1. Establish the patient’s clinical diagnosis.

2. What labs would best indicate a need for insulin to control this patient's blood sugar?

CASE STUDY 3

A 34-year-old man comes to the ophthalmology clinic for a routine eye examination. He believes his sight is good and has no current concerns. Examination shows bilateral retinal microaneurysms and hard exudates. Laboratory studies show HbA1c level of 7.3%.

1. Make the proper diagnosis.

2. Prescribe treatment of diabetic retinopathy.

CASE STUDY 4

A 10-year-old girl complaints on increased thirst and urination for 2 months. Her mother says that she has also been losing weight over the last month. Personal and family medical histories are non-contributory. Examination shows a thin and tired appearing child. She also has dry mucous membranes and delayed capillary refill. Laboratory investigations show a blood glucose of 13,4 mmol/l, an undetectable serum C-peptide and positive anti-islet antibodies.

1. Make the proper diagnosis.

2. Prescribe most proper treatment.

CASE STUDY 5

A 54-year-old man with type 2 diabetes mellitus of 12 years' duration with an ulcer over the bony prominence on the plantar surface of his rocker bottom deformity which remained unhealed for 2 years. He experiences pain after walking over 300 meters. He was referred to the diabetic foot clinic and was treated with a total-contact cast and Dermagraft. The foot healed in 7 months and has remained healed. X-ray showed multiple feet deformations. Laboratory studies reveal an HbA1c of 6.7 percent.

1. Make the proper basic diagnosis.

2. Make the diagnosis of DM chronic complication.

CASE STUDY 6

A 53-year-old man comes to the office because of numbness and paraesthesias at the tips of his fingers on both hands for 4 months. At night, this sensation sometimes worsens to a burning pain. He says he has increased thirst and urination, weight loss, and frustrating impotence during the last year. He has decided to leave his career due to these functionally disabling limitations. Examination shows decreased sensation of the affected extremities.

1. What is the basic diagnosis?

2. What is the diagnosis of DM complication?

CASE STUDY 7

A 46-year-old woman presents for her yearly physical examination. Her medical history is notable only for borderline hypertension and moderate obesity. She has a family history of diabetes and hypertension. The patient has not followed the recommended lifestyle changes. Today, her blood pressure is 140/90 mmHg, and her BMI is 28 kg/m2. Her examination is notable for acanthosis nigricans at the neck. A fasting plasma glucose level is 10 mmol/l.

1. What is your diagnosis? Explain it.

2. What is your next step in diagnosis conformation?

CASE STUDY 8

An 18-year-old adolescent female is brought to the emergency room by her mother because the daughter seems confused and is behaving strangely. The mother reports the patient has always been healthy and has no significant medical history, but she has lost 5 kg recently without trying and has been complaining of fatigue for 2 or 3 weeks. The patient has fatigue and sleep disturbance, recently she has been getting up several times at night to urinate. This morning, the mother found the patient in her room, complaining of abdominal pain, and she had vomited. She appeared confused and did not know that today was a school day. On examination, the patient is slender, lying on a bad with eyes closed, but she is responsive to questions. She is afebrile, and has a heart rate 118 bpm, blood pressure 125/85 mm Hg, with deep and rapid respirations at the rate of 24 breaths per minute. Upon standing, her heart rate rises to 145 bpm, and her blood pressure falls to 110/85 mm Hg. Her oral mucosa is dry. Her chest is clear to auscultation, and her heart is tachycardic with a regular rhythm and no murmur. Her abdomen is soft with active bowel sounds and mild diffuse tenderness, but no guarding or rebound. Her neurologic examination reveals no focal deficits.

Laboratory studies include serum Na 131 mEq/L, K 5.3 mEq/L, Cl 95 mEq/L, CO 29 mEq/L, blood urea nitrogen (BUN) 35 mg/dL, creatinine 1.3 mg/dL, and glucose 27 mmol/l. Arterial blood gas reveals pH 7.12 with PCO_2 24 mm Hg and PO_2 95 mmHg. Urine drug screen and urine pregnancy test are negative, and urinalysis shows no haematuria or pyuria, but 3+ glucose and 3+ ketones. Chest radiograph is normal.

