Diabetes mellitus

Methodic materials for international students (IV-VI year)

Author: N.A.Filippova, assistant professor

Published: 2004

Definition

Diabetes mellitus is a chronic polyethiological disease characterized by fasting hyperglycaemia and hyperglycaemia during the day and accompanied by severe disturbances of carbohydrates, lipids, proteins and minerals metabolism due to absolute or relative insulin deficiency. In case of absolute insulin deficiency severe decrease of its synthesis by pancreatic islet beta-cells and its secretion are present, so insulin blood level is very low (type I). In case of relative insulin deficiency (type II) there are no changes of insulin synthesis or secretion, so its blood level is either normal or even high due to the up-regulation mechanisms, however, there is decrease of peripheral tissues sensitivity to insulin.

One more condition related to diabetus mellitus but not included into this term is impaired glucose tolerance, which is a mild version of the diabetic defect, whether progressive or not, although 2 to 5 per cent of those so classified progress to diabetic (WHO) glucose levels annually.

Prevalence: type I

In general: 3-4% of population with gradual increase of prevalence

The prevalence depends on the population; this dependence can be explained by both genetic and environmental factors. In general, the disease is predominantly one of white Caucasian populations and is relatively rare in both oriental and black populations; in Europe the gradient between northern and southern countries exists with some exceptions.

A. In Europe:

- extremely high incidences in Scandinavian countries (35/100000 per year), Denmark, United Kingdom
- much lower incidences in France and Italy except Sardinia, where it is very high and similar to those in Scandinavia (it appears to be related to genetic factors, particularly HLA alleles)
- exceptions: Iceland (incidence is low and closer to the usual Mediterranean figures, this is more possibly due to the environmental and dietary peculiarities because there is no significant genetic differences with other northern countries) and Estonia, which is ethnically extremely similar to the Finns, but the incidence is approximately one-third of that seen in Finland.

B. in Japan the incidence it is 2/100000 per year.

C. accurate data for the incidence of the disease in Africa is unavailable, but the disease is probably extremely rare in this population with a risk of less than 3/100000 per year.

The increase of incidence: is noted in Scotland, Norway, and Denmark in northern Europe, but not observed in studies from North America or from Poland, Sweden, and Finland.

Male: female ratio: in type I – equal, in type II – females dominate

Seasonal incidence: several studies have reported seasonal variation in the incidence which is greater during the winter months.

Migration: environmental factors play a substantial role in the geographical variation of disease incidence. Studies of Japanese in America, Ashkenazi Jews in Canada, and Asians in the United Kingdom have all suggested that the incidence in populations at low risk of the disease will rise if they enter a region with a relatively high incidence.

Classification

According to WHO classification, clinical classes of diabetus mellitus and significant classes of its risk are divided:

Clinical classes

1. **Diabetus mellitus**

A. *type I: insulin-dependent (diabetus of the young) – 10-15% of all patients**

B. *type II: insulin-independent (in most of patients age is over 40 - diabetus of the adults)***:

- with obesity – 85-90% of type II diabetus
- without obesity

2. **Secondary symptomatic diabetus**

A. associated with endocrine glands diseases (contrainsular hormones):

- Acromegaly
- Cushing syndrome
- Pheochromacytoma
- Conn syndrome
- Glucagonoma
- Somatostatinoma

B. Diseases of pancreas

- Chronic pancreatitis
- Cancer
- Pancreatectomy

- Tropical fibrocalculous disease (in those born in the tropics, particularly India and East Africa, and is very rare among those who later leave these areas; destruction of the pancreatic islets of Langerhans due to initially exocrine pancreatic lesion caused by multiple small calculi in the finer branches of the pancreatic duct); it has similarities with diabetes secondary to acute or chronic pancreatitis.

C. Hemochromatosis

D. Genetic syndromes

3. Impaired glucose tolerance

A. With obesity

B. With normal body weight

C. Due to the intake of drugs, other conditions and symptoms

4. Diabetus of pregnant (in pregnant only)

Significant risk classes

A. potential impaired tolerance to glucose – increased risk of diabetus development:

- obesity
- females with children born with weight more than 4 kg
- antibodies to pancreatic islets

B. preceding impaired tolerance to glucose, diabetus of pregnant in case history

* In I type of diabetus the slow progressing type (LADA – latent autoimmune diabetus of the adults) is defined; it develops in young people with normal body mass and has gradual onset, so that during the first 2-3 years insulin treatment is not necessary; it is associated with HLA B8, B15, DR3 and DR4; antibodies to islets are present.

** In II diabetus, the separate entity - MODY –- maturity-type onset diabetes of the young, is defined, it is usually associated with the obesity; the patients have a variety of abnormalities of the glucokinase gene, which is important in the metabolism of glucose in both hepatic and pancreatic beta-cells

Aethiology and pathogenesis

Type I diabetes: prevalence is 0.2-0.4%

Genetic susceptibility:

- about 1/3 of disease susceptibility is genetic; risk in siblings is substantially greater than in the normal population (6 per cent versus 0.4 per cent)

- the complex pattern of inheritance, the relatively high frequency of non-familial disease, and the increasingly rapid reduction in risk for first-, second-, and third-degree relatives all suggest that multiple loci are involved.
- main two loci encoding susceptibility have been defined, HLA (the main) and insulin (INS), although together these account for no more than 30 per cent of total genetic susceptibility.
- The most typical phenotype includes DR3, DR4, B8, B15, this phenotype is associated with antibodies to beta-cells; approximately 90 per cent of Caucasian type I diabetics carry either HLA DR3 or DR4 specificities compared with 45 per cent of the general population; DR3 and DR4 heterozygotes have an increased susceptibility compared with DR3,3 or DR4,4 homozygotes. Other HLA haplotypes (DR1, DR8, and DR5) also have a more modest susceptibility to the disease. Disease protection is provided by the HLA-DR2 haplotype.
- The INS locus on chromosome 11p is also associated with disease susceptibility.

Immune mechanisms

- I type of diabetus is a result of an autoimmune destruction of the islets of Langerhans and causes substantial destruction of the total capacity of the islet beta-cells to secrete insulin.
- The background of the disease is the lack of CD8+ lymphocytes function and presence of islets-specific T-lymphocytes sensibilized to protein 34kDa, which is glutamic acid dehydrogenaze and is present on the membranes of insulin-secreting beta-cells of the pancreas
- During the 1st year of the disease the T- , B-lymphocytes and macrophages are infiltrating the islets, so that so called insulitis develops
- Most type I patients have circulating autoantibodies to beta-cell antigens, including insulin and glutamic acid decarboxylase, as well as anti-islet-cell antibodies.
- Islet-cell antibodies are usually found in the plasma for a period of 1-2 years after diagnosis, but in a minority (perhaps 20 per cent) these may persist for the remainder of the patient's life. Members of this subgroup, sometimes called type Ib, are particularly liable to suffer other autoimmune diseases or conditions believed to involve disturbed immune mechanisms, for example coeliac disease or rheumatoid arthritis.

