МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

DISEASES OF ENDOCRINE SYSTEM «DIABETES MELLITUS – TYPE 1 AND TYPE 2, MODERNN METHODS OF THERAPY. THE COMATOSE CONDITIONS IN PATIENTS WITH DIABETES MELLITUS»

Methodological recommendations
for students of IV course

«ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ. ЦУКРОВИЙ ДІАБЕТ 1 ТА 2 ТИПУ, СУЧАСНІ МЕТОДИ ЛІКУВАННЯ. КОМАТОЗНІ СТАНИ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ»

Методичні вказівки
для студентів IV курсу

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MODULE №1 “THE FUNDAMENTALS OF DIAGNOSIS, TREATMENT AND PREVENTION OF MAIN DISEASES OF THE ENDOCRINE SYSTEM”

TOPIC -"DIABETES MELLITUS - TYPE 1 AND TYPE 2, MODERN METHODS OF THERAPY. THE COMATOSE CONDITIONS IN PATIENTS WITH DIABETES MELLITUS.

Topicality

Nowadays medicine possesses a substantial arsenal of preparations, which enable doctors not only to save the lives of patients with diabetes mellitus, but also to return their work capacity. There are numerous oral glucose-lowering agents, different insulin preparations; new treatment directions are being constantly developed. Patients with diabetes mellitus often visit doctors of other specialties (ophthalmologists, surgeons, general practitioners, gynecologists, etc.), so students of medical universities should know the means and methods of treatment of diabetes mellitus as well as to be able to apply them on practice.

The educational purposes:

- To teach students the main principles of treatment of a diabetes type 1 and 2;
- To acquaint students with the criteria of compensation of a carbohydrate metabolism in patients with diabetes type1 and 2;
- To teach students the modern principles of diet therapy in diabetes;
- To acquaint students with the dosed physical activity and rules of its appointment;
- To acquaint students with glucose-reducting pharmacotherapy, training the patient for self-control;
- To teach students the principles of insulin therapy: classification of insulin preparations, the indications and contraindications for their use, regimens, complications;
- To acquaint students with health resort treatment of patients with diabetes.

What should a student know?

- Basic principles of treatment of diabetes, metabolic compensation criteria, achievement of normoglycemia;
- Current principles of diet therapy of diabetes mellitus: physiology, energy value, limitation of refined carbohydrates, the use of dietary fiber, minerals etc.
- Dosed physical load and the rules for its use;

- Oral hypoglycemic agents: sulfonylurea derivatives, non-sulfonylurea secretagogues, biguanides, thiazolidinediones, acarbose; description, mechanism of action, side effects, indications and contraindications;
- Insulin: characterization of essential drugs, indications, contraindications, classification, dosage adjustment, profiles, complications;
- Health resort treatment of patients with diabetes.

What should the student be able to do?

- To substantiate the diagnosis of patients with diabetes mellitus, determine the type, severity of illness, degree of compensation;
- To evaluate and glycemic and glucosuric profiles, daily glucosuria, the state of protein and lipid metabolism, electrolite balance according to laboratory tests;
- To determine the results of biochemical studies, degree of compensation of diabetes mellitus;
- To identify the diet energy value and to distribute carbohydrates during the day depending on the level of glycemia and the effect of hypoglycemic drugs;
- To define the indications for the use of various hypoglycemic drugs;
- To correct the dosage of hypoglycemic drugs;
- To evaluate the efficiency of treatment;
- To prevent and to treat complications associated with the use of hypoglycemic drugs;
- To define the indications and contraindications for health resort treatment;
- To write prescriptions for insulin preparations and oral glucose-lowering agents.

The list of practical skills which the student should possess:

- Substantiation of diagnosis of diabetes mellitus, its type, severity, degree of compensation,.
- To evaluate glycemic and glucosuric profile, around the clock glucosuria, state of protein and lipid metabolism, electrolite balance;
- To establish a degree of compensation of diabetes mellitus according to the results of biochemical assays and HbAlc;
- To appoint the daily menu for the diabetes patient (to establish daily energy value of a diet, distribution of carbohydrates throughout a day depending on glycemia level and efficiency of glucose-lowering agents);
- To prescribe the dosed physical load, determine its intensity and duration;
- To substantiate the indications for hypoglycemic preparations, their dosage, efficiency of treatment in accordance with its terms, to perform a possible correction;

- To describe the follow-up schedule for patient with diabetes mellitus, set the terms of dynamic supervision of patient by endocrinologist, physician and other specialists;
- To establish the indications for health resort treatment;
- To write the prescriptions for glucose-lowering medications.

The topic content

Diabetes of type 1 and 2, modern methods of therapy.
Treatment of DM type 1 and 2 includes the following:

- Diet and exercise
- For type 1 DM, insulin
- For type 2 DM, oral antihyperglycemics, insulin, or both

General Dietary Guidelines:

For people who have diabetes, the treatment goals for a diabetes diet are:

- Achieve near normal blood glucose levels. People with type 1 diabetes and people with type 2 diabetes who are taking insulin or oral medication must coordinate calorie intake with medication or insulin administration, exercise, and other variables to control blood glucose levels.
- Protect the heart and aim for healthy lipid (cholesterol and triglyceride) levels and control of blood pressure.
- Achieve reasonable weight. Overweight patients with type 2 diabetes who are not taking medication should aim for a diet that controls both weight and glucose. A reasonable weight is usually defined as what is achievable and sustainable, and helps achieve normal blood glucose levels Children, pregnant women, and people recovering from illness should be sure to maintain adequate calories for health.

Overall Guidelines. There is no such thing as a single diabetes diet. Patients should meet with a professional dietitian to plan an individualized diet within the general guidelines that takes into consideration their own health needs.
For example, a patient with type 2 diabetes who is overweight and insulin-resistant may need to have a different carbohydrate-protein balance than a thin patient with type 1 diabetes in danger of kidney disease. Because regulating diabetes is an individual situation, everyone with this condition should get help from a dietary professional in selecting the diet best for them.
Several good dietary methods are available to meet the goals described above. General dietary guidelines for diabetes recommend:

- Carbohydrates should provide 45 - 65% of total daily calories. The type and amount of carbohydrate are both important. Best choices are

vegetables, fruits, beans, and whole grains. These foods are also high in fiber. Patients with diabetes should monitor their carbohydrate intake either through carbohydrate counting or meal planning exchange lists. “Counting” the amount of carbohydrate in the meal is used to calculate the preprandial insulin dose. In general, patients require 1 unit of rapid-acting insulin for each 15 g of carbohydrate in a meal.

- Fats should provide 25 - 35% of daily calories. Monounsaturated (such as olive, peanut, canola oils; and avocados and nuts) and omega-3 polyunsaturated (such as fish, flaxseed oil, and walnuts) fats are the best types. Limit saturated fat (red meat, butter) to less than 7% of daily calories. Choose nonfat or low-fat dairy instead of whole milk products. Limit trans-fats (such as hydrogenated fat found in snack foods, fried foods, and commercially baked goods) to less than 1% of total calories.
- Protein should provide 12 - 20% of daily calories, although this may vary depending on a patient's individual health requirements. Patients with kidney disease should limit protein intake to less than 10% of calories. Fish, soy, and poultry are better protein choices than red meat.
- Lose weight if body mass index (BMI) is 25 - 29 (overweight) or higher (obese).