1. What is the most likely diagnosis?

2. What is your next step?

CASE STUDY 9

A patient comes to the clinic for a fasting plasma glucose test. On two separate occasions, the result has been 6.5 mmol/l and 6.7 mmol/l.

1. What is your diagnosis?

2. What is your management strategy?

CASE STUDY 10

A 54-year-old male lawyer has uncontrolled diabetes mellitus for over a year. He did not take any hypoglycaemic drugs. He has had a previous heart attack and is taking several cardiovascular and antihypertensive medications.

His physical examination today is normal. He admits to feeling a little tired, recently, and has been getting up at night to urinate at least two to three times per week.

Last HbA1C – 9.2 %.

Lipid profile: total cholesterol – 4 mmol/l, LDL – 1.8 mmol/l, HDL – 1 mmol/l, Triglycerides – 2.5 mmol/l. Creatinine: 0.8 mg/dL.

Microalbuminuria: negative.

ALT: normal, AST: normal.

Postprandial glucose – 13 mmol/l.

Blood pressure 130/90 mmHg.

Cardiovascular condition: previous myocardial infarction. Eye examination - normal. Foot examination - normal pulses and sensation. His height is 1,67 m, weight is 81 kg.

1. Establish clinical diagnosis.

2. Determine the BMI and the degree of obesity.

3. Prescribe treatment as well as recommendations.

APPENDIX F

(obligatory)

ANSWERS

CASE STUDY 1

1. Type 2 diabetes mellitus, moderate severity, compensation state.

2. BMI is 31 kg/m2, obesity I degree.

3. Grade I of arterial hypertension.

4. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

CASE STUDY 2

1. Type 2 diabetes mellitus, moderate severity, decompensation state.

2. The need for insulin to control the blood sugar in this patient is indicated by HbA1c of 9 %.

CASE STUDY 3

1. Type 2 diabetes mellitus, moderate severity, subcompensation state. Diabetic retinopathy, non-proliferative stage.

2. Control of blood sugar level (diet, exercise, medications and/or insulin).

CASE STUDY 4

1. Type 1 diabetes mellitus, moderate severity, decompensation state.

2. Basic-bolus intensive insulin therapy with a daily glucose monitoring.

CASE STUDY 5

1. Type 2 diabetes mellitus, moderate severity, compensation state.
2. Diabetic foot syndrome grade 2, neuroischaemic form. Diabetic lower extremity angiopathy stage 2a. Diabetic bilateral lower extremity sensory neuropathy.

CASE STUDY 6

1. Type 2 diabetes mellitus, moderate severity, decompensation state.
2. Diabetic neuropathy, sensory form, autonomic form.

CASE STUDY 7

1. Most likely diagnosis: Given her hypertension, obesity, family history, fasting plasma glucose level is 10 mmol/l and the finding of acanthosis nigricans, this patient most likely has type 2 diabetes.
2. Next step: The fasting/postprandial glucose level should be repeated to confirm the diagnosis. If the next result is less than 7 mmol/l, then an oral glucose tolerance test should be performed.

CASE STUDY 8

1. Most likely diagnosis: diabetic ketoacidosis (DKA).
2. Next step: rehydration to improve her volume status and insulin therapy to resolve the ketoacidosis. See page 83.

CASE STUDY 9

1. Impaired hyperglycaemia.
2. Recommend weight loss and lifestyle management. By diagnostic criteria, this patient falls into the definition of impaired fasting glucose. Although she does not yet meet the criteria for diabetes, she is at greater risk for developing diabetes in the future and for macrovascular disease. Interventions such as weight loss will decrease her insulin resistance and following a diet lower in simple sugars and fats may place less stress on her pancreas and increase the time to development of outright diabetes.