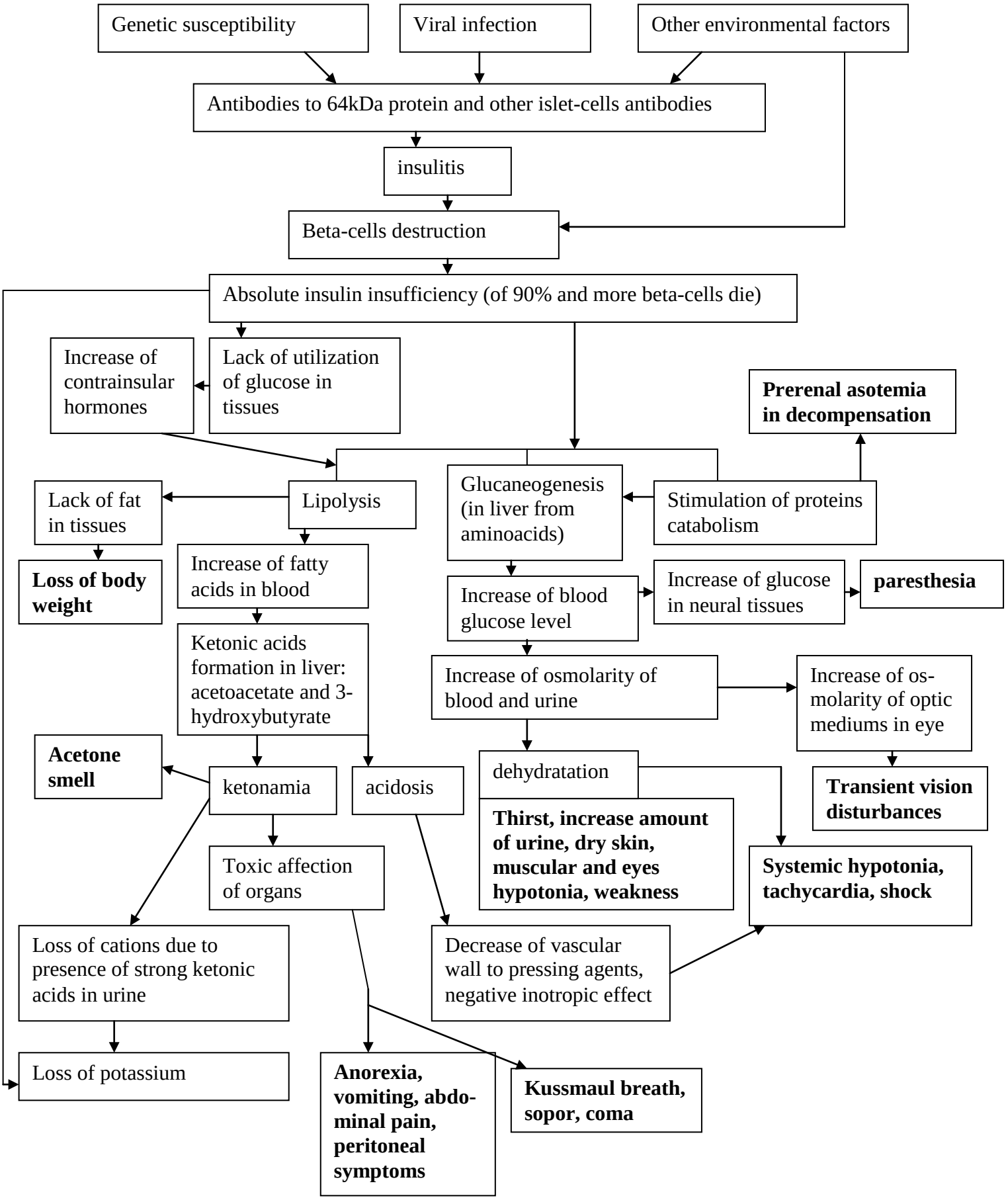
Viral infection:

- there has been much speculation about the role of a viral pathogen which is responsible, directly or indirectly, for islet damage
- seasonal variation in frequency and young age of onset are consistent with a viral pathogen
- Coxsackie, parotitis and rubella viruses and mumps virus are main candidates, but many others, including retroviruses, have been implicated; cytomegalovirus role is discussed. However, the exact nature of such infectious pathogens has not yet been defined.

- The aminoacids sequence in these viruses has similarities with that in 64kDa protein, so the sensibilized cytotoxic lymphocytes are destroying not only viruses but also beta-cells.

Environmental factors

- twin data suggest strongly that the majority of susceptibility (2/3) must be environmental.
- the main factor is viral infection: see above
- toxins: N-Nitroso derivatives are known to destroy beta-cells (nitrates and nitroso compounds in the diet etc)
- some investigators also mention the role of exposure to cow's milk in early life and associate the rising incidence of the disease may correlate with the declining prevalence of breast-feeding


Genetic susceptibility
Viral infection
Other environmental factors
Antibodies to 64kDa protein and other islet-cells antibodies
insulitis
Beta-cells destruction
Absolute insulin insufficiency (of 90% and more beta-cells die)
Increase of contrainsular hormones
Lack of utilization of glucose in tissues
Prerenal asotemia in decompensation
Lack of fat in tissues
Lipolysis
Glucaneogenesis (in liver from aminoacids)
Stimulation of proteins catabolism
Loss of body weight
Increase of fatty acids in blood
Increase of blood glucose level
Increase of glucose in neural tissues
paresthesia
Ketonic acids formation in liver: acetoacetate and 3-hydroxybutyrate
Increase of osmolarity of blood and urine
Increase of os-molarity of optic mediums in eye
Acetone smell
ketonamia
acidosis
dehydratation
Transient vision disturbances
Thirst, increase amount of urine, dry skin, muscular and eyes hypotonia, weakness
Toxic affection of organs
Systemic hypotonia, tachycardia, shock
Loss of cations due to presence of strong ketonic acids in urine
Decrease of vascular wall to pressing agents, negative inotropic effect
Loss of potassium
Anorexia, vomiting, abdo-minal pain, peritoneal symptoms
Kussmaul breath, sopor, coma

Clinical manifestations (pathogenesis is described in scheme):

- Typically presents before 30 years, but can occur at any age.
- Usually acute onset; 1 year after the onset there are usually less than 10% of beta-cells remaining
- Thirst, polyuria, enuresis
- Loss of body weight (sometimes severe – 10 kg in 2 weeks)
- Sometimes onset with ketoacidosis
- Disappearance of symptoms in case of adequate insulin replacement
- Complications: severe nephropathy; retinopathy appears after 10 years after the onset; neuropathy usually present; IHD not more common than in patients without diabetus
- May be associated with Hashomoto autoimmune thyroiditis, Addison disease, B12-deficiency anaemia

Type II diabetes mellitus: not insulin-dependent, without trend to ketoacidosis, without beta-cells antibodies, not autoimmune, without association with HLA

The prevalence:

- UK - 2 per cent of the population; recent studies suggest values of 8 to 12 per cent, depending on ethnic mix.
- Patients typically present clinically between 50 and 65 years of age, but may be as young as 15 to 20 years or of any age above 65.
- the existence of ethnic populations with an extremely high prevalence of the disease (Pima Indians or Nauruans) suggests that genetic polymorphisms may have been selected in these populations to allow them to have adapted to survive more effectively during earlier periods of prolonged starvation; subsequent exposure of such populations to Western diets might leave them at a substantial metabolic disadvantage in coping with the high-carbohydrate high-fat diets of the modern world.
- high incidence of obesity and type II diabetes in the developing world might be accounted for by the prevalence of genetic polymorphisms that are relatively rare in Western populations.

