Uzhhorod National University

Medical Faculty 2

Feysa S.V., Tovt-Korshynska M.I., Shushman I.V.

TREATMENT OF DIABETES MELLITUS

Guidelines for workshops

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Preface.

In guidelines set out basic information about the non-pharmacological (diet, physical activity) and pharmacological treatment of DM. It includes classification of main groups of antidiabetic drugs, their mechanism of action, dosage, indications and contraindications for use, side effects. Recommended as a supplementary educational footage for students of IV, VI course of Medical faculty.

Рецензенти:

- **Погоріляк Р.Ю.** – завідувач кафедри громадського здоров'я і гуманітарних дисциплін медичного факультету №2 Ужгородського національного університету, д.мед.н., доцент
- **Росул М.М.** – доцент кафедри терапії та сімейної медицини факультету післядипломної освіти Ужгородського національного університету, к.мед.н., доцент

Розглянуто на засіданні кафедри внутрішніх хвороб медичного факультету №2 ДВНЗ «Ужгородський національний університет» 14 квітня 2017 р. (протокол №9) та рекомендовано як методичні рекомендації для проведення практичних занять з ендокринології для студентів медичного факультету №2

CONTENT

TREATMENT OF DIABETES MELLITUS

The treatment of patients with Diabetes Mellitus (DM) is very important and may be difficult because of problems in achieving of normal glucose control. There is good evidence that hyperglycemia conveys risks for all of the common long-term complications of DM, which are the major cases of excess morbidity and mortality in diabetics.

Differential diagnostics of diabetes mellitus type 1 and 2

Feature	Type 1	Type 2
Age, associated with onset of a disease	Childhood, adolescence, or early adulthood	Adult, average age (40 years and older)
Family history of a disease	Not often	Frequently
Influence of seasonal factors on the detection of a disease	Autumn-winter period	No
Phenotype	Thin	Obesity
Haplotypes	B8, B15, Dw3, Dw4, DRw3, DRw4	No connection
Developing of a disease	Fast (sudden, explosive onset)	Slow
Symptoms of a disease	Severe	Poor or absent
Urine	Sugar and acetone	Sugar
Ketoacidosis	Inclined	Resistant
Serum insulin (IRI)	Low or absent	Normal or increased
Antibodies against islet cells	Present	Absent
Treatment (basic)	Exogenous insulin	Diet
Concordance of monoovular twins, %	50	100

The goals in caring for patients with diabetes mellitus include the elimination of symptoms; microvascular (eye and kidney disease) risk reduction through control of glycemia and blood pressure (BP); macrovascular (coronary, cerebro-vascular, peripheral vascular) risk reduction through the control of lipids and hypertension, smoking cessation, and utilizing aspirin therapy; and metabolic risk reduction through control of glycemia. Such care requires appropriate goal setting,regular complications monitoring, dietary and exercise modifications, medications, appropriate self-monitoring of blood glucose (SMBG), and laboratory assessment. Focus on glucose alone does notprovide adequate treatment for patients with diabetes mellitus. Treatment involves multiple goals(glycemia, lipids, BP).

The main principles of DM therapy.

1. Maintenance of metabolic status at normal level or as close to normal as possible (especiallyblood glucose and lipid concentration).
2. Achievement and maintenance of normal or reasonable body weight.
3. Maintenance (preservation) of working capacity.
4. Prophylaxis of acute and chronic complications.

Treatment of DM must be individualized and includes:

1. Diet.

2. Oral hypoglycemic agents or insulin (indications for each vary with the type of DM andseverity of the disease).
3. Exercise program.
4. Phytotherapy (plant's therapy).
5. Nontraditional methods of treatment.
6. Education of the patients about the nature of the disease, the importance of its control, all aspects of self-management and routine practices to minimize the development or severity of the diabetes' complications. Physician has to educate, motivate and monitor progress.Patient must understand the importance of differing life-style.

DIET

is the keystone of the treatment of the DM.

Criteria of DM compensation:

Indexes	***Level of compensation***		
	good	***sufficient***	***insufficient***
Fasting glycaemia (mmol/l)	4,4 – 6,7	< 7,8	> 7,8
2 hours after meals	4,4 –- 8,0	< 10,0	> 10,0
Glucosurea (%)	0	0,5	> 0,5
Hb Alc (%)	< 6,5	6,5 – 8	> 8
Cholesterol (mmol/l)	< 5,0	5,0 – 6,5	> 6,5
Triglycerides (mmol/l)	< 1,7	1,7 – 2,2	> 2,2
HDL (mmol/l)	> 1,1	0,9 – 1,1	< 0,9
Body mass index (kg/m^2)	males < 25 females < 24	< 27 < 26	> 27 > 26
Blood pressure	< 135/85	< 160/95	> 160/95

The main principles of diet.