Several different dietary methods are available for controlling blood sugar in type 1 and insulin-dependent type 2 diabetes:

- Diabetic exchange lists (for maintaining a proper balance of carbohydrates, fats, and proteins throughout the day)
- Carbohydrate counting (for tracking the number of grams of carbohydrates consumed each day)
- Glycemic index (for tracking which carbohydrate foods increase blood sugar)

Sample Exchange List

Food group	Patient can have.....	Or exchange it for...
Fruit (each serving contains about 15 grams carbohydrates)	1 small or medium piece of fresh fruit	1/2 cup fruit juice,or canned or chopped fruit
Vegetable (each serving contains about 5 grams carbohydrates)	1 cup raw vegetables	1/2 cup cooked vegetables or vegetable juice
Starch (each serving contains about 15 grams carbohydrates)	1 slice or ounce bread	1/2 cup pasta, cereal, starchy vegetable
Sugar, honey, molasses	1 teaspoon	4 grams carbohydrates

Milk (does not include cream, yogurt or cheese)	1 cup milk	12 grams carbohydrates and 8 grams protein
Meat	1 ounce meat, fish, poultry, cheese or yogurt	1/2 cup dried beans
Fat (includes nuts, seeds and small amounts of bacon and peanut butter)	1 teaspoon oil, butter or margarine	5 grams fat

Weighing and Measuring. Weighing and measuring food is extremely important to get the correct number of daily calories.

- Along with measuring cups and spoons, choose a food scale that measures grams.
- Food should be weighed and measured after cooking.
- After measuring all foods for a week or so, most people can make fairly accurate estimates by eye or by holding food without having to measure everything every time they eat.

Timing. Patients with diabetes should not skip meals, particularly if they are taking insulin. Skipping meals can upset the balance between food intake and insulin and also can lead to low blood sugar and even weight gain if the patient eats extra food to offset hunger and low blood sugar levels.

Patients should coordinate insulin administration with calorie intake. In general, they should eat three meals each day at regular intervals. Snacks are often necessary.

Lifestyle changes of diet and exercise are extremely important for people who have pre-diabetes, or who are at high risk of developing type 2 diabetes. Lifestyle interventions can be very effective in preventing or postponing the progression to diabetes. These interventions are especially important for overweight people. Even moderate weight loss can help reduce diabetes risk.

The American Diabetes Association recommends that people at high risk for type 2 diabetes eat high-fiber (14g fiber for every 1,000 calories) and whole-grain foods. High intake of fiber, especially from whole grain cereals and breads, can help reduce type 2 diabetes risk.

Patients with diabetes also need to be aware of their heart health nutrition, in particular, controlling high blood pressure and cholesterol levels.

Special Considerations for People with Kidney Failure

Diabetes can lead to kidney disease and failure. People with early-stage kidney failure need to follow a special diet that slows the build-up of wastes

in the bloodstream. The diet restricts protein, potassium, phosphorus, and salt intake. Fat and carbohydrate intake may need to be increased to help maintain weight and muscle tissue.
People who have late-stage kidney disease usually need dialysis. Once patients are on dialysis, they need more protein in their diet. Patients must still be very careful about restricting salt, potassium, phosphorus, and fluids. Patients on peritoneal dialysis may have fewer restrictions on salt, potassium, and phosphorus than those on hemodialysis.

Exercise*:* Physical activity should increase incrementally to whatever level a patient can tolerate. Some experts believe that aerobic exercise is better than isometric exercise for weight loss and protection from vascular disease, but resistance training also can improve glucose control, and all forms of exercise are beneficial.
Regular exercise is defined as completing 150 minutes of moderate intensity aerobic activity a week.
Aerobic activity at moderate intensity basically means exercising at a level that raises patient's heart rate and makes him sweat. This includes a multitude of sports. For example: fast paced walking, light jogging, bike riding, rowing, playing doubles tennis or badminton, water aerobics.
Patients who experience hypoglycemic symptoms during exercise should be advised to test their blood glucose and ingest carbohydrates or lower their insulin dose as needed to get their glucose slightly above normal just before exercise. Hypoglycemia during vigorous exercise may require carbohydrate ingestion during the workout period, typically 5 to 15 g of sucrose or another simple sugar.
Patients with known or suspected cardiovascular disease may benefit from exercise stress testing before beginning an exercise program, while activity goals may need to be modified for patients with diabetic complications such as neuropathy and retinopathy.

Treatment of DM type 1

Insulin preparations:
Insulin is required for all patients with type 1 DM if they become ketoacidotic without it; it is also helpful for management of many patients with type 2 DM. Insulin replacement should ideally mimic β-cell function using 2 insulin types to provide basal and prandial requirements (physiologic replacement); this approach requires close attention to diet and exercise as well as to insulin timing and dose. Most insulin preparations are now recombinant human, practically eliminating the once-common allergic reactions to the drug when it was extracted from animal sources. Except for

use of regular insulin IV in hospitalized patients, insulin is administered subcutaneously. A number of analogs, created by modifications of the human insulin molecule that alter subcutaneous absorption rates, are available. Insulin types are commonly categorized by their time to onset and duration of action.

Classification of Human Insulin Preparations

Insulin Preparation	Onset of Action	Peak Action	Duration of Action
Rapid-acting			
Lispro, aspart, glulisine	5–15 min	45–75 min	3–5 h
Short-acting			
Regular	30–60 min	2–4 h	6–8 h
Intermediate-acting			
NPH	About 2 h	4–12 h	18–26 h
Long-acting			
Glargine	1–2 h	No peak	24 h
Detemir	1–2 h	No peak	14–24 h
Premixed			
70% NPH/30% regular	30–60 min	Dual (NPH & R)	10–16 h
50% NPH/50% regular	30–60 min	Dual (NPH & R)	10–16 h

75% NPL/25% lispro	5–15 min	Dual (NPL & lispro)	10–16 h
70% NPA/30% aspart	5–15 min	Dual (NPA & aspart)	10–16 h

NPA - neutral protamine; NPH - neutral protamine Hagedorn; NPL - neutral protamine lispro.

Rapid-acting insulins, including lispro and aspart, are rapidly absorbed because reversal of an amino acid pair prevents the insulin molecule from associating into dimers and polymers. They begin to reduce plasma glucose often within 15 min but have short duration of action (< 4 h). These insulins are best used at mealtime to control postprandial spikes in plasma glucose.
Regular insulin is slightly slower in onset (30 to 60 min) than lispro and aspart but lasts longer (6 to 8 h). It is the only form for IV use.
Neutral protamine Hagedorn (NPH, or insulin isophane) is intermediate-acting; onset of action is about 2 h after injection, peak effect is 4 to 12 h after injection, and duration of action is 18 to 26 h.
Insulin glargine and insulin detemir have no discernible peak of action and provide a steady basal effect over 24 h.
Combinations of NPH and regular insulin and of insulin lispro and lispro protamine (a form of lispro modified to act like NPH) are commercially available in premixed preparations.
Different insulin types can be drawn into the same syringe for injection but should not be premixed in bottles except by a manufacturer. Many prefilled insulin pen devices are available as an alternative to the conventional vial and syringe method. Insulin pens may be more convenient for use away from home and may be preferable for patients with limited vision or manual dexterity.

Insulin regimens for type 1 DM:

I. **Conservative therapy:** twice/day split-mixed (split doses of rapid- and intermediate-acting insulins) before breakfast and dinner. Indications: early stages of DM type 1 when some degree of β-cell function is preserved and therefore, the glycemic control can be achieved with less intensive effort.

II. **Multiple daily injections**: is more physiologic basal-bolus regimen, which simulates the normal pattern of insulin secretion. Such

regimen usually includes single fixed (basal) dose of long-acting and variable prandial (bolus) doses of rapid-acting insulin.

III. **Insulin pump**. Lispro, aspart, or regular insulin can be given continuously using an insulin pump. Continuous subcutaneous insulin infusion pumps can eliminate the need for multiple daily injections, provide maximal flexibility in the timing of meals, and substantially reduce variability in glucose levels. Disadvantages include cost, mechanical failures leading to interruptions in insulin supply, and the inconvenience of wearing an external device. Frequent and meticulous self-monitoring and close attention to pump function are necessary for safe and effective use of the insulin pump.