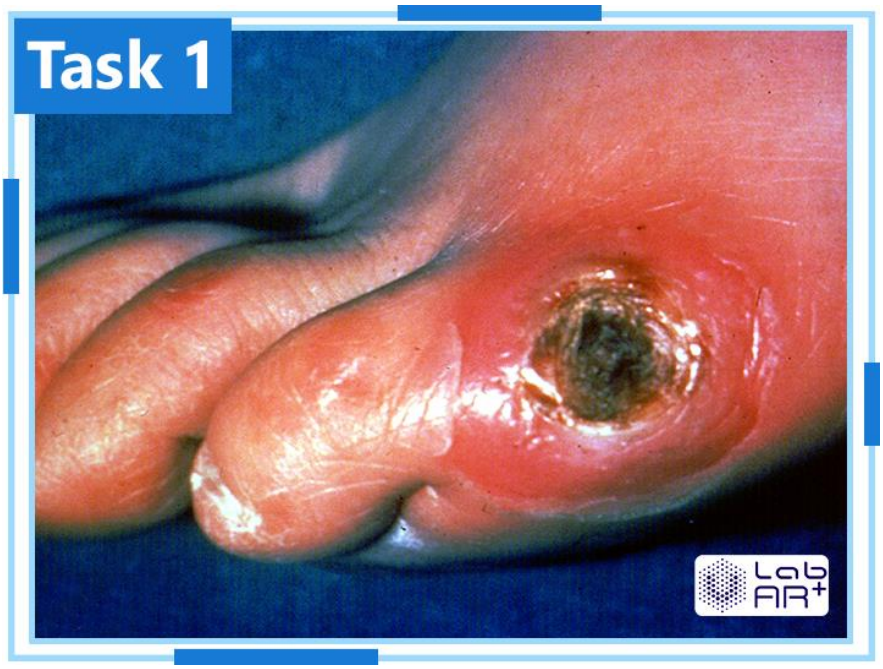
CASE STUDY 10

1. Type 2 diabetes mellitus, moderate severity, decompensation state.
2. He has a BMI of 29, overweight.
3. - Oral hypoglycaemic therapy: metformin 500 mg 3 times daily because patient is overweight, and metformin reduces body weight too besides controlling blood sugar level.
   - Anti-lipidemic therapy (statins): atorvastatin 10mg once daily after supper.

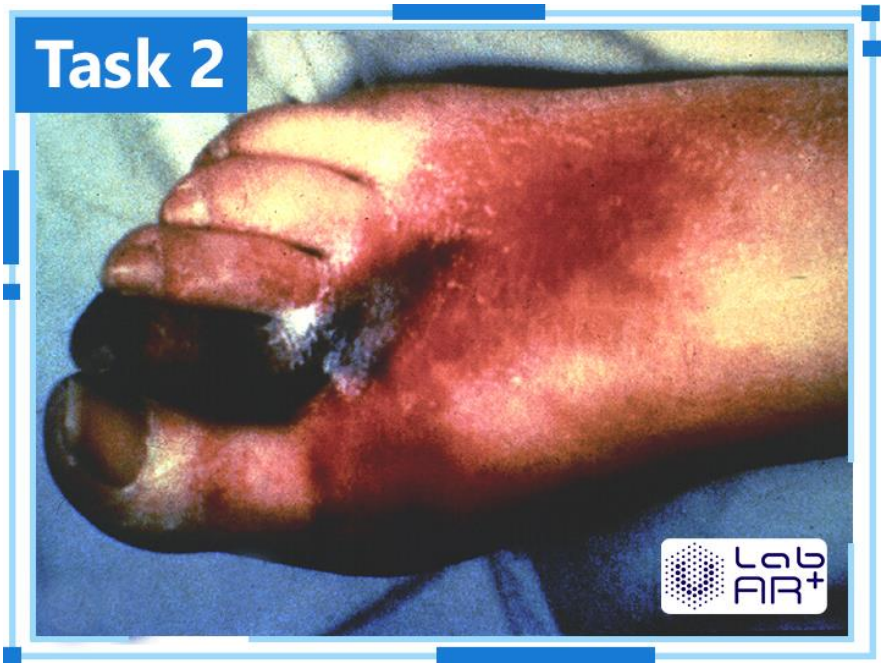
Recommendations: moderate exercise. Diet should contain more fruits and vegetables. Minimize the use of fatty foods especially animal fats.