1. Balanced diet (diet should include physiologic meal components: carbohydrate comprises 50 –60 % of total calories, fat – 24 – 25 % and protein – 16 – 15 %).
2. Normal-calorie diet in patients with Type I DM (35-50 kcal/kg of ideal weight (weight = height-100)) and low-calorie diet in obese persons (mostly in patients with type II DM (20 – 25 kcal/kg of ideal weight)). We try to decrease weight in obese patients on 1-2 kg/month by such diet. (Obesity leads to insensitivity of muscle and adipose tissue to insulin, presumable as theresult of decreased binding of insulin to its plasma membrane receptor. Hyperglycemia is the face of increased insulin secretion and hyperlipoproteinemia are secondary to this abnormality.The defect in insulin binding and secretion is corrected by weight reduction.)

3. Regimen has to consist of 4 – 5 – 6 small feedings a day. (The most frequent regimenconsists of 4 feedings a day, in which breakfast comprises 30 % of total calories, dinner – 40%, lunch – 10 %, supper – 20 %. Sometimes patients need second breakfast (when they have atendency to develop hypoglycemia). In such case it comprises 15 % of the total calories and wedecrease the quantity of calories of the first breakfast and dinner).
4. Exclusion of high-calorie carbohydrates (sugar, biscuits, white bread, alcohol).
5. Increasing the quantity of high fiber-containing foods (fruits (exclusion: banana, grapes),vegetables, cereal grains, whole grain flours, bran. Patients need 40 g fibers per day.
6. Limiting of meat fat, butter, margarine in diet, decrease red and brown meats, increase poultryand fish, encourage skim milk-based cheeses. Should be used skim or low-fat milk, not morethan 2 – 3 eggs weekly.
7. Alcohol should be avoided as much as possible because it constitutes a source of additional calories, it may worsen hyperglycemia, and it may potentiate the hypoglycemic effects of insulin and oral hypoglycemic agents.
8. Sometimes (mostly in obese diabetics) achievement and maintenance of normal body weight may be enough to eliminate the need for oral hypoglycemic agents or insulin. So, the diet should be planned in such way that the patient can follow it for the rest of his or her life without starving or becoming malnourished.

ORAL HYPOGLYCEMIC AGENTS.

Inadequate control of hyperglycemia by the diet and exercise interventions suggests glucose-lowering agents.

Oral hypoglycemic agents are useful only in chronic management of patients with Type II DM. The most commonly used are: the sulfanilureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones (potentiation of insulin action, glitazones), glinides (non-sulfanylureas insulinstimulators) etc.

Sulfonylureas are time-honored insulin secretagogues (ie, oral hypoglycemic agents) and probably have the greatest efficacy for glycemic lowering of any of the oral agents.

Meglitinides are much more short-acting insulin secretagogues than sulfonylureas, with pre-prandial dosing potentially achieving more physiologic insulin release and less risk for hypoglycemia. Their glycemic efficacy is possibly less than sulfonylureas.

Biguanides are old agents that reduce hepatic glucose production and may have a minor effect on glucose utilization in the periphery (antihyperglycemics, hepatic insulin sensitizers). Insulin must be present for biguanides to work. Metformin has been used successfully for the last few years with very low risk. It is the only oral diabetes drug that reliably facilitates modest weight loss. It was successful at reducing macrovascular disease endpoints in patients who were obese. The results