Pathogenesis:

Genetic predisposition

1. **Marked familial incidence**, in twin studies, concordance varying from below 60 per cent to above 85 per cent

2. substantial genetic heterogeneity; in general, disease is multifactorial

genetic abnormalities involve:

A. defect in insulin receptors genes

- Several specific syndromes with extreme insulin resistance exist(deletions, splicing defects, and single-base-pair substitutions of insulin receptor genes), these mutations may result in defects in receptor synthesis, receptor transport, insulin binding, transmembrane signalling, or receptor recycling.

Leprechaunism: glucose intolerance and extremely high insulin levels.

Rabson-Mendenhall syndrome: insulin resistance, acanthosis nigricans, ectodermal abnormalities (teeth and nails), and pineal hyperplasia.

Type A insulin resistance: insulin resistance, acanthosis nigricans and hyperandrogenism, is most common in females. These patients all have impaired glucose tolerance associated with hyperinsulinaemia.

- Severe forms of insulin resistance are associated with homozygocity for insulin receptor mutations, but heterozygous patients occasionally have more modest degrees of insulin resistance consistent with a diagnosis of type II diabetes.

B. genes with products of metabolic importance (glucokinase variants, glycogen synthetase variants)

- Some patients with maturity-type onset diabetes of the young (MODY) have a variety of abnormalities of the glucokinase gene, which is important in the metabolism of glucose in both hepatic and pancreatic beta-cells.

C.* genes with product*s hormonal importance (abnormal insulin, gross increase in the proinsulin to insulin ratio)

D. genes with an unknown product, (for example mitochondrial DNA deletions and duplications).

- Clinically, the diabetes associated with mitochondrial DNA abnormalities may be linked with myopathy or deafness
- combination of diabetes and deafness is associated with an A to G mutation in position 3243 of leucine tRNA. This mutation appears to interfere with the synthesis of leucine tRNA and also with its ability to bind a transcription termination factor.
- this mutation is common in large number of families, particularly in families with some evidence of sensory hearing disturbance. The role of this mutation in the more common type II diabetes has not yet been established.

3. Some variants of the disease are related to links between a lipoprotein locus abnormality and the conjunction of glucose intolerance, hypertension, and some types of hyperlipidaemia (syndrome X) which occurs more often than the chance concurrence of these three common abnormalities.

Adaptation to early environment

1. adult phenotype is strongly affected by nutritional and other intrauterine factors, as well as by the postnatal environment.
2. deficient fetal nutrition, probably more often resulting from placental deficiencies than from maternal malnutrition
3. there is a proposal that hyperglycaemia (diabetes and impaired glucose tolerance) at the age of about 60 years is more common in those with lower birthweights; marked tendency of type II diabetic patients to obesity may also stem from a maladaptation to reduced energy supply during very early growth; this may explain the paradox that obesity is more common in members of social classes IV and V who are usually less well off.

Pancreatic amyloid

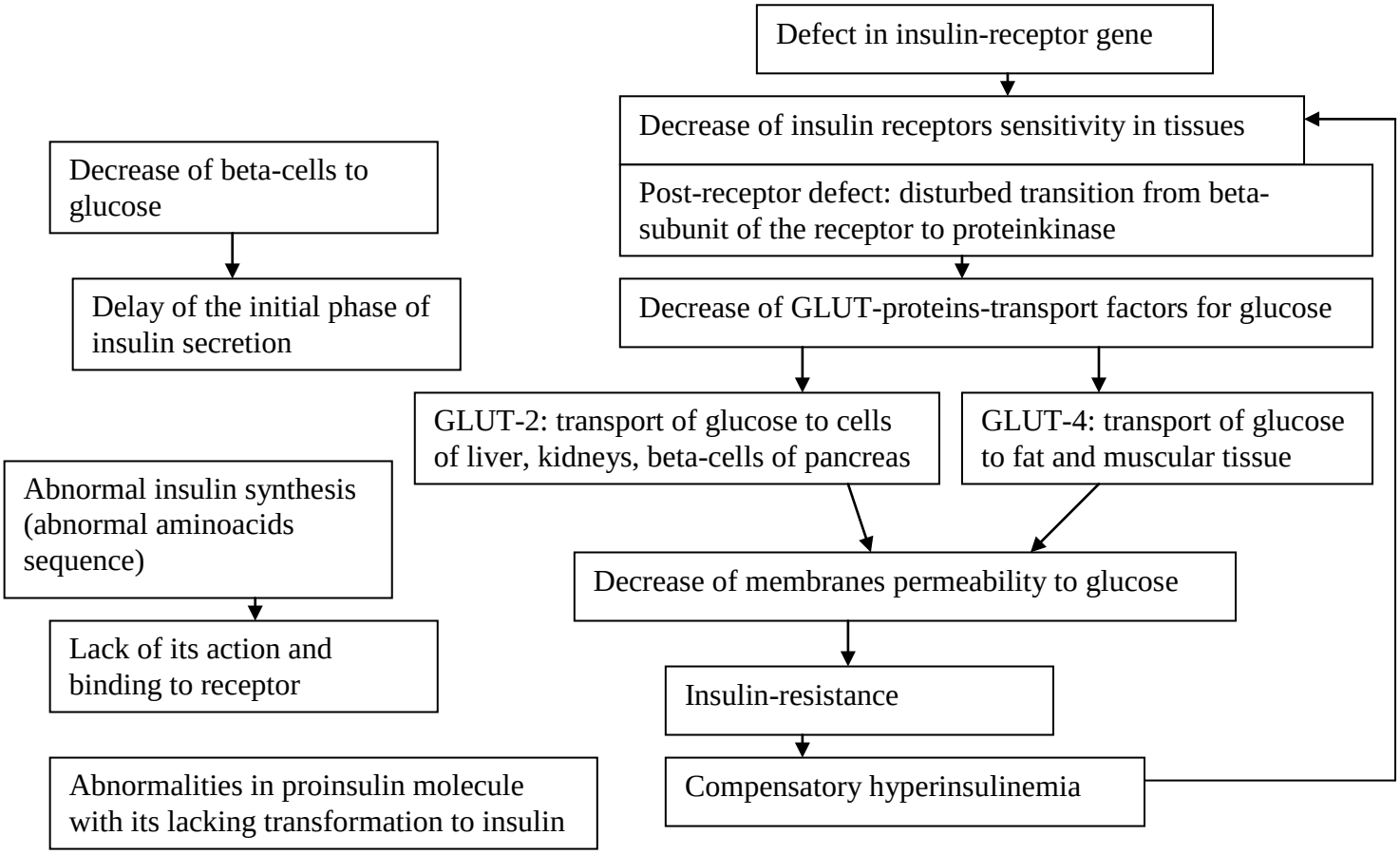
Amylin or islet amyloid polypeptide:

- lies outside the surviving b-cells of the morbid islet and may be concentrated near the islet's small blood vessels
- amylin is secreted from b-cells together with insulin
- there is stronger evidence that it has a paracrine influence within the islets, inhibiting insulin secretion.
- the amylin is either secreted to excess or differs in fine structure, it may polymerize in the intercellular spaces of the islets

-it remains to be demonstrated whether islet amyloid deposits are primary or secondary influences in b-cell failure in type II diabetes.

Beta-cell overstimulation

- when b-cells are strongly stimulated for any length of time they secrete more proinsulin (intact and split) per unit insulin secreted.
- It has been suggested that this disturbance, possibly allied to a constitutional abnormality in the cellular processing of proinsulin, damages b-cells.
- the overstimulation is ascribed to the excess food intake that must have occurred during the development of obesity in typical type II patients.



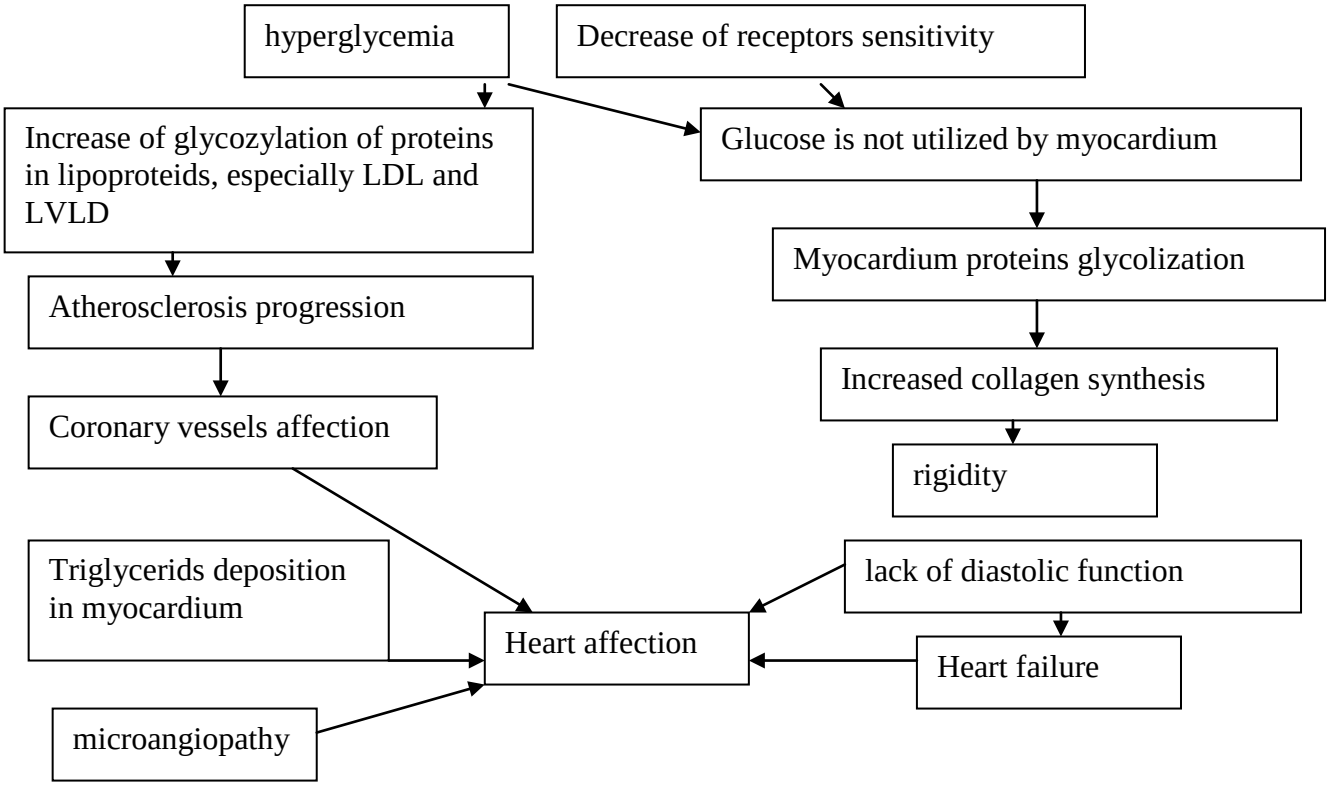
Maturity onset diabetes of the young (MODY)

- type II diabetes with younger onset (25-40 years old)
- MODY-1 – defect of adenosine-desaminase gene (chromosome 20) – more severe
- MODY-2 – gexokinase gene (chromosome 7) – mild course
- MODY-3 – defect is unknown

Clinical symptoms of type II diabetes:

- the same as for type I but less marked
- in 50% asymptomatic; sometimes purulent skin disorders (furuncules etc), vaginitis, itching may be the only clinical manifestations
- obesity is revealed in 85-90% of patients and is usually of android type (with most of fat on the upper part of trunk, face and abdomen and significantly less fat in extremities and gluteal zones; ratio)

Diabetes and cardiovascular complications



In general:

- cardiovascular mortality in diabetes II type is 2 times more in males and 4 in females if compared to patients without diabetes
- strokes are 2-3 times higher
- myocardial infarction is 2-3 times higher
- mortality in 3-12 month after the infarction is 50-75%

Secondary diabetes:

- endocrine diseases (see above)
- pancreatic diseases (severe indurative pancreatitis, cancer, pahcreatectomy)
- hemochromatosis
- tropical calcific pancreatic diabetes (former called type III diabetes) found in India, parts of Africa, and South America, which is often, but not necessarily, associated with poverty and malnutrition in youth. Aetiological factors are probably dietary
- poor islet-cell development due to malnutrition and hence failure of function in early adult life.
- direct toxicity from cyanogens is an unproven cause of beta-cell damage, although undercooked yams and overchewed betel nuts have been suspected as specific agents.

- a number of inherited syndromes, ranging from DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) via the progeria of Werner's syndrome to the obesity usual in both the Laurence-Moon-Biedl and Prader-Willi syndromes.
- It is suspected that in conditions with abnormal connective tissue (for example Werner's syndrome and ataxia telangiectasia) there may be abnormalities involving interaction between insulin and insulin-like growth factors and/or their receptors.
- Diabetes (usually IDDM) may also accompany the various mitochondrial myopathy syndromes, as may a variety of other endocrine defects.