APPENDIX G

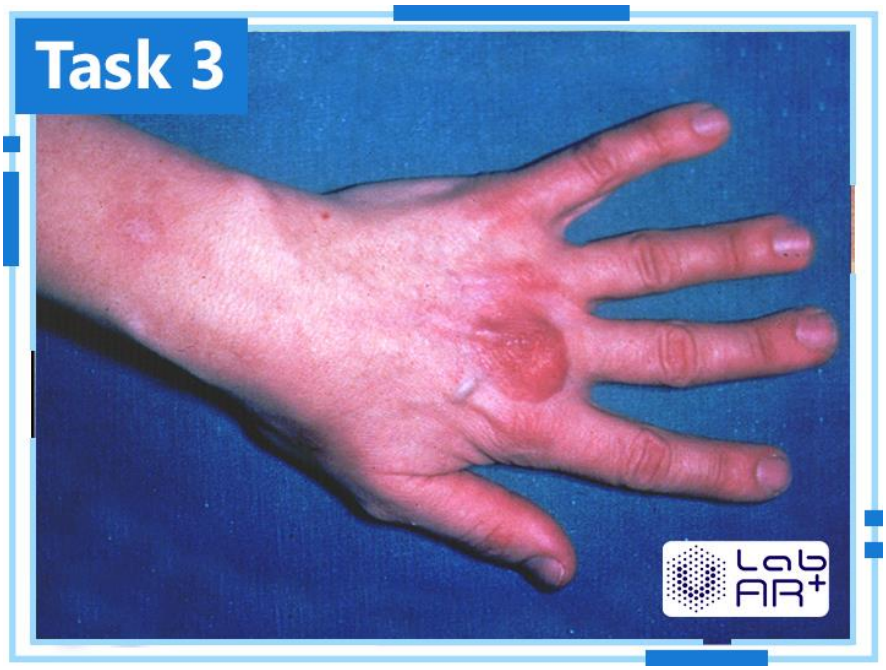
INTERACTIVE PRACTICAL EXAM WITH AUGMENTED REALITY ELEMENTS



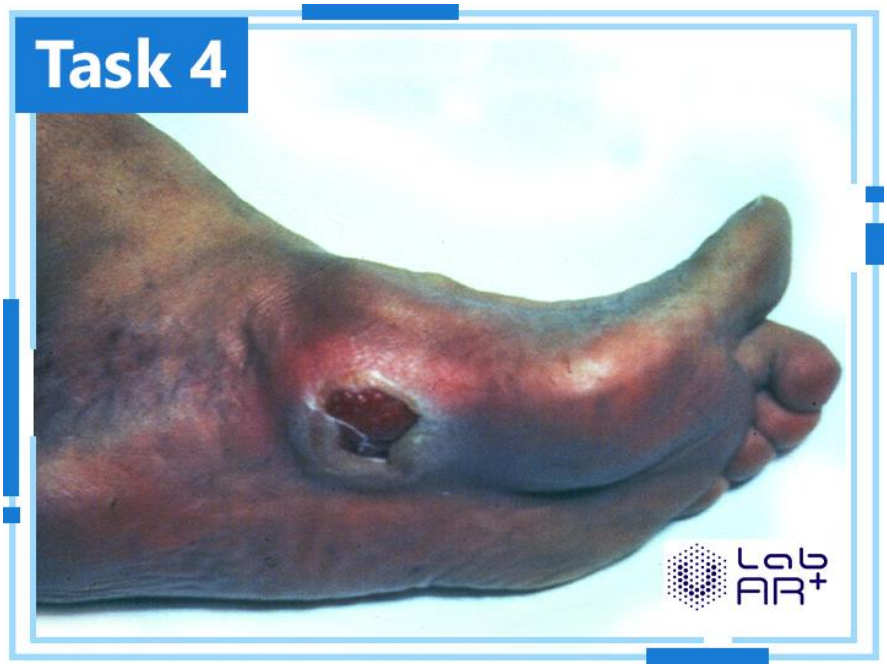
1. What does this photograph show?
2. What are the usual sites of these lesions and why do they occur?
3. What are the possible sequelae?