with concomitant sulfonylurea in heterogeneous population were conflicting, but overall, this drug probably improves macrovascular risk.
Alpha-glucosidase inhibitors prolong the absorption of carbohydrates. Their induction of flatulence greatly limits their use. These agents should be titrated slowly to reduce gastrointestinal intolerance.Their effect on glycemic control is modest, affecting primarily postprandial glycemic excursions.
Thiazolidinediones (glitazones) are the new class of drugs that reduce insulin resistance in the periphery (sensitize muscle and fat to the actions of insulin) and perhaps to a small degree in the liver (insulin sensitizers, antihyperglycemic drugs). They activate peroxisome proliferator–activatedreceptor (PPAR) gamma, a nuclear transcription factor, that is important in fat cell differentiation and fatty acid metabolism. Their major action is probably actually fat redistribution. These drugs may have beta cell preservation properties. Their glycemic efficacy is moderate, between alpha-glucosidase inhibitors and sulfonylureas. They are the most expensive oral agents.
Glitazones require the presence of insulin to work. They generally decrease triglycerides andincrease HDL-C, but they increase LDL-C (perhaps large buoyant LDL, which may be less atherogenic). While these drugs have many desirable effects on inflammation and the vasculature, edema and weight gain may be problematic adverse effects in patients taking glitazones, especially when administered with insulin or insulin secretagogues. These effects may induce or worsencongestive heart failure in patients with left ventricular compromise and occasionally in patients with normal left ventricular function. A recently recognized possible side effect of these agents is macular edema. Recent animal work suggests that concomitant therapy with the diuretic amiloride may reduce fluid retention related to glitazone therapy.
Incretin-mimetic, exenatide stimulates glucose-dependent insulin release (as opposed to oral insulin secretagogues, which may cause non–glucose-dependent insulin release and hypoglycemia), as wellas reducing glucagon and slowing gastric emptying. Animal data suggest that this drug preventsbeta cell apoptosis and may in time restore beta cell mass. This latter property, if proven in humans,would have tremendous therapeutic potential. This drug requires twice daily injections and is more expensive than high-dose glitazone therapy. It has the advantage of ease titration (only twopossible doses, with most patients progressing to the higher dose) than insulin.

*Sulfonylurea*s include:

- the first generation: Tolbutamide, Chlorpropamide, Tolazemide, Acetohexamide (now are not used in treatment of diabetics);
- the second generation: Glibenclamide (Maninil (3,5 mg, 5 mg), Daonil (5 mg)), Glipizide(Glurenorm (0,03), Minidiab (5 mg)), Gliclazide (Diamicron (0,08)), Gliquidon;
- the third generation: Glimepiride (Amaryl (1 mg, 2 mg,4 mg)).

Action:

1) influence on the pancreatic gland:
   - increasing of the P-cells sensitivity to the glucose and as a result higher secretion of glucose;
   - stimulation of the exocytosis of insulin by insulocytes;
2) nonpancreatic influence:
   - increasing number of the receptors to insulin;
   - normalization of receptors' sensitivity to insulin;
   - increasing of glucose transportation inside muscle cells;
   - stimulation of glycogen synthesis;
   - decreasing of glycogenolysis and glyconeogenesis;
   - decreasing of glucagon secretion and others.

Drugs	***Mg in 1 tabl.***	***Daily dose***	***Duration of action***	***Peculiarities***
2nd generation drugs (mg)				
Glibenclamid (Maninil, Euglucan, Daonil, Glinil, Gilamat, Gliben, Glucoven)	1; 1,75; 3,5; 5	1-2	12-24	
Glibornurid (Glutrid)	25	25-75	8-12	
Gliquidon (Glurenorm, Beglicor)	30	30-120	8-12	Without hepato- and nephrotoxic effects, metabolism through the intestinum
Gliclazid (Diamicron, Diabeton, Predian, Glizid) Diabeton MR	80 30	80-320 30-120	8-12 24	Normalizes micro-circulation, blood aggregation
Glipizid (Minidiab, Glucontrol, Antidiab)	5	20	8-12	
3 rd generation drugs (mg)				
Glimepirid (Amaryl)	1-4	4	24	

Indications:

1. patients with Type II DM (over the age of 35 - 50 years) who do not suffer severe metabolic abnormalities (hyperglycemia), ketosis or hyperosmolality;
2. duration of diabetes less than 15 years.

Contraindications.

1. Type I DM;
2. blood diseases;
3. acute infections, heart, cerebral diseases;
4. trauma, major;
5. pregnant diabetics or lactation;
6. III - IV stages of angiopathy (but Glurenorm can be used in patients with chronic renal failure because of gastrointestinal tract excretion);
7. coma and precoma.

Side effects.

1. hypoglycemia (hypoglycemic effect of sulfanilureas will be the most obvious in 7 – 12 days from the beginning of treatment);

2. allergy;
3. influence on gastrointestinal tract (nausea and others);
4. leucopenia (decreasing of the quantity of white blood cells, platelets);
5. primary or secondary failure (primary failure defined as an inadequate response during the first month of treatment with maximum dosage, occurs in approximately 5 % of patients. Secondary failure is defined as a recurrence of hyperglycemia after an initial satisfactory response. Secondary failure may be due to non-adherence to either diet or sulfonylurea therapy, to disease progression, or to loss of efficacy of the agent).