Diagnosis

1. **Glucose level and glucose tolerance test**

Hours	Blood glucose level (capillary blood), mmol/l		
	Healthy	Impaired tolerance	Diabetes
Fasting	<5.8	5.8-6.8	>6.8 (in venous blood >7.8)
In 1 hour	<8.5	8.5-11.2	>11.2
In 2 hours	<7.7	7.8-11.2	>11.2
In 3 hours	<6.5	7.7-11.2	>11.2

Indications to oral glucose tolerance test:

- risk factors
- severe furunculosis and purulent skin diseases
- itching
- paradontosis
- catharacta in young
- test is performed if fasting glucose is up to 5.8-6.0 mmol/l (measured twice); if fasting level is >6.8 diagnosis of diabetus mellitus is stated and test is not performed
- before the test, for 3 days normal diet (carbohydrates no less than 300 daily) is kept, the drugs influencing on glucose metabolism are excluded

2. **Glucose in urine:**

In normal conditions – is not detected (except renal glucosuria – if decrease of renal threshold for glucose is present, for example in pregnant)

3. **Glycosilated haemoglobin level in blood:**

In normal conditions, 6-7% of haemoglobin are glycosilated; the method is used for estimation of control adequacy

Indicators	Control		
	Good	Adequate	Bad
Glucose level in blood: fasting (mmol/l)	<6.7	<7.8	>7.8
Glucose level in blood: after meals	<8	<8.8	>8.8
Glucose in urine (in case of normal threshold)	0	<0.5%	>0.5%
Glycosilated haemoglobin in blood	<7%	<8%	>8%
Cholesterol level in plasma (mmol/l)	<5.2	<6.5	>6.5
Triglycerides level in plasma (mmol/l)	<1.7	<2.2	>2.2
HDL cholesterol level in plasma (mmol/l)	>1.1	>0.9	<0.9
Body mass index kg/m2, males	<25	<27	>27
Body mass index, females	<24	<26	>26
Blood pressure	<140/90	<160/95	>160/95

4. **Ketone acids in urine:** also may be present in alcoholics, in long-time fasting; in case of adequate diabetes control ketone acids may occur in lack of carbohydrates intake, in case of hyperglycemia – in lack of insulin
5. **Glucagone test:** to evaluate what type of diabetes is present in patient:

- before meals 1 mg of glucagon is used i.v.; in 6 min C-peptide level is investigated in blood
- level more than 1pmol/l – II type of diabetes
- level lower than 0.32 pmol/l – I type
- level 0.32-1.1 – correct determination of diabetes type is impossible

6. **Kidneys investigation (glomerular filtration, proteinuria)**
7. **Lipid spectrum**
8. **Ophthalmologist investigation – to evaluate retinopathy presence**
9. **Neurological examination – neuropathy**
10. **ECG, Holter monitoring, exersize test, echoCG and stress-echo-CG: to evaluate the presence of latent IHD**

Treatment

Goals of treatment:

- reaching and keeping of normoglycemia
- body weight normalizing
- prevention and treatment of complications
- normalizing of lipids spectrum and BP
- in children – to enable normal growth and development

Successful treatment is impossible without good compliance, so education is extremely necessary.

Type I diabetus: 3 obligatory components insuline, diet, physical activity

Type II diabetus: depends on the concrete patient, includes also daily physical activity, which has hypoglycaemic effect

- only dietary treatment
- diet + oral drugs
- diet + oral drugs + insulin
- in case of secondary absolute insulin deficiency development (10-15 years after onset) – insulin+diet
- insulin is used also in surgical manipulations, severe acute and chronic diseases, diseases of liver with its insufficiency, chronic renal failure

Diet

1. Calorage:

- in case of normal body weight (index of body weight 20-25 kg/m2): 1600-2500 kkal daily
- in case of excessive body weight – index of body weight 26-29 kg/m2: 1300-1200
- obesity (body weight index >30 kg/m2): 1200-1000; in severe obesity up to 600 kkal daily
- in reduced body weight (index <20 kg/m2): increase up to 3000-3500 kkal daily (diabetus I type mainly)

2. Quality of food

- 55-60% carbohydrates
- 15-20% proteins
- 20-30% fats (2/3 - vegetable)
- cholesterol no more than 300 mg daily, especially in patients with hypercholesterolemia

excluded:

- sugar and sugar-containing products
- bread, porridges, potatoes and most of fruits – reduced; taken every day at the same hours and same amount to avoid the marked changes of glucose level in blood

vegetables and fruits, which don't contain glucose (blueberry, lemons, grapefruits, green apples) - in frames of given calorage without reducing

animal proteins – better bird meat and non-fatty fish; eggs – 2-3 weekly; in preclinical stage of nephropathy – 60-70 g daily

The simple carbohydrates content is regulated by the evaluation of the food products in bread units (one unit equals 12.5 g of carbohydrates and is containing in 25 g of bread)

40-50 g of fibers (pektines, cellulose etc) – oats, apples coating – prevent glucose absorbtion in intestine and lead to more slow its increase in blood as well as decrease lipids level in blood

3. Glucose replacing treatment

Saccharine – 0.05 2-3 times daily

Aspartam

Fructose

4. Contraindications for low calorage treatment (900-600 kkal daily)

- severe diabetic retinopathy, nephropathy with nephrotic syndrome; chronic renal failure
- severe diabetic neuropathy
- unstable angina
- severe anaemia
- pshychichiatric diseases
- severe chronic diseases
- gout
- severe liver diseases with function disturbances

Oral glucose lowering drugs:

1. **Acarbose** – depression of glucosidases splitting di- polysaccharides to glucose

Indications: moderate hyperglycemia after food with normal fasting levels in case of both dietary treatment and other drugs use; at the beginning of treatment – 50 mg during meals once daily, if necessary – increase up to 150-300 mg 3 times daily

Contraindications: pregnancy, intestine diseases, malabsorbtion syndrome

Side effects: meteorism, diarrhea, increase of transaminases levels and decrease of serum iron

2. Biguanids: have extrapancreatic action, however, presence of insulin is necessary

- decrease glucose absorbtion in gut
- decrease of gluconeogenesis
- increase of peripheral receptors sensitivity to insulin (activate phosphorilation of insuline receptors, so improve the insulin binding) so they are treating the insulin resistance and hyperinsulinemia
- decrease of appetite and body mass
- hypolipedemic effect (due to insulin blood level decrease, but, possibly also direct due to the depression of enzymes participating in cholesterol, triglycerids and apoproteins synthesis)
- improve blood rheology and immune system state
- antiatherogenic and antiprolipherative effect