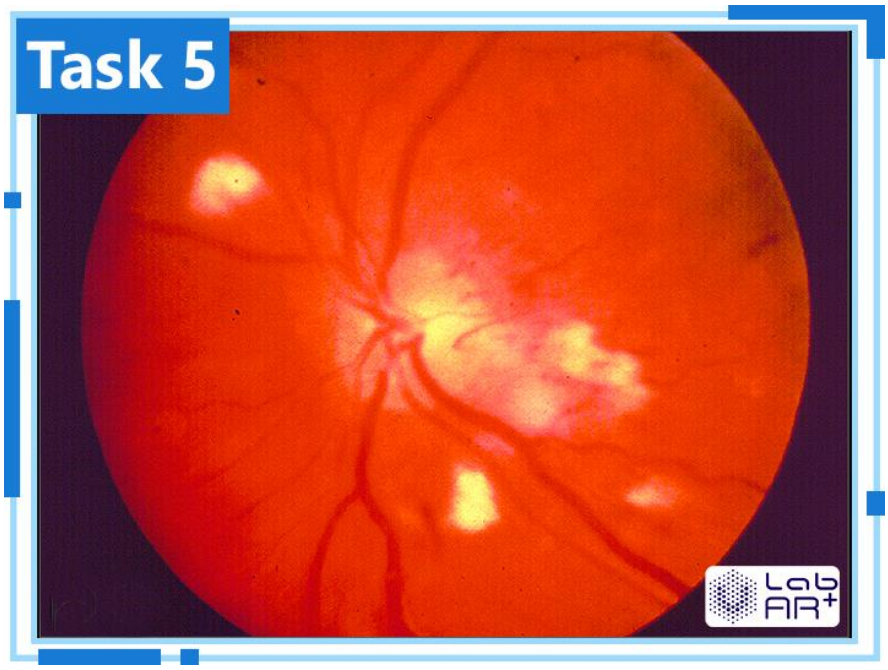
1. What are the main features of this photograph?
2. What is the likely underlying cause?
3. What are the major risk factors?



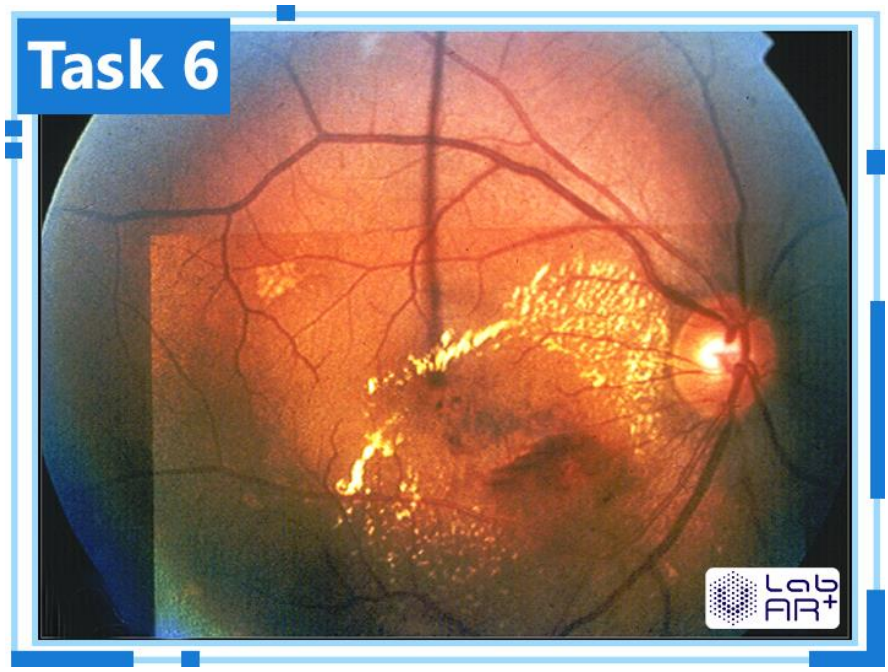
1. What does this photograph show? Where does it usually occur?
2. What is the natural history of the condition and what are its features?
3. What are the treatment options?