Commonly used ***sulphonylureas:***

	Glibenclamide	***Gliclazide***	***Glipizide***
Duration of action	12 – 20 hours	10 – 12 hours	6 – 12 hours
Recommended dosage	2,5 – 5 mg/d	40 – 320 mg/d	2,0 – 40 mg/d
Route of excretion	Renal	Largely metabolized by liver, therefore can be used in renal failure	Largely metabolized by liver, therefore can be used in renal failure
Avoid	In renal failure, old patients because they are more prone to develop hypoglycemia (use short acting drugs in old age)	In hepatic impairment	In hepatic impairment

Biguanides include: Metformin (Siofor 500, 850 mg), Adebit, Bufarmin. (The usual starting dose is 500 mg 12 – hourly with meal increasing gradually to max 1 g 8–hourly.)

Commonly used biguanides

Name of drug	***Dose in 1 tabl.***	***Daily dose***	***Duration of action (hours)***
Metformin (Dianormet, Siofor, Metfogamma, Metfordar) Glucophage Forte	0,25; 0,5 0,5; 0,85	0,5–1,5 0,5–2,0	8–10 12–14
Buformin (Adebit) Buformin Retard	0,05 0,17	0,1–0,2 0,17–0,34	8–10 12–14

Action:

1) inhibition of gastrointestinal glucose absorption;
2) decreasing of glyconeogenesis, lipogenesis;
3) enhancing glucose transport into muscle cells;
4) increasing the quantity of insulin's receptors;
5) stimulation of anaerobic and partly aerobic glycolysis;
6) an anorexic effect.

Indications:

Obesed patients with Type II DM, with middle severity of the disease without ketosis. They can beused with the combination of sulfanilureas when sulfonylureas alone have proved inadequate to treat DM.

Contraindications:
1) heart and lung diseases with their insufficiency (chronic heart and lung failure);
2) status with hypoxemia;
3) acute and chronic liver and kidney diseases with decreased function;
4) pregnant diabetics, lactation;
5) old age;
6) alcoholism;
7) coma and precoma.

Side effects.
1) allergy;
2) gastrointestinal tract disorders;
3) lactoacidosis.

Alpha-glucosidase inhibitors:
Acarbosa (Glucobay 50, 100 mg) (It is taken with each meal, usually with first bolus of food).

Alpha-glucosidase inhibitors

Name of drug	***Dose in 1 tabl.***	***Daily dose***	***Duration of action (hours)***
Acarbosa (Glucobay, Glucor, Prandase, Precose)	0,05; 0,1	0,15–0,6	2,7–9,6
Miglitol	0,025; 0,05; 0,1	0,05–0,3	2–4
Guar Gum (Guarem)	5,0 (granules)	15–30	–

Action:
1) inhibition of gastrointestinal tract absorption (blocking of α-glucozidase);
2) lowering of postprandial glucose level (postprandial "spikes" in blood glucose are increasingly implicated as a major cause of cardiovascular complications);
3) partly reducing fasting glucose levels by indirectly stimulating insulin secretion in patients who retain β-cell function (and acarbose has a protective effect on β-cells).

Contraindications:

Chronic gastrointestinal disorders: pancreatitis, colitis, hepatitis.

Side effects: flatulence, abdominal bloating, diarrhea.

Non-sulfanylureas insulin stimulator.
Repaglinide (Novonorm 0,5 mg, 1 mg, 2 mg) (Starting dose is 0,5 mg 15 – 20 min before each meal, maximum dose is 4 mg before each meal (16mg/d)).
Nateglinid (Starlix 0,06; 0,12; 0,18).

Action:
- these drugs stimulate insulin production at meal times;
- very rapidly absorbed from the intestine and metabolized in liver;
- plasma half-life is less than 1 hour.

Indications:
can be used in elderly with Type 2 DM (due to short half-life) and in renal impairment (because it ismetabolized in liver).

Side effects:
hypoglycemia, transient elevation of liver enzymes, rash and visual disturbances.