Taking into consideration all mentioned above, the intensive treatment, defined as glucose monitoring ≥ 4 times/day and ≥ 3 injections/day or continuous insulin infusion, is more effective than conventional treatment (1 to 2 insulin injections daily with or without monitoring) for preventing diabetic retinopathy, nephropathy, and neuropathy. However, intensive therapy may result in more frequent episodes of hypoglycemia and weight gain and is generally effective only in patients who are able and willing to take an active role in their self-care.

In general, most patients with type 1 DM can start with a total dose of **0.2 to 0.8 units of insulin/kg/day**. Obese patients may require higher doses. Physiologic replacement involves giving 40 to 60% of the daily insulin dose as an intermediate- or long-acting preparation to cover basal needs, with the remainder given as a rapid- or short-acting preparation to cover postprandial increases. This physiologic regimen allows greater freedom of lifestyle because patients can skip or time-shift meals and maintain normoglycemia. However, no specific insulin regimen has proved more effective than others, and these recommendations are for initiation of therapy; thereafter, choice of regimens generally rests on physiologic response and patient and physician preferences.

Complications of insulin therapy:

A. HYPOGLYCEMIA

Hypoglycemic reactions, the most common complication of insulin therapy, may result from delay in taking a meal or unusual physical exertion. With more type 1 patients attempting "tight" control, this complication has become even more frequent. Hypoglycemia causes signs of autonomic hyperactivity, both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger), that may progress to coma and convulsions.

1. **Altered awareness of hypoglycemia**- Since autonomic responses correlate strongly with "awareness" of hypoglycemia, many poorly controlled diabetics - whose nervous systems have adapted to chronic hyperglycemia - may trigger adrenergic alarms at levels of blood glucose above the usual hypoglycemic range. Conversely, type 1 patients overtreated with insulin may be unaware of critically low levels of blood glucose because of an adaptive blunting of their alarm systems owing to repeated episodes of hypoglycemia. This has been shown to be reversible if higher average blood glucose levels are maintained in these patients to avoid recurrent hypoglycemia over a period of several weeks.
2. **Lack of glucagon response in type 1**- For unexplained reasons, patients with type 1 lose their glucagon responses to hypoglycemia (but not to amino acids in protein-containing meals) within a year or so after developing diabetes. These patients then rely predominantly on the sympathetic nervous system to counterregulate hypoglycemia and are at special risk in later years when aging, autonomic neuropathy, or frequent hypoglycemic episodes blunt their sympathetic responses.
3. **Hypoglycemia with subsequent hyperglycemia**: Hyperglycemia may follow hypoglycemia either because too much sugar was ingested or because hypoglycemia caused a surge in counter-regulatory hormones (glucagon, epinephrine, cortisol, growth hormone). Too high a bedtime insulin dose can drive glucose down and stimulate a counter-regulatory response, leading to morning hyperglycemia (*Somogyi phenomenon*). A more common cause of unexplained morning hyperglycemia, however, is a rise in early morning growth hormone (*dawn phenomenon*). In this case, the evening insulin dose should be increased, changed to a longer-acting preparation, or injected later.
4. **Prevention and treatment of hypoglycemia**- Because of the potential danger of insulin-induced reactions, the diabetic patient should carry packets of table sugar or a candy roll at all times for use at the onset of hypoglycemic symptoms. Typically, 15 g of glucose or sucrose should be ingested. Patients should check their glucose levels 15 min after glucose or sucrose ingestion and ingest an additional 15 g if their glucose level is not > 4,4 mmol/L. For patients who are unconscious or unable to swallow, hypoglycemia can be treated immediately with glucagon 1 mg sc or IM or a 50% dextrose solution 50 mL IV (25 g) followed, if necessary, by IV infusion of a 5% or 10% dextrose solution to maintain adequate plasma glucose levels.

B. IMMUNOPATHOLOGY OF INSULIN THERAPY

At least five molecular classes of insulin antibodies are produced during the course of insulin therapy in diabetes, including IgA, IgD, IgE, IgG, and IgM. With the increased therapeutic use of purified pork and especially human insulin, the various immunopathologic syndromes such as insulin allergy, immune insulin resistance, and lipoatrophy have become quite rare since the titers and avidity of these induced antibodies are generally quite low. However, in parts of the world where less purified forms of beef insulin are still used, these disorders remain a clinical concern among some insulin-treated patients.

1. **Insulin allergy** - Insulin allergy, or immediate-type hypersensitivity, is a rare condition in which local or systemic urticaria is due to histamine release from tissue mast cells sensitized by adherence of anti-insulin IgE antibodies. In severe cases, anaphylaxis results. When only human insulin has been used from the onset of insulin therapy, insulin allergy is exceedingly rare. Antihistamines, corticosteroids, and even desensitization may be required, especially for systemic hypersensitivity. There have been case reports of successful use of insulin lispro in those rare patients who have a generalized allergy to human insulin or insulin resistance due to a high titer of insulin antibodies.

2. **Immune insulin resistance** - Most insulin-treated patients develop a low titer of circulating IgG anti-insulin antibodies that neutralize to a small extent the action of insulin. With the old animal insulins, a high titer of circulating antibodies sometimes developed, resulting in extremely high insulin requirements - often more than 200 units daily. This is now rarely seen with the switch to highly purified pork or human insulins and has not been reported with the analogs.

C. LIPODYSTROPHY AT INJECTION SITES

Atrophy of subcutaneous fatty tissue leading to disfiguring excavations and depressed areas may rarely occur at the site of injection. This complication results from an immune reaction, and it has become rarer with the development of pure insulin preparations. Injection of these preparations directly into the atrophic area often results in restoration of normal contours. Lipohypertrophy, on the other hand, is a consequence of the pharmacologic effects of insulin being deposited in the same location repeatedly. It can occur with purified insulins and as well. Rotation of injection sites will prevent lipohypertrophy. There is a case report of a patient who had intractable lipohypertrophy with human insulin but no longer had the problem when he switched to insulin lispro.

Pancreas transplantation

Pancreas transplantation is a form of pancreatic β-cell replacement that can restore normoglycemia in diabetic patients. Because the recipient exchanges risks of insulin injection for risks of immunosuppression, eligibility is limited mostly to patients who have type 1 diabetes with renal failure and who are thus candidates for kidney transplantation; > 90% of pancreas transplantations include transplantation of a kidney. At many centers, repeated failure to control glycemia with standard treatment and episodes of hypoglycemic unawareness are also eligibility criteria. Relative contraindications include age > 55 and significant atherosclerotic cardiovascular disease, defined as a previous myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or a positive stress test; these factors dramatically increase perioperative risk.
Possible options include:

- Simultaneous pancreas-kidney transplantation
- Pancreas-after-kidney transplantation
- Pancreas-alone transplantation

Treatment of DM type 2

Oral antihyperglycemic drugs are the primary treatment for type 2 DM, although insulinis often added when ≥ 2 oral drugs fail to provide adequate glycemic control.

Sulfonylureas (SUs) are insulin secretagogues. They lower plasma glucose by stimulating pancreatic β-cell insulin secretion and may secondarily improve peripheral and hepatic insulin sensitivity by reducing glucose toxicity. First-generation drugs are more likely to cause adverse effects and are used infrequently. All SUs promote hyperinsulinemia and weight gain of 2 to 5 kg, which over time may potentiate insulin resistance and limit their usefulness. All also can cause hypoglycemia. Risk factors include age > 65, use of long-acting drugs (especially chlorpropamide, glyburide, or glipizide), erratic eating and exercise, and renal or hepatic insufficiency. Hypoglycemia caused by long-acting drugs may last for days after treatment cessation, occasionally causes permanent neurologic disability, and can be fatal. SUs may also exhaust β-cell function.