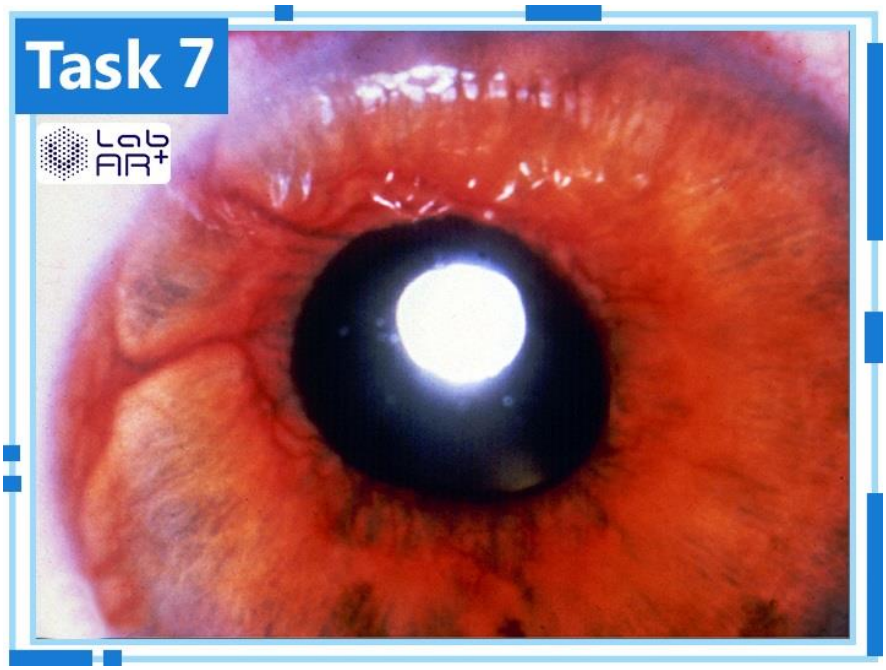
1. What does this photograph show?
2. Why is this abnormality in such an unusual site?
3. What are the possible sequelae?



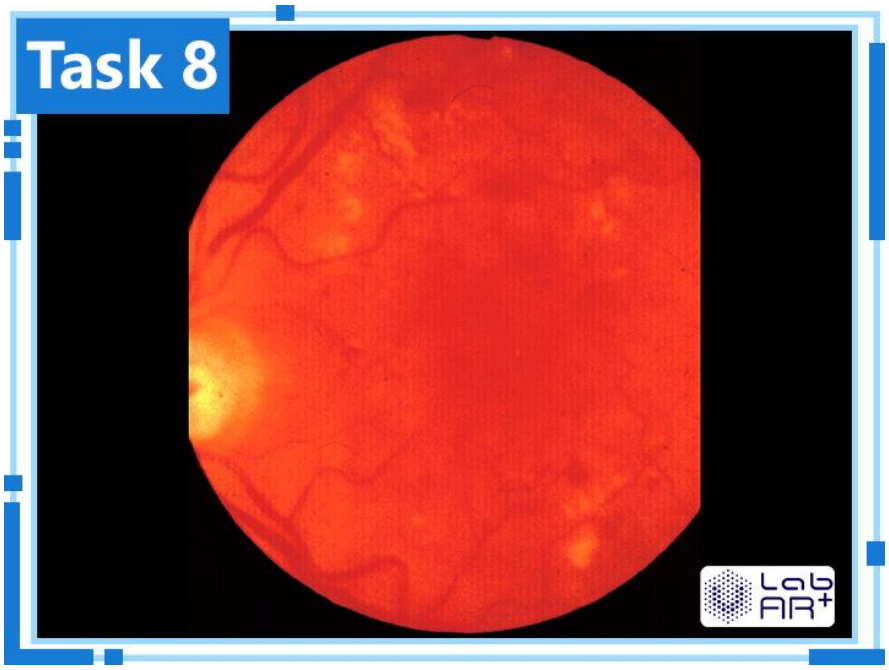
1. What abnormalities are shown in this retinal photograph?
2. What do these abnormalities signify?
3. Would you treat this condition, and, if so, what type of treatment would you use?