- at postreceptor level activate thyrosinkinase, so improve lipids/proteins ratio in cell membrane, improve its permeability for glucose, activate transport of glucose ti cells due to the increase of GLUT-4 transport protein sensitivity

Indications:

- diabetus II type with obesity in case of dietary treatment inefficacy
- diabetes II without obesity in case of treatment by sulphonurea drugs inefficacy or hyperlipidemia

Contraindications:

- type I diabetes
- acute complications (coma)
- heart/respiratory failure, acute IHD manifestations
- pregnancy
- surgery, chronic renal and hepatic failure

Side effects

- danger of lactacidosis is almost absent
- metallic taste in the mouth, loss of appetite, nausea, diarrhea – rare
- B12 anaemia due to depression of its absorbion
- Allergy

In case if remains moderate post-food hyperglycemia – acarbose is to be added

In case of daily normoglycemia but fasting hyperglycemia - intermediate action insulin in dose 8-12 units is to be added in the evening (suppress hypergluconeogenesis in early morning and fasting hyperglycemia)

If ineffective, sulphonurea drugs are to be used

Drugs:

Group	Names	1 tablet dose	Daily dose	Action	Number of intakes daily
Buthylbiguanides	buformin; glibutid, adebit	0.05	0.3	Slow begin-ning, lasts for 5-8 hrs	3-4 after meals
	Buformin-retard; Silubin-retard	0.1	0.3	16-20 hrs	1 in the morning after meals
Dimethylbiguanides	Siophor	0.5, 0.85	3.5	8-12 hrs	2-3 daily after meals
	Metformin	0.25	3.0	6-8 hrs	3-4 after meals
	Diphormin-retard	0.5	2.0	14-16	1-2 after meals in the morning (and evening)
	Glucophag-retard	0.85	3.0	16-20 hrs	1 in the morning after meals

3. Sulphonurea

- increase of sensitivity of beta-cells to insuilin through specific receptors on the beta-cells surface
- improve I phase of insulin secretion
- increase insulin level in plasma
- in case if taken for a long tome – increase tissue sensitivity to insulin, so its level in blood is decreased

Group	Names	1 tablet dose	Daily dose	Action	Number of intakes daily
Carbutamide	Bucarban, oranil	0.5	2.0	Start – 30-60 min, lasts for 10-12 hrs	2 times 30-40 min before meals, interval 10-12 hrs
Tolbutamid	Butamed, orabet	0.25, 0.5	2.0	30-60 min 10-12 hrs	Same, interval 8-10 hrs
Chlorpropamid	Diabineze	0.1, 0.25	0.75	30-60 min 24 hrs	Once in the morning 30 min before meals
Glibenclamid	Manninil, daonil	0.005	0.015	30 min 24 hrs	1-2 times 30 min before meals, 10-12 hrs interval
	Micronized manninil	0.00175 0.0035		10 min 10 hrs	1-2 times, 5-10 min before meals, interval 10 hrs
Glypizid	Minidiab	0.0025	0.03	30 min 16-18 hrs	1-2 times 30 min before meals, interval 12h
Glyclazid	Diabeton	0.08	0.32	30 min 20 hrs	2-3 times 30 min before meals
Glycvidon	Glurenorm	0.03	0.12	30 min 10 hrs	1-3 times 30 min before meals

Indications:

- diabetes II type with normal body mass in case of inefficacy of dietary treatment
- diabetes II type with obesity in case if biguanids are ineffective or contraindications are present (respiratory or heart failure)
- combination with acarbosa is possible if modurate hyperglycemia after meals is present or with insulin if fasting hyperglycemia and normal level after meals are present (intermediate insulin in the evening -21.00-22.00 is used)

Contraindications

- the same as biguanids except respiratory and heart failure

Side effects

- hypoglycaemia from subclinical (headache, sleaplessness, anxiousy) up to coma; the patients should know about that and be learned to take drugs 20 min before carbohydrate meals as well as to be learned to know what to do in case of hypoglycaemia; however, modern drugs II generation rarely induce hypoglycaemia
- allergic reactions
- metallic taste in the mouth, nausea

- rare – hypothyrosis
- rare – agranulocytosis

In case of inefficacy biguanids treatment is started

In case of inefficacy of biguanids insulin treatment is started; indications for insulin use are the signs of absolute insulin deficiency:

- absence of effect of oral drugs
- decrease of body mass
- thirst, polyuria appearance
- C-peptide in test with glucagone <0.6 nmol/l

4. Insulin

Anabolic polypeptide hormone, consisting from 2 aminoacids chain (short – 21 acids – and long – 30 acids), connected by two bisulfid branches. Its precursor is proinsulin stored in Golji complex in granules (86 aminoacids – one chain).

In case of glucose level in beta-cells is increased, proinsulin is hydrolyzed and insulin and C-peptic – part of proinsulin molecule, earlier connected with insulin (35 aminoacids) are excreted in equal levels. C-peptid is not active, its half-life period is 3-4 times slower, so its level in blood is higher. C-peptid is a marker of insulin-synthesizing function of beta-cells.

Functions of insulin

Stimulation	Reduction
Permeability of cell membranes for glucose, aminoacids, potassium	Glycogenolysis
Utilization of glucose in cells	
Protein synthesis	Lypolysis
Lypogenesis	
Cholesterol and lipoproteins synthesis	Ketogenesis
Lipoproteinlypase activity, LDL syndthesis from VLDL	
Sensitivity and number of the receptors for LDL in arterial walls	Proteolysis
Growth factor	
Proliferation of smooth muscular cells in arterial wall	Glyconeogenesis
Water and sodium reabsorbtion in renal tubules	

Indications

- I type of diabetes
- Acute complications of diabetes
- Inefficacy of oral drugs
- II type of diabetes with severe chronic complications – high degree retinopathy, diabetic glomerulosclerosis with nephrotic syndrome or chronic renal failure, severe polyneuropathy
- II type of diabetes in pregnancy, large operations, severe chronic diseases and severe infections

Classification of insulins

A. depending of how pure is the drug (standard and highly pure)

B. Human (obtained by method of recombinant gene engineering) and animal

C. Duration of action: extremely short (lyspro-hymalog); short, intermediate, long, combined

Methods of the use of insulin

- by 1, 0.5, 0.3 ml special individual syringes with thin needles, after the injection syringe and needle are cleaned by spirit and kept in refrigerator
- injections are subcutaneous to abdominal wall, thigh, shoulder, upper external quadrant of gluteal muscle

Short-acting =regular	20-25 min	2.5-4 hrs	6-8 hrs	Actrapid	All the insulins are water-soluble; only them can be used i.v.	Acute complications, operations, severe diseases (conditions when the necessary dose may seriously vary)
				Velosulin, humulin BR	Used by pumps-method infusions (phosphate buffer-containing solution preventing aggregation of insulin in tube)	
Intermediate	40min-2 hrs	6-12 hrs	18- 24	Protaphan	Are not used i.v.	The most often use
Prolonged	4-6 hrs	12-22 hrs	30-36 hrs	Ultralente Ultratard Ultralente humulin	Are not used i.v.	Used more rare because of possibility of prolonged hypoglycemia
Combined	Combination of short time and intermediate action insulins					

Delivery-systems: infusion systems, indicated in ketoacidosis, before and during the operations.