Classification of sulfonurea preparations

	Drug	**Acts Over**	**Dose Range**	**Rel. Potency**	**Doses /Day**
1st Gen	Orinase (tolbutamide)	6-10 hrs	500 - 3000 mg	1	2-3

	Tolinase (tolazamide)		100 - 1000 mg	3	1-2
	Diabinese (chlorpropamide)	24-72 hrs	100 - 500 mg	6	1-2
2nd Gen	Glucotrol (glipizide)	12 hrs	2.5 - 40 mg	75	1-2
	Glucotrol XL (ext. rel. glipizide)	24 hrs	2.5 - 20 mg	150	1
	Micronase, Diabeta (glyburide)	18-24 hrs	1.25 - 2.0 mg	150	1-2
	Glynase (micronized gly.)	24 hrs	3 - 12 mg	250	1-2
3rd Gen	Amaryl (glimepiride)	24 hrs	1 - 8 mg	350	1

Non-sulfonylurea insulin secretagogues (repaglinide, nateglinide) stimulate insulin secretion in a manner similar to SUs. They are faster acting, however, and may stimulate insulin secretion more during meals than at other times. Thus, they may be especially effective for reducing postprandial hyperglycemia and appear to have lower risk of hypoglycemia. There may be some weight gain, although apparently less than with SUs.

Nateglinide, dose range 60–120 mg 3 times daily with meals, duration of action 3–4 hrs

Repaglinide, dose range 0.5–4 mg 3 times daily with meals, duration of action 3–4 hrs

Biguanides lower plasma glucose by decreasing hepatic glucose production (gluconeogenesis and glycogenolysis). They are considered peripheral insulin sensitizers, but their stimulation of peripheral glucose uptake may simply be a result of reductions in glucose from their hepatic effects. Biguanides also lower lipid levels and may also decrease GI nutrient absorption, increase β-cell sensitivity to circulating glucose, and decrease levels of plasminogen activator inhibitor 1, thereby exerting an antithrombotic effect. The drugs commonly cause GI adverse effects (dyspepsia, diarrhea), which for most people recede with time. Biguanides are contraindicated in patients at risk of metabolic acidosis.

Metformin, regular-release: 500 mg once/day–1250 mg twice daily, duration of action 6–10 hrs

Metformin, extended-release: 500 mg–2 g once/day, duration of action 24 hrs

Thiazolidinediones (TZDs) decrease peripheral insulin resistance (insulin sensitizers), but their specific mechanisms of action are not well understood. The drugs bind a nuclear receptor primarily present in fat cells (peroxisome-proliferator-activated receptor-γ [PPAR-γ]) that is involved in the transcription of genes that regulate glucose and lipid metabolism. TZDs also increase HDL levels, lower triglycerides, and may have anti-inflammatory and anti-atherosclerotic effects. Major adverse effects: weight gain, fluid retention, anemia (mild). Hepatotoxicity is rare, but liver function monitoring required.

Rosiglitazone 2-8 mg daily, duration of action 24 hrs, may increase risk of heart failure, angina, MI, stroke, and fracture. Not in use currently.

Pioglitazone 15-30 mg once daily, duration of action 24 hrs.

α-Glucosidase inhibitors (AGIs) competitively inhibit intestinal enzymes that hydrolyze dietary carbohydrates; carbohydrates are digested and absorbed more slowly, thereby lowering postprandial plasma glucose. AGIs are less effective than other oral drugs in reducing plasma glucose. Side effects include dyspepsia, flatulence, bloating and diarrhea. Must be taken at the very beginning of meal.

Acarbose 25–100 mg 3 times daily with meals, duration of action 6–10 hrs

Miglitol 25–100 mg 3 times daily with meals, duration of action 6–10 hrs

Dipeptidyl peptidase-4 inhibitors block glucagon-like peptide-1 (GLP-1) breakdown by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4).

Saxagliptin 2.5–5 mg once/day, duration of action 24 hrs

Sitagliptin 100 mg once/day, duration of action 24 hrs

Linagliptin 5 mg once/day, duration of action 24 hrs

GLP-1 agonists enhance glucose-dependent insulin secretion and slow gastric emptying. Exenatide (an incretin hormone) may also reduce appetite and promote weight loss and stimulate β-cell proliferation. It is given by injection 5 or 10 μg twice daily before meals and may be used in combination with oral antihyperglycemics. Other GLP-1 agonists, including a long-acting form ofexenatide are available or being developed.

The ***amylin analog*** pramlintide mimics amylin, a pancreatic β-cell hormone that helps regulate postprandial glucose levels. Pramlintide suppresses postprandial glucagon secretion, slows gastric emptying, and promotes satiety. It is given by injection and is used in combination with mealtime insulin. Patients with type 1 DM are given 30 to 60 mcg subcutaneously before meals, and those with type 2 DM are given 120 mcg.

Insulin therapy in patients with DM type 2. In many patients with DM type 2, glucose levels are adequately controlled with lifestyle changes or oral drugs, but insulin should be added when glucose remains inadequately controlled by ≥ 2 oral drugs. Insulin also should replace oral drugs in

women who become pregnant. The rationale for combination therapy is strongest for use of insulin with oral biguanides and insulin sensitizers. Regimens vary from a single daily injection of long- or intermediate-acting insulin (usually at bedtime) to the multiple-injection regimen used by patients with type 1 DM. In general, the simplest effective regimen is preferred. Because of insulin resistance, some patients with type 2 DM require very large doses (> 2 units/kg/day). A common complication is weight gain, which is mostly attributable to reduction in loss of glucose in urine and improved metabolic efficiency.

Emergencies in patients with diabetes mellitus.

Hypoglycemic coma

Hypoglycemic coma is an acute complication of diabetes caused by acute decrease of blood glucose, followed by reduction of glucose utilization by brain tissue and brain hypoxia.

Etiology:

1. An overdose of insulin or hypoglycemic agents (chlorpropamide, tolbutamide), the discrepancy between the dose of insulin and the need for it.
2. Lack of carbohydrates injestion.
3. The long break between meals.
4. Excessive muscular work.
5. Reducing of insulin-inactivating ability of the liver and kidneys due to decreased insulinase activity in patients with comorbid diabetes and liver disease/kidney disease.
6. Labile course of diabetes.
7. Post-ketoacidic state.
8. Alcohol intoxication.
9. Adenoma of B cells (insuloma).

Pathogenesis:

Hypoglycemia is accompanied by activation of the sympathoadrenal system, increased levels of epinephrine, norepinephrine. Hypoglycemia also leads to stimulation of the hypothalamus, increased activity of the pituitary and adrenal cortex with increased production of contrainsulinary hormones - ACTH, growth hormone, glucocorticoids.

Hypoglycemia causes severe impairment of brain supply - hypoxia, cortex hypofunction. The development of irreversible changes is possible. Patients might develop cerebral paresis, edema of the brain, thrombosis.

Clinical manifestations of hypoglycemic coma.

Hypoglycemic coma develops rapidly, often suddenly.

Severity of clinical manifestations depends on the sensitivity of the central nervous system to hypoglycemia.

Mild hypoglycemic state.

The feeling of hunger. Worry, anxiety, irritability, aggressiveness. Severe weakness, pallor, sweating, chills, tremor. Headache, dizziness, hyperesthesia. Numbness of the tongue, lips. Tachycardia. Nausea, vomiting.

Severe hypoglycemic condition

Acute excitation, aggressiveness, hallucinations, fear, inappropriate behavior. Disorders of conciousness, confusion. Increased tendon and periosteal reflexes. Positive Babinsky's symptom. Tonic and clonic convulsions. The development of meningeal syndrome is possible, which includes reduced tendon reflexes, muscle hypotonia, anisocoria, nystagmus, sluggish pupillary reaction. Pupils are broadened, eyeballs tone is normal. Body temperature and respiration is normal. Pulse is normal or accelerated. Attacks of angina can be transformed into a myocardial infarction. Possible strokes.