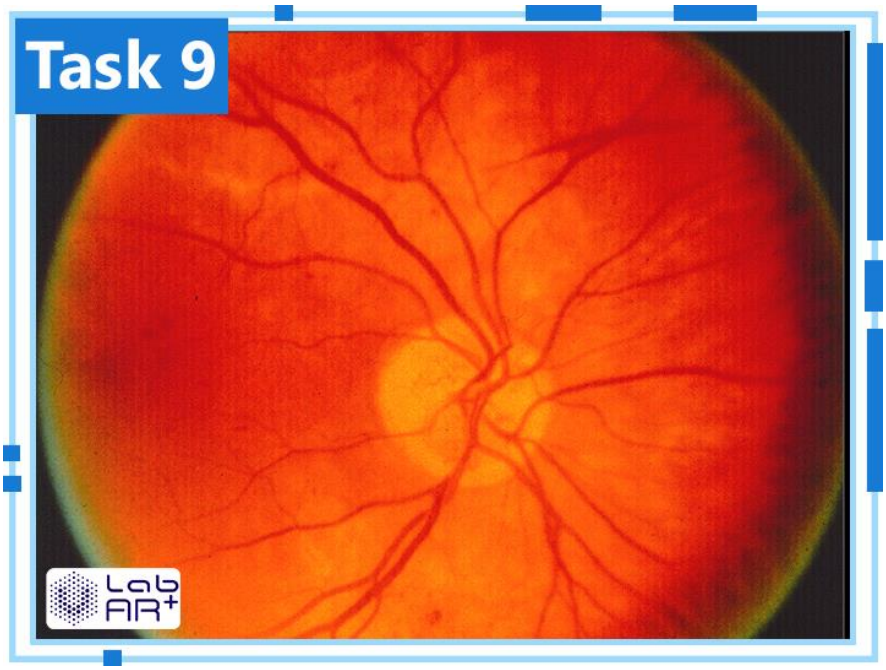
1. This figure shows a retinal photograph of a 65 year-old, male, type 2 diabetic patient complaining of a sudden loss of vision in one eye. What is the diagnosis?
2. What are the two main causes of visual loss in this condition?
3. Which factors predispose a patient to this problem and what investigations should be performed to confirm the diagnosis?



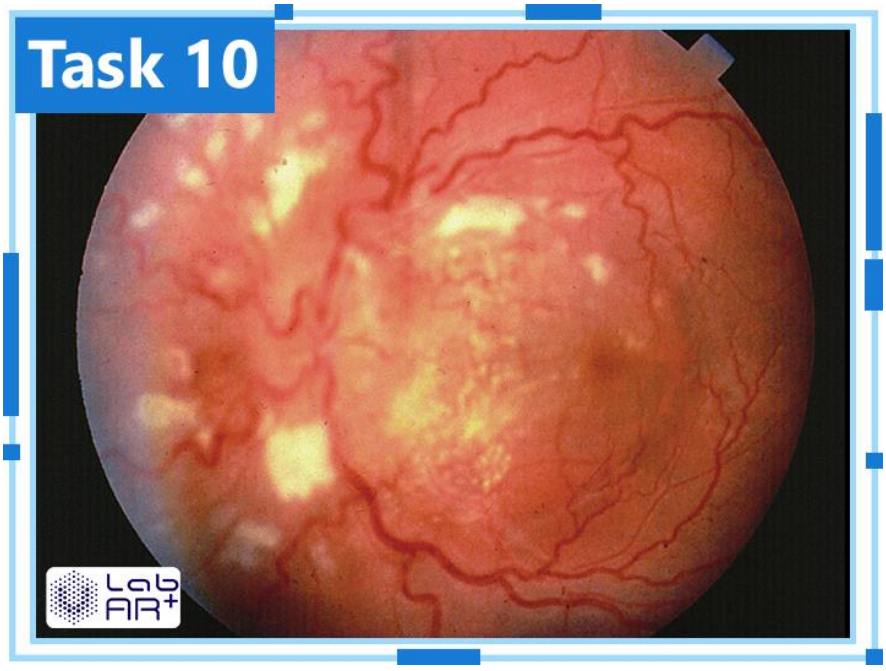
1. What is shown in this photograph?
2. What may result from this condition?
3. What is the treatment?