Not used in chronic treatment

Treatment of type I diabetus

- begins with once or twice daily intermediate insulin injection
- in short duration of the disease the dose is counted as following: 0.5-0.6 units per kilogram of body mass
- in long duration of the disease – maximal dose is 0.8-1.0 units per kilogram
- as a rule, physiological dose 40-50 units daily is used
- 2/3 of the dose is used in the morning (7-9.00 a.m.), 1/3 – in the evening (20.00-22.00)
- the increase of dose is gradual, from 8-12 units in the morning and 4 in the evening, then the dose is increased up to 20-26 in the morning and 12-14 in the evening, sometimes up to 32 and 14 respectively

- simple carbohydrates (bread, porridges, potatoes) are given 30-40 min after the injections, then every 3 hours
- if up to 12-13.00 hyperglycemia persists, and later the level of glucose is normal, short acting insulin is added in the morning (injected separately)
- in case of persisting fasting hyperglycemia – night hypoglycaemia should be excluded (blood glucose measurement at night) – Somoji phenomen – morning hyperglycemia induced by nocturnal hypoglycaemia
- nocturnal hyperglycemia – gradual increase of evening insulin dose
- hyperglycemia in the morning – lente insulin 4-6 units in the evening; 30-40 min after the injection simple carbohydrates are to be taken
- in case if daily dose is 40-50 units and there are severe fluctuation of blood glucose, basic-bolus regimen is used: as a basis 2/3 of dose is used twice daily as intermediate insulin, 20-25 min before every meals 4-8 units of short-acting insulin is used.
- Treatment control – fasting, before and 2hrs after meals blood glucose levels; urine 23-8.00; 8-17.00; 17-23.00

Complications

A. hypoglycaemia (<3-2.8 mmol/l)

Causes

- overdosage
- missed food intake
- excessive physical exertion (in normal condition decrease of tissues sensitivity to insulin is due to increase of secretion of contrainsular hormones and gluconeogenesis in liver; in insulin treatment glucogenesis is depressed by insulin)

Clinical manifestations

- initial (sympathoadrenal) stage of encephaloglucopenia: excess of catecholamines – tachycardia, tremor, perspiration, headache, anxiety; may be absent in patients with autonomic system neuropathy; also is masked by beta-blockers
- CNS disfunction due to lack of glucose in brain – inadequacy of habit, increase of muscular tonus, diplopy, epilepsy-like cramps, coma, oedema of brain

Treatment

- sweet tea (5-6 pieces of sugar)
- simple carbohydrates containing products
- when not in home, to have 6-8 pieces of sugar, bread, bisquits

- in case of consciousness loss – 1 ml of glucagone i.m., in absence of effect – 40% glucose 20-80 ml i.v. injection; then level of glucose is to be measured (in may be normal, however the brain function is not yet restored
- the special “card of diabetes patient” is to be present confirming that the patient suffers from diabetes and receives insulin (in case of consciousness is lost)

Treatment of early morning hypoglycaemia

- Somoji phenomenon –the cause is the use of large doses of intermediate insulin at night, so nocturnal hypoglycaemia at 3-4.00 is present, causing hypergluconeogenesis and morning hyperglycemia; the treatment is reduction of the evening dose
- Down-phenomenon – decrease of tissue sensitivity to insulin between 5-6.00 a.m. due to the physiological increase of contrainsular hormones production – moderate hypoglycaemia (more marked if combined with Somoji phenomenon)

B. Allergic reactions – rare especially in human insulin (humulin, humulente etc) – both local and anaphylactoid
C. Insulin resistance – mostly in II type of diabetes (decrease of receptors sensitivity); the second mechanism is antibodies formation (level is to be investigated in resistant patients)
D. lypoatrophy – loss of fat in places of injection due to combined action of spirit and insulin

5. Surgery in diabetes

Planned operation with narcosis

- stable normoglycemia is to be reached (5.0-10.0 mmol/l during the day) before the operation
- II type of diabetes: cessation of oral drugs, at the day of operation short acting insulin (actrapid) is to be used subcutaneously with i.v. infustion of 5% or 10% glucose or dextrose 100-150 ml per hour; blood glucose is to be measured every 4-6 hrs; in case of 7-11.0 mmol/l 4-8 units are used; in case of 11.00-14.00 mmol/l – 8-12 units; after the operation when the patient is allowed to eat short time insulin is used 4 times daily before meals according to the given scheme; then – returning to drugs treatment
- I type: before the operation the evening dose of intermediate insulin is 2 time reduced (the patient doesn’t eat in the evening); in the morning of operation day – 50% dose of intermediate insulin; i.v. infusion of glucose or dextrose, control of glucose every 3-4 hrs, the scheme of increased glucose correction the same as in II type; after the operation when the patient is allowed to eat – 6-8 units before every meal, then returning to the intial treatment

Emergency operations

- correction by insulin before and during operation according to the given scheme; 5-10% glucose infusion 100-150 ml per hour during operation; the doses are the same as given

Acute surgical diseases in ketoacidosis patients

- the operation can be performed if ketoacidosis is treated (4-8 hours are necessary for the compensation)
- during the operation – short acting insulin according to the given scheme; 5-10% glucose infusion

6. Treatment of hyperlipidemia

Acute complications

Diabetic ketoacidosis

Definition - severe complication of diabetes mellitus – clinical and biochemical syndrome characterized by high hyperglycemia (14-16 mmol/l), hyperketonemia, systemic acidosis, electrolyte metabolism disturbances and dehydratation due to absolute insulin deficiency and excess of contrainsular hormones

Prevalence

10-11% of patients admitted due to diabetes

Mortality – 3-4%

In most of cases develops in type I, rarely in type II.