Deep hypoglycemic coma.

Complete loss of consciousness, deep coma. Areflexia. Discontinuance of convulsions. Discontinuance of sweating. Hypothermia. Superficial breathing. Bradycardia, hypotension.

Differential diagnosis is made with non-diabetic hypoglycemia.

Hiperinsulinizm primary (original, complete): severe heart failure, inflammatory and destructive lesions of liver and kidney failure.

Hiperinsulinizm secondary (functional, symptomatic): surgery on the gastrointestinal tract - gastrectomy, gastrostomy with accelerated absorption of carbohydrates and release of insulin.

Excessive food intake after a long hunger period.

Hypersensitivity to insulin.

Hypoglycemia may develop in patients with certain endocrine diseases: Simmonds syndrome, pituitary dwarfism, hypothyroidism, Addison's disease, congenital adrenal hyperplasia.

Deficiency of contrainsulinary hormones may occur in renal glucosuria, malnutrition, pregnancy, lactation, liver cirrhosis, cholangitis, cholecystitis, extrapancreatic tumors.

Laboratory diagnosis

An acute decrease of the blood glucose.

Against the background of hypoglycaemia may develop "hungry" ketosis and acidosis due to activation of gluconeogenesis.

Treatment

1. Intravenous injection of 40% glucose 20-40-100 ml. The criterion of dose adequacy is restored consciousness. Then proceed with the infusion of 5% glucose to prevent recurrence of hypoglycemia.
2. Intramuscular injection of 1 ml of 1% glucagon, re-enter after 10 minutes.
3. Subcutaneous injection of 0.5-1.0 ml of 0.1% solution of adrenaline, 150-200 mg hydrocortisone intravenously or intramuscularly. In case of recurrent hypoglycemia 1-2 ml of glucagon should be injected IM every 2 hours and glucocorticoids (hydrocortisone 75 mg or 30 mg of prednisolone) - intravenously four times a day.
4. To improve cerebral circulation: 5-10 ml of 25% solution of magnesium sulfate IV.
5. Because of the danger of edema of the brain during prolonged hypoglycemic coma 15-20% solution of mannitol (0.5-1.0 g per 1 kg of body weight) should be prescribed.
6. Moist oxygen oinhalations.

Diabetic ketoacidosis (DKA)

DKA is an acute metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis.
Etiology:
1. Late diagnosis of diabetes.
2. Inadequate treatment of diabetes - insulin cancellation or low insulin dose, which is insufficient to meet the body's metabolic requirements.
3. The acute increase in the need for insulin, causing decompensation of carbohydrate metabolism:
a) physical stress (trauma, surgery, burns, frostbite);
b) mental stress;
c) serious intercurrent illness (infection, inflammation, vascular accident);
d) fatty liver;
d) lipid diet.
4. Prolonged vomiting of various origins.
Pathogenesis
Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unrestrained lipolysis, as does alanine because of muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by

inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced, acetoacetic acid and β-hydroxybutyric acid, are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration.

Hyperglycemia due to insulin deficiency causes an osmotic diuresis that leads to marked urinary losses of water and electrolytes. Urinary excretion of ketones obligates additional losses of Na and K. Serum Na may fall from natriuresis or rise due to excretion of large volumes of free water. K is also lost in large quantities, sometimes > 300 mmol/24 hours. Despite a significant total body deficit of K, initial serum K is typically normal or elevated because of the extracellular migration of K in response to acidosis. K levels generally fall further during treatment as insulin therapy drives K into cells. If serum K is not monitored and replaced as needed, life-threatening hypokalemia may develop.

Clinical manifestations of DKA

Symptoms and signs of DKA include those of hyperglycemia with the addition of nausea, vomiting, and - particularly in children - abdominal pain. Lethargy and somnolence are symptoms of more severe decompensation. Patients may be hypotensive and tachycardic from dehydration and acidosis; they may breathe rapidly and deeply to compensate for acidemia (Kussmaul respirations). They may also have fruity breath due to exhaled acetone. Fever is not a sign of DKA itself and, if present, signifies underlying infection. In the absence of timely treatment, DKA progresses to coma and death.

Acute cerebral edema, a complication in about 1% of DKA patients, occurs primarily in children and less often in adolescents and young adults. Headache and fluctuating level of consciousness herald this complication in some patients, but respiratory arrest is the initial manifestation in others. The cause is not well understood but may be related to too-rapid reductions in serum osmolality or to brain ischemia. It is most likely to occur in children < 5 yr when DKA is the initial manifestation of DM. Patients with the highest blood urea nitrogen and lowest $PaCO_2$ at presentation appear to be at greatest risk. Delays in correction of hyponatremia and the use of HCO_3 during DKA treatment are additional risk factors.

Laboratory diagnosis

The measurments of arterial pH, serum ketones, blood glucose and calculation of anion gap should be performed.

Also serum electrolytes, blood urea nitrogen and creatinine, and osmolarity should be measured. Urine should be tested for ketones. Patients who

appear significantly ill and those with positive ketones should have arterial blood gas DKA is diagnosed by an arterial pH< 7.30 with an anion gap > 12 and serum ketones in the presence of hyperglycemia. A presumptive diagnosis can be made when urine glucose and ketones are strongly positive. Urine test strips and some assays for serum ketones may underestimate the degree of ketosis because they detect acetoacetic and not β-hydroxybutyric acid, which is usually the predominant ketoacid.

Symptoms and signs of a triggering illness should be pursued with appropriate studies (cultures, imaging studies). Adults should have an ECG to screen for acute myocardial infarction and to help determine the significance of abnormalities in serum K.

Other laboratory abnormalities include hyponatremia, elevated serum creatinine, and elevated plasma osmolality. Hyperglycemia may cause dilutional hyponatremia. Serum amylase and lipase are often elevated, even in the absence of pancreatitis (which may be present in alcoholic DKA patients and in those with coexisting hypertriglyceridemia).

Treatment

- 0.9% saline IV
- Correction of any hypokalemia
- Insulin IV (as long as serum K is ≥ 3.3 mmol/L)
- Rarely IV $NaHCO_3$ (if pH < 7 after 1 h of treatment)

The most urgent goals are rapid intravascular volume repletion, correction of hyperglycemia and acidosis, and prevention of hypokalemia. Identification of precipitating factors is also important. Treatment should occur in intensive care settings because clinical and laboratory assessments are initially needed every hour or every other hour with appropriate adjustments in treatment.

Intravascular volume should be restored rapidly to raise blood pressure and ensure glomerular perfusion; once intravascular volume is restored, remaining total body water deficits are corrected more slowly, typically over about 24 h. Initial volume repletion in adults is typically achieved with rapid IV infusion of 1 to 3 L of 0.9% saline solution, followed by saline infusions at 1 L/h or faster as needed to raise blood pressure, correct hyperglycemia, and keep urine flow adequate. Adults with DKA typically need a minimum of 3 L of saline over the first 5 h. When blood pressure is stable and urine flow adequate, normal saline is replaced by 0.45% saline. When plasma glucose decreases to < 11.1 mmol/L, IV fluid should be changed to 5% dextrose in 0.45% saline.

Hyperglycemia is corrected by giving regular insulin 0.1 unit/kg IV bolus initially, followed by continuous IV infusion of 0.1 unit/kg/h in 0.9% saline solution. Insulin should be withheld until serum K is ≥ 3.3 mmol/L. Insulin

adsorption onto IV tubing can lead to inconsistent effects, which can be minimized by preflushing the IV tubing with insulin solution. If plasma glucose does not fall by 2,8 to 4,2 mmol/L in the first hour, insulin doses should be doubled.