1. This picture is a retinal photograph of a 70 year-old, male patient with type 2 diabetes complaining of gradual visual loss. What is the diagnosis?
2. What are the features, that support the diagnosis?
3. What urgent investigation should be performed what treatment may be required

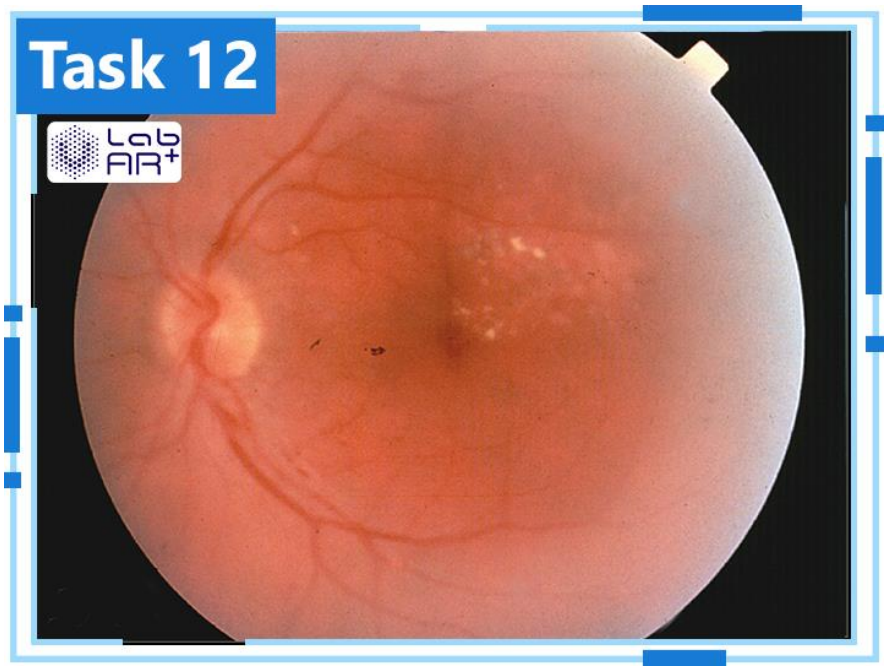


1. This is a retinal photograph of a 40-year-old female with long-standing type 1 diabetes. What abnormalities are shown?
2. Would the patient be expected to complain of visual problems?
3. Is treatment required? If so, what?



1. This figure is a retinal photograph of a 50 year-old male with long-standing type 1 diabetes. What is the diagnosis?
2. Explain the findings, that led to the diagnosis?

1. This retinal photograph from an asymptomatic 75-year-old female patient shows abnormalities detected at her diabetic annual review. Her visual activity was 6/6 bilaterally, but the findings prompted a referral to the specialist ophthalmology clinic. What abnormalities are shown and what is the diagnosis?
2. Was the referral appropriate?
3. What is the treatment?



1. A 60-year-old type 2 diabetic patient of 10 years duration has noted significant deterioration in vision on the right (6/60) but maintains a visual activity of 6/6 on the left eye. What two different diagnoses are shown?

Appendix G continuation

1. This retinal photograph was taken in a 55-year-old female insulin treated diabetic of 20 years' disease duration. She was unable to drive at night. What are these appearances and suggest a diagnostic label?
2. This patient is also deaf from the age of 20 years and has two diabetic sons. What, in association with the retinal changes, does this suggest?

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Навчальне видання

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ЦУКРОВИЙ ДІАБЕТ.

ПРАКТИЧНЕ КЕРІВНИЦТВО З ЕЛЕМЕНТАМИ ДОПОВНЕНОЇ РЕАЛЬНОСТІ

Навчальний посібник

(Англійською мовою)

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