Aethiology

- acute onset of type I DM
- insulin treatment cessation
- severe stresses, surgery, infections, acute disease, provoking ketoacidosis both in I and II types of DM

Pathogenesis: see scheme

Additions:

- Kussmaul respiration appears in case of pH is 7.2 and lower

- Decrease of potassium, sodium, phosphate is present, however due to potassium efflux from the cells its level may be increased up to 6-7 mol/l

Clinical manifestations

3 stages: initial ketoacidosis, sopor, coma

Acidosis may be moderate (pH 7.3-7.2); severe (7.2-7.05) and very severe (7.05-6.8)

- Onset is gradual, several hours - 1-2 days
- Initial ketoacidosis: symptoms of aggravations of diabetes course – thirst, polyuria, muscular weakness, anorexia, nausea, vomining (up to numerous episodes), 40% -

abdominal pain, even similar to that in surgical diseases (paralytic ileus); skin is dry with low turgor, dry mucosae, soft eyeballs, smell of acetone, CNS depression with weak contact with patient

- Kussmaul respiration is present, in pH 7 and less it may disappear (narcosis of respiratory center); progression of symptoms leads to spoor; the risk of aspiration pneumonia is present
- Progression leads to circulatory collapse and prerenal renal failure; acetone smell may disappear due to superficial breath, coma develops. If not treatment, patient dies in 1-2 days

Laboratory diagnosis

- glucose level is over 16 mmol/l; may be lower if there is loss of glucose with urine
- ketonic acids in blood (detected by "keto-stripes"), 10-20 times higher than normal
- pH<7.3 of arterial blood
- urine: glucose, acetone
- blood osmolarity >300 mosm/l, formula for counting is 2(Na)+ (glucose (mg%)/18) or 2 (Na+K)+ glucose+urea or (Na+K)+ (glucose mg%/18 +(urea/6)

normal values are 280-300 mosm/l

- sodium decrease to 130-125 mmol/l
- bicarbonate 5-15 meq/l
- pCO2 15-20 mm Hg (hyperventilation)
- 90% of patients – increase of amylase
- increased WBC (maybe severe)
- creatinin 0.3-0.4 mmol/l due to protein catabolism and prerenal renal failure

Treatment

Aims of treatment:

1. rehydratiation
2. BP stabilizing, improving renal blood flow, increase of H+ ions excretion
3. to stop hyperglyconeogenesis, ketogenesis, normlize glucose, electrolytes levels and pH

Treatment is to be done in intensive care unit with good air oxygenation

Blood glucose, acetone, electrolytes, pH, osmolarity, gases are to be monitored; gastric probe is used to prevent aspiration of vomiting masses; urine cathether if necessary; ECG monitoring

Before the admission

- 50-80 ml 40% glucose with 0.9% sodium chloride i.v. +0.4 mg (1 ampule) of naloxone + 100 mg thiamine, after which infusion of 0.9% sodium chloride begins

Reason: because it is impossible to exclude hypoglycaemia and narcotic coma without laboratory tests.

After the diagnosis statement

1. **Insulin: short acting, human: actrapid HM, homorap, humulin R**

- initially – 10-20 units iv bolus
- than 5-6 units per hour infusion (1 ml (40 units) of insulin is dissolved in 400 ml of 0.9% sodium chloride; in this case 5-6 units will be in 50-60 ml of the solution); before the infusion the system is to be treated by short-acting insulin to prevent the absorbtion of insulin by the plastic and glass
- blood glucose controle every 1.5-2hrs
- infusion is continued with the same velocity up to glucose level is 14-16 mmol/l, then it is reduced to 2 units per hour; at the same time infusion of 10% glucose in sodium chloride 200-300 ml per hour to prevent hypoglycaemia up to the period when the patient is able to eat
- when the patient is able to eat, 6-8 units before every meals is used
- in case if the level of glucose is not reduced in 1.5-2 hrs, dose of insulin is doubled and used 20-40 units in bolus and then 10 units pre hour infusion; then in case of marked decrease of glucose level insulin is reduced to 5 units per hour, then – see above

2. Rehydratation

In adult, fluid deficiency in ketoacidosis reaches 4-5 liter

1 hour of treatment – 0.9% sodium chloride – 1-1.5-2 l i.v.

2 hour – 1-1.5 liters

3 hour – 1-0.5 liters

4 hour – 0.5 liters

beginning from 5 hour - 250-300 ml per hour

beginning from blood glucose level 14-6 mmol/l 10% glucose infusion is started

3. Potassium

Can be lost due to vomiting and polyuria; but due to efflux from cells may be increase up to 6 mmol/l

Acidosis correction leads to influx of potassium to cells, so in case if it will not be infused, hypokaliemia will develop. Potassium level should be kept at 4.0-5.0 mmol/l

In case of potassium is 4.5-5.0 – 1g of potassium chloride- 10 ml of 10% is used; 3-4 mmol/l - 2 grams, <3.0 – 3 g (30 ml 10%); 6 mmol/l and hogher – potassium is not infused

10 days after acidosis correction – 10% solution per os 3 times daily – 1 soup spoon with juice or soup; potassium-rich products – bananas, tomato juice

4. Sodium bicarbonate

Indications

– pH 7.0 and less
– pH 7.1-7.0 if arrhythmia, hypotony and deep coma is present

In other cases it is not necessaryl used in 2.74% solution 400 ml rapidly during the first hour, pH shouldn't exceed 7.1-7.15 (risk of alkalosis leading to potassium influx and fatal arrhythmia)

Side effects - tissue hypoxia due to dissociation of haemoglobin disturbances, hypopotassiemia, CNS acidosis

5. Infection – antibiotics – penicillin 1.5-2 mln units daily

Hyperosmotic coma

High hyperglycemia, hyperosmolarity, marked dehydratation without acidosis and hyperketonemia.

In aged patients with II type of DM, prevalence 0.03% of all diabetes patients

Pathogenesis is similar to ketoacidosis, but there is no lack of insulin, so ketogenesis is not activated and there is no acidosis

Predisposing factors – infections, acute diseases, surgery, stroke, saluretics disturbances.

In these conditions markedly increase the level of contrainsular hormones, which leads to decrease of tissue sensitivuity to insulin and stimulates proteolysis and gluconeogenesis. Insulin level is slightly decreased, so there is no adequate utilization of glucose by tissues

Clinical manifestations

- gradual onset – hours - 1-2 days
- severe weakness, thirst, polyuria
- anorexia and gastrointestinal symptoms are less marked
- local CNS symptoms may be present due to excessive influx of glucose to brain cells an sorbitol formation, which leads to brain cells affection.
- Severe dehydratation and hyperosmolarity lead to hypotonia, myocardial contractility decrease, olyguria and cma

Laboratory tests

- high glucose level without acetonemia
- osmolarity >330 mosm/l
- blood – leucocytosis, shift to the left
- pH normal, but sometimes may be decreased due to lactate formation

Treatment

1. Insulin – same

2. Fluid –

If circulatory collapse is present – isotonic sodium chloride, in other cases – 0.045% NaCl

8-10 hours – i.v. 4-6 liters, volume is reduced in case of central venous pressure increased

5-10% glucose is started i.v. after blood level reaches 14 mmol/l

3. Potassium – same
4. Antibiotics 0 same
5. Heparine 5-10000 units 2 times daily to prevent disseminated intravascular coagulation

Lactacidose

In case of lack of oxygen with lactate increase – heart and respiratory failure, infarction, sepsis, biguanides overdoses; poor prognosis

Signs – dehydratation is not so marked, Kussmaul respiration is present, low pH; blood glucose is mildly elevated or normal or high, lactate more than 6 mmol/l

Treatment –

1. fluid
2. bicacbonate – pH should be kept 7.2 and higher; or dichloroacetate (activation of piruvat dehydrogenase, decrease of lactate formation)