Ketones should begin to clear within hours if insulin is given in sufficient doses. Sometimes the clearance of ketones may appear to lag because of conversion of β-hydroxybutyrate to acetoacetate as acidosis resolves. Serum pH and HCO_3 levels should also quickly improve, but restoration of a normal serum HCO_3 level may take 24 h. Rapid correction of pH by HCO_3 administration may be considered if pH remains < 7 after about an hour of initial fluid resuscitation, but HCO_3 is associated with development of acute cerebral edema (primarily in children) and should not be used routinely. If used, only modest pH elevation should be attempted (target pH of about 7.1), with doses of 50 to 100 mmol over 30 to 60 min, followed by repeat measurement of arterial pH and serum K.

When plasma glucose becomes < 11.1 mmol/L in adults, 5% dextrose should be added to IV fluids to reduce the risk of hypoglycemia. Insulin dosage can then be reduced to 0.02 to 0.05 unit/kg/h, but the continuous IV infusion of regular insulin should be maintained until the anion gap has narrowed and blood and urine are consistently negative for ketones. Insulin replacement may then be switched to regular insulin 5 to 10 units subcutaneously every 4 to 6 h. When the patient is stable and able to eat, a typical split-mixed or basal-bolus insulin regimen is begun. IV insulin should be continued for 1 to 4 h after the initial dose of subcutaneous insulin is given.

Hypokalemia prevention requires replacement of 20 to 30 mEq K in each liter of IV fluid to keep serum K between 4 and 5 mmol/L. If serum K is < 3.3 mmol/L, insulin should be withheld and K given at 40 mEq/h until serum K is ≥ 3.3 mmol/L; if serum K is > 5 mmol/L, K supplementation can be withheld. Initially normal or elevated serum K measurements may reflect shifts from intracellular stores in response to acidemia and belie the true K deficits that almost all DKA patients have. Insulin replacement rapidly shifts K into cells, so levels should be checked hourly or every other hour in the initial stages of treatment. Hypophosphatemia often develops during treatment of DKA, but phosphate repletion is of unclear benefit in most cases. If indicated (if rhabdomyolysis, hemolysis, or neurologic deterioration occurs), K phosphate 1 to 2 mmol/kg of phosphate, can be infused over 6 to 12 h. If K phosphate is given, the serum Ca level usually decreases and should be monitored.

Treatment of suspected cerebral edema is hyperventilation, corticosteroids, and mannitol, but these measures are often ineffective after the onset of respiratory arrest.

Nonketotic hyperosmolar syndrome (NKHS)

NKHS is an acute complication of diabetes caused by blood hyperosmolality and pronounced intracellular dehydration without ketosis.

NKHS is rare - 0.23% of patients with diabetes. Most often this complication develops in patients older than 50 years or with concomitant obesity in children (teenagers). Mortality is high - 50%.

Precipitating factors:

1) Severe dehydration - vomiting, diarrhea, blood loss, increased urine output, burns, frostbite;
2) excessive injection of solutions of glucose and saline solutions;
3) intercurrent infectious diseases;
4) surgery;
5) prolonged treatment with diuretics, massive doses of corticosteroids, immunosuppressants.
6) hemodialysis, peritoneal dialysis.

Pathogenesis of NKHS

- Acute hyperglycemia blocks ketogenesis.
- Reduction of excretory renal function with reduced excretion of Na, Cl and urea in the urine: hipernatremia, hyperchloremia, hyperazotemia.
- Expressed blood hyperosmolality.
- Dehydration intracellular, intercellular.
- Hypovolemia.
- Clotting of blood. Thrombosis, thromboembolism.
- Dehydration of tissues.

Clinical manifestations of NKHS

Hyperosmolar coma develops gradually over several days, rarely - overnight. The predecessors of NKHS are: polyuria, polydipsia, sometimes polyphagia. Then develops fatigue, signs of dehydration, drowsiness, confusion.

Blood hyperosmolality is accompanied by a pronounced tendency to thrombosis, severely impaired microcirculation in different tissues - especially in the brain and kidneys. The clinical manifestations caused by cerebrovascular accident include the early and severe functional neurological symptoms. Thrombosis of renal vessels is the cause of acute renal failure.

There are pronounced signs of tissues dehydration - dryness of skin and decreased skin turgor, muscle hypotension, reduction of eyeballs tone.

Neurological disorders. Bilateral spontaneous nystagmus, hemianopsia. Aphasia. Seizures, epileptic attacks. Hemiparesis and paralysis. Tendon reflexes are absent, there are pathological reflexes (Babinsky's, etc.). Muscle hypertonicity or muscle hypotonia. Vestibular disorders. Hallucinations are possible. Disorders of consciousness - drowsiness, sopor, coma. Hyperthermia of central origin.
Renal disease: early, frequent oliguria, anuria.
Change in peripheral tissues. Pronounced dryness of skin, mucous membranes, decreased skin turgor.
Eye disorders: lowering the tone of the eyeballs, constricted pupils, sluggish reaction of pupils to light.
Respiratory disorders: superficial and rapid breathing, no Kussmaul's breathing, no smell of acetone.
The derangements of the cardiovascular system. Tachycardia, arrhythmia. Hypotension, collapse, shock. Thrombosis of peripheral arteries and veins. Possible swelling of the lower extremities and scrotum.
Disorders of the gastrointestinal tract: vomiting, flatulence, abdominal pain, intestinal obstruction in case of late hypokalemia.
Laboratory diagnosis
CBC: signs of clotting: increased hemoglobin, hematocrit, leukocytosis.
General test of urine: glucosuria, hyponatruria, proteinuria, cylindruria, hematuria.
Hyperglycemia 50 - 200 mmol / L.
Hyperosmolality up to 500 mOsm / L (normal range 285-295 mOsm / L).
Osmolarity of blood is determined by the formula: osmolality (mOsm / L) = glycemia (mmol/L) + urea (mmol/L) + 2(K+Na) (mmol/L) + ((protein g/L*0,243) :8)
Hyperchloremia.
Hypernatremia.
Hyperkalemia before treatment with insulin or normokalemia.
Hypokalemia after initiation of insulin therapy.
Albuminosis.
Hiperazotemia.
The levels of pH, bicarbonate levels, ketone bodies are normal.
Treatment of NKHS
1. Rehydration.
Inject hypotonic solution of NaCl 0.45% 2 L / hr during the first 2 hours, followed by 1 liter / hour to normalize osmolarity of blood and venous pressure. When the glucose level reaches 14 mmol / L the infusion of 2.5% glucose solution should be started. Altogether 8-12 liters of fluid should be injected during 1st day of treatment.

2. Correction of hypokalemia.
Potassium preparations are injected only when blood glucose level achieves 14 mmol / l. If blood potassium levels are less than 3.5 mmol / l and there is no anuria, 10-20 mmol of KCl (7,5-15 ml of 10% KCl) for 1 liter solution of NaCl per hour should be injected.
3. Insulin therapy.
Insulin is injected only IV 8-12-16 units hourly to lower blood glucose below 14 mmol / L.
When the blood glucose level achieves 14 mmol / l, subcutaneous insulin should be used 6-8 units every 3 hours.
4. To prevent brain edema and improving its metabolism 50 ml of 1% glutamic acid should be used.
5. Oxygen therapy.
6. Prevention of thrombosis - heparin 5000-6000 IU 4 times daily intramuscularly.
7. Symptomatic therapy.
In case of hypotension - 1-2 ml of 0.5% doxa or other mineralocorticoids, plasma substitutes (gemodez, albumin, reopolyglukine).
Antibiotics if indicated.

Lactic coma

Lactic coma is an acute complication of diabetes that develops due to accumulation of lactic acid and the occurrence of metabolic acidosis. It is a rare state, however it has high mortality rate - 50%.
Etiology
1. Advanced age (susceptibility to hypoxia).
2. Comorbidity with hypoxia (heart disease, pulmonarydisorders, chronic alcoholism).
3. Acute hypoxia (traumatic shock, cardiogenic shock, toxic shock, acute infectious or inflammatory disease, bleeding, collapse, myocardial infarction).
4. Endogenous toxicity (hepatic or renal failure, leukemia, severe infection).
5. Exogenous intoxication (methanol, ethanol).
6. Pharmacogenic acidosis caused by biguanides, fructose, polyhydric alcohols, salicylates, sodium lactate.
Precipitating factors:
1) Excessive exercise (lactic acid is synthesized by working muscles);
2) vitamin deficiencies, especially vitamin B1;
3) magnesium deficiency;
4) acute intoxication.
Pathogenesis of lactic coma

Hypoxia.
Hypersecretion of catecholamines, growth hormone, glucocorticoids.
Inhibition of aerobic glycolysis.
Stimulation of anaerobic glycolysis.
Increased production of lactic acid.
Decreased activity of pyruvate dehydrogenase, which converts pyruvic acid in acetyl-CoA - blocks pyruvic acid oxidation.
Accumulation of pyruvic acid and its reduction to lactic acid.
Blockade of H + secretion by the kidneys.
Disorders of the ratio of oxidized NADF and reduced NADF H2.
Disorders of pyruvic acid transportation in mitochondria.
Clinical manifestations of lactic coma
Coma may develop quickly, within a few hours.
Prodromal period is sometimes accompanied by dyspeptic symptoms (anorexia, nausea, vomiting), rapid breathing, muscle pain and angina (lactic acid is a strong "muscle poison"), impaired psycho-emotional state. Mortality is high - 50-80%, because even at levels of lactic acid 7 mmol / l the irreversible changes in tissues develop.
CNS: lethargy, drowsiness. Excitation, delirium, insomnia, motor restlessness. Gradually evolving coma.
The lesions of the cardiovascular system: adrenergic receptor blockade in peripheral vessels - severe and persistent hypotension, collapse, hypothermia. Blockade of adrenergic receptors of myocardium - a stable bradycardia, decreased contractility of the myocardium, the development of progressive heart failure refractory to therapy. Intravascular thrombosis.
Renal disease: oliguria and then anuria.
Lesions of the gastrointestinal tract: indigestion, nausea, vomiting.
Muscles lesions: muscle pain, muscle hypotonia.
Respiratory disorders: rapid superficial breathing, then Kussmaul's breathing caused by acidosis.
Laboratory diagnosis
Hyperglycemia or normoglycemia.
Increased lactic acid levels (normal range - 0.6-1.2 mmol / l ; 2 mmol / l - renal threshold).
Reduction of pyruvic acid (normal range 0,06-0,12 mmol / l).
The acute increase in lactic acid \ pyruvic acid index (normally 10: 1).
Acidosis - lowering of the pH (normal pH : 7,35-7,45).
Lowering of the standard bicarbonate (normal range 20-27 mmol / L).
Reduction of reserve alkalinity (normal range 55-75%).
Hyperkalemia.
Hyperazotemia.

Treatment

1. Correction of acidosis.

If pH is less than 7 : 1-2 liters of 2.5% sodium bicarbonate 100 mmol / hour (340 ml of 2.5% solution per hour). Infusion is stopped when pH achieves 7.

2. Stimulation of the conversion of lactic acid in pyruvic acid by 1% methylene blue 50-100 ml, 2.5 mg per 1 kg body weight of the patient.

3. Insulin therapy.

Should be done even in case of normoglycemia - IV 6-8 units of short-acting insulin in 500 ml of 5% glucose.

4. Correction of hypotension - plasma expanders and hydrocortisone 250-500 mg.

5. Oxygen therapy.

6. Hemodialysis as indicated in anuria.

The control of initial level of knowledge

1. Tactics to remove insulin resistance in patients with type 1 diabetes who receive prolonged insulin include:

A. The treatment with highly purified insulin;

B. Use of semi-human insulin;

C. The addition of oral sulfonurea preparations;

D. All of the above.

2. What foods should be recommended for patients with diabetes?

A. soy;

B. Lean meat;

C. Low-fat cheese

3. Side effects of sulfonureas on the blood appear as:

A. Thrombocytopenia;

B. Leukopenia;

C. Agranulocytosis;

D. All of the above definitions

4. Which drug should be rationally prescribed to a patient with type 2 diabetes and comorbid chronic pyelonephritis?

A. Chlorpropamide;

B. Glibenclamide;

C. Gliburide;

D. Glipizide

5. Which of the foods are the richest ones with potassium and therefore can be recommended for patients with diabetes?
A. Oats;
B. Dried prunes;
C. Raisins;
D. Pumpkin;
E. Carrots

6. Is it appropriate to prescribe two glucose lowering sulfanilamide drugs for the treatment of type 2 diabetes?
A. No;
B. Yes;
C. Depending on the situations

7. Which of the following antihypertensive drugs are more appropriate to assign for diabetic patients with hypertension in the presence of symptoms of cardiac autonomic diabetic neuropathy?
A. Prasosin;
B. Reserpine;
C. Aldomet;
D. Clonidine

8. What preparation should be given preference for improvement (normalization) of lipid metabolism in patients with diabetes?
A. tocopherol acetate;
B. nicotinamide;
C. Lipostabil;
D. Riboksin

9. What types of insulin can often cause an allergic reaction?
A. Crystal;
B. Single peak;
C. Monocomponent

10.What types of insulin resistance can occur in diabetes?
A. Pre-receptor;
B. Receptor;
C. Post-receptor;
D. All of the listed above

Endocrinology (initial level of knowledge) correct answers:

1	2	3	4	5	6	7	8	9	10
B	C	D	C	B	A	D	C	A	D

The control of final level of knowledge

1. When transfering the patient who was treated by pork insulin to human insulin the dose of the human one should:
A.stay without changes;
B.increase;
C.decrease.

2. What resorts in Ukraine are indicated for treatment of patients with diabetes?
A.Mirgorod;
B.Truskavets;
C.Berezovsky mineral waters;
D.All of them

3. What berries have glucose-reducing action?
A.Wild strawberry;
B.Raspberry;
C.Mountain ash;
D.Blueberry;
E.All of them

4. The most expressed sugar-reducing action have:
A.Rye;
B.Barley;
C.Oats

5. Which of the specified signs is not an indication for insulin prescription:
A.Progressing loss of body weight
B.Pregnancy

C.Infectious diseases
D.Obesity
E.Diabetic angiopathy of the II - III grade

6. The insulins of short action are all mentioned below, except of:
A.Aktrapid
B.Monotard
C.Monosulin
D.Humulin
E.Homorapid

7. While calculating a dose of insulin all specified indicators are considered, except of:
A.Body mass of the patient
B.Duration of the disease
C.Type of diabetes
D.Grade of glycaemia
E.Ketoacidosis

8. The side effects of insulin therapy are all designated, except of:
A. Lipodystrophy
B. Vitiligo
S. Insulin edemas
Д Insulin resistance
E.Somogui phenomenon

9. Preparations of sulfonylurea are all mentioned below except of:
A.Chlorpropramide
B.Tolbutamide
C.Miglitol
D.Glimepiride
E.Gliburide

10. Contra-indications to prescription of biguanids are all specified, except:
A. Diabetes 1 type with tendency to ketoacidosis
B. Diabetes 2 type in patients with excessive body weight
S.Atherosclerosis
D.Pregnancy
E.Surgery

Endocrinology (final level of knowledge) correct answers:

1	2	3	4	5	6	7	8	9	10
C	D	E	C	D	B	C	B	C	B

Situational problems

1. A patient 16 years old has type 1 diabetes since the age of 6 years. No complications. He uses 6 units of insulin "Aktrapid" and 20 units of "Monotard" in the morning, and 4 units of "Aktrapid" and 12 units of "Monotard" in the evening. Height - 179 cm, weight - 80 kg. Glycemic profile: glucose 7.6 mmol / l, 13.00 - 8.6 mmol / l, 18.30 - 9 mmol / l, 22.00 - 7.2 mmol / l. Diuresis - 1.7 liters. Glycosuria - 5 g / l, portion - 300 ml. What is the tactics of further treatment?

A.Increase the dose of "Monotard" in the evening.
B.Increase the dose of "Monotard" in the morning.
C.Prescribe short action insulin in the dinner time.
D. Leave the dose without changes.
E. Increase the dose of "Actrapid" in the morning and in the evening.

2. The patient with diabetes of second type receives insulin "Protaphan" 32 IU before a breakfast and 16 IU before a supper. Last glycaemic profile: 8.00 - 7,5 mmol/l, 13.00 - 12,0 mmol/l, 18.00 - 14.2 mmol/l, 21.00. - 16.0 mmol/l, 3.00 - 9,0 mmol/l. What actions of the doctor would be reasonable for the prevention of further carbohydrate metabolism decompensation?

A.Change a dose of insulin " Protaphan " in the morning to 30 IU, and in the evening to 12 IU.
B.Decrease quantity of carbohydrates during a supper.
C. Decrease quantity of carbohydrates during a dinner.
D. Change a dose of insulin " Protaphan " in the morning to 36 IU, and in the evening to 20 IU.
E. Prescribe the other insulin.

3. The patient has sugar diabetes of second type, he is treated by insulin of the prolonged action. Fluctuation of level of glucose throughout a day - 15,2-22,0 mmol/l, fasting glucose - 28,6 mmol/l. What is the further medical tactics?

A.Preparations of sulfonylurea.
B.Biguanides.

C.Insulins of prolonged action.
D.Diet.
E.Insulins of short action

4. The patient is 46 years old. He's been sick with diabetes during 9 years. He receives insulin Humodar 26 IU in the morning and 18 IU in the evening. He complains to weakness in the morning, a headache. Objective data: pulse - 72/minute, arterial blood pressure- 125/70 mm hg. Heart sizes are norm. The liver +4 cm. Glucose of blood: 8.00 - 14 mmol/l; 12.00 - 9 mmol/l; 17.00 - 11 mmol/l; 2.00 - 3,8 mmol/l. What is the reason for the patient's condition?

A.Not enough dose of insulin in the morning
B. An insufficiency of evening dose of insulin
C. Presence of hepatosis
D. A climacteric syndrome
E. Spare dose of insulin in the evening

5. The man of 52 years old, throughout 18 years has been ill with diabetes. One year ago he had cystitis. He takes maninil- 5 mg 3 times a day. Objective data: height - 176 cm. Weight - 82 kg. Fasting glycaemia - 10,3-12,4 mmol/l. Proteinuria- 0,033 g/l. What are the most reasonable measures for prevention of diabetic nephropathy?

A. Changing maninil to insulin
B. Increase the dose of maninil
C. Changing the energy value of food
D. To add insulin
E. Antibacterial therapy

6. The woman of 52 years old, receives insulin of the short and prolonged action before breakfast and supper due to diabetes. Every day before supper she feels a pain of compressing character behind the sternum, with irradiation into the left hand, weakness. Height-168 cm. Weight - 76 kg. How to prevent the development of the described above symptoms?

A.Changing the energy value of food
B.Therapy by nitrates
C. Therapy by Ca-channels blockers
D. Therapy by sufonylureas of II generation
E. Changing an insulin dose

7. Patient of 13 years old complains on thirst, polyuria, weakness. He lost 4 kg during last 2 weeks. Objective data: the general condition is satisfactory, no smell of acetone present. Fasting glucose - 32 mmol/l, urine glucose - 6 %, acetone (+). What would be your tactics in this case?

A.Diet therapy
B. Therapy by sufonylurea of III generation
C. Therapy by metformin
D. Therapy by sufonylurea of II generation
E. Insulin therapy

8. Patient B., 46 years old, has a height 170 cm, body weight 93 kg. Within 2 months was on the diet with restriction of caloric content, has lost 5 kg. Fasting glucose - 12 mmol/L. Which glucose-lowering therapy should be preferred?

A. Therapy by sufonylurea of I generation
B Insulin therapy
C. Therapy by sufonylurea of III generation
D. Metformin
E. Therapy by sufonylurea of II generation

9. Patient 64 years old, who suffers from type 2 diabetes, fell ill with infectious hepatitis A. In the past 2 years he received glyburide 15 mg per day. Fasting glucose -13.6 mmol/L. Identify tactics for further treatment:

A.Therapy by sufonylurea of III generation
B. Biguanides
C.Increase the dose of glyburide to 20 mg
D.Add acarbose
E.Insulin therapy

10. Patient of 55 years old, had his diabetes discovered accidentally during routine hospital check. Not treated. Objective data: height - 170 cm, body weight - 106 kg. Normal skin humidity. Pulse - 76/min., rhythmic. Heart sounds are muted. BP - 160/90 mm Hg. mercury. Fasting glucose -7.9 mmol / l. Glucose level in daily urine - 1%, urine output - 2.5 liters. What is the primary treatment strategy?

A.therapy by metformin
B.only diet therapy
C. therapy by glyburide
D. therapy by repaglinide
E. insulin therapy

CORRECT ANSWERS

1. Д	**5. A**	**9. E**
2. Д	**6. E**	**10. B**
3. E	**7. E**	
4. E	**8. Д**	

Control questions

1. Principles of treatment of the patient with diabetes.
2. Criteria of indemnification of a diabetes.
3. Methods of treatment of diabetes.
4. Principles of diet therapy of diabetes.
5. Definition of carbohydrate balance and tolerance to carbohydrates.
6. Glucose-lowering preparations of sulfonylurea, their characteristics, the action mechanism, the indications, contra-indications for their use.
9. Sulfonurea resistance, treatment.
10.Biguanides, their characteristics, the action mechanism, the indications, contra-indications to their use, side effects.
11.Insulin therapy, the indication for its use.
12. Insulin preparations.
13. Methods of insulin therapy.
14. Complication of insulin therapy, their treatment.
15. Health-resort treatment of patients with diabetes, the indications, contra-indications, examples of resorts.
21. Physiotherapy in diabetes, the indications.
22. The role of physical exercise in diabetes treatment.
23. Self-control of patient with diabetes.

Practical problems

- To substantiate the diagnosis of a diabetes, establish type, severity of disease, indemnification degree;.
- To evaluate glycaemic and glucosuric profile, round-the-clock glucosuria, a condition of albuminous and lipid metabolism, electrolyte balance;
- To establish degree of indemnification of a diabetes by results of biochemical researches;
- To appoint the menu to the patient withdiabetes (to establish the energy value of a diet for a day, distribution of carbohydrates throughout a day depending on glycaemia level and efficiency of action of the glucose-lowering preparations);
- To prescribe physical excercise, to establish its intensity and approximate timing;
- to substantiate the indications for glucose-lowering preparations, their dose, efficiency of treatment according to its term;
- To make the scheme of follow-up of the patient with diabetes, to establish the terms of dynamic supervision by endocrinologist, internist and other physicians;
- To establish the indications to health-resort treatment;

- To write recipes for glucose-lowering preparations.

Further reading:

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Навчальне видання

ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ. ЦУКРОВИЙ ДІАБЕТ 1 ТА 2 ТИПУ, СУЧАСНІ МЕТОДИ ЛІКУВАННЯ. КОМАТОЗНІ СТАНИ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ

Методичні вказівки
для студентів IV курсу

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