Non-sulfanylureas insulin stimulators

Name of drug	***Dose in 1 tabl.***	***Daily dose***	***Duration of action (hours)***
Repaglinid (Novonorm, Roglid) (meglitinide analogs)	0,001; 0,002; 0,003; 0,004	0,004–0,009	3–4
Nateglinid (Starlix) (D-Phenilalanine-derivative)	0,06; 0,12; 0,18	0,18–0,54	1,5–3

Thiozolidindiones
Rosiglitazon (Avandia, Rosinorm) Dose in 1 tabl. 0,002; 0,004; 0,008
Pioglitazon (Actos, Pionorm) Dose in 1 tabl. 0,015; 0,03; 0,045

Commonly used thiozolidinediones:

Name of drug	*Dose in 1 tabl.*	*Daily dose*	*Duration of action (hours)*
Rosiglitazone (Avandia, Rosinorm)	0,002; 0,004; 0,008	0,004–0,008	Up to 24 hours
Pioglitazone (Actos, Pionorm)	0,015; 0,03; 0,045	0,015–0,03	

Action of thiozolidinediones:

- Agonist the receptors of the nucleus PPARγ of the fat, muscle tissues and liver;
- Increasing of the glucose passage to these tissues;
- Increasing of insulin synthesis in the b-cells;
- Increasing of the insulin amount;
- Increasing of glycogen synthesis in the liver;
- Decreasing of gluconeogenesis;
- Decreasing of triglycerides.

Indications to thiozolidinediones usage :

- Type 2 DM, when diet and exercises are no effective;
- Using with sulfanilureas, biguanides, insulin in case of their insufficient efficacy.

Contraindications to thiozolidinediones usage:

- Diabetic coma, precoma, ketoacidosis;
- Acute and chronic diseases of the liver;
- Heart failure;
- Pregnancy, lactation;
- Children, teenagers;
- Allergic reactions to the drug.

Side effects of thiozolidinediones:

- Hypoglycemic conditions (rarely);
- Peripheral edema;
- Anemia;
- Obesity.

Combined drugs: Glibomet consists of Glibenclamid 2,5 mg and Metformin 400 mg.

INSULIN

Insulin has been available for the treatment of patients with DM since 1921. For many years, the most commonly used preparations consisted of combination of pancreatic bovine and porcine insulin. Contamination of small amounts (2 to % percent) of other pancreatic hormones, such as glucagon, pro insulin, C peptide, somatostatin, and pancreatic polypeptide, was the rule. Subsequent purification have yielded purer (almost 100 %) preparations of beef insulin, pork insulin, or combination of two, with a biologic activity of 26 to 28 units/mg as compared to 22 to 24 units/mg for the older preparations. The most recent development has been the preparation of biosynthetic human insulin. Two procedures have been utilized. In the first, alanine in the 30 position of the B-chain of pork insulin is substituted enzymatically by threonine. The resulting "humanized pork" insulin has the amino acid sequence of human insulin (Actrapid, Monotard made by Novo-Nordisk). The second approach involves synthesis by Escherichia coli (E. Coli) by recombinant DNA technology. The hormone can be produced by single fermentation in which pro insulin is made first and then cleaved into insulin and C peptide, or by separate fermentation in which A and B peptide are synthesized first and then joined into insulin (Humulin, Lilly). Synthetic human insulin does not have great advantages over purified pork insulin, except for slightly faster onset of the action. Hypokalemia, C-peptide suppression, and secretion of epinephrine, cortisol, growth hormone and prolactine may be reduced with human insulin. The synthetic hormone has the potential to be less antigenic than the pork insulin. Causes of potential use for human insulin include resistance to exogenous insulin, beef or pork insulin allergy, lipodystrophy, gestational diabetes. Anticipated short-term administration, and newly diagnosed young diabetic patients.

A multitude of insulin preparations are available, and the major difference in their duration of action (Table). Figures on onset, peak and duration of action are applicable to normal non-insulin-treated subjects.

Only short-acting insulin should be given intravenously; all the types can be injected subcutaneously.

<u>Indications for insulin therapy</u>

1. All patients with Type I DM.
2. Some patients with Type II DM:
   - uncontrolled diabetes by diet or oral hypoglycemic agents;
   - ketoacidosis, coma;
   - acute and chronic liver and kidneys disease with decreased function;
   - pregnancy and lactation;
   - II – IV stages of angiopathy;
   - infection diseases;
   - acute heart and cerebral diseases;
   - surgery.

Initiation and modification of insulin therapy to achieve diabetic control.

The daily insulin requirement in patients:

- on the first year of the disease is 0,3–0,5 unite of insulin per kilogram of body weight (0,5 – if the patient with ketosis or DKA);
- on the next years is 0,6–0,8–1,0 unite/ kg of body weight. We can use traditional or multiple component insulin program. The last is better (it is more physiologic).

Insulin preparations:

Group	*Preparations*	*Onset, h*	*Peak of action, h*	*Duration of action, h*
Ultra-short-acting (insulin analogues for rapid onset of insulin action)	Humalog Hovorapid	5 – 10 min.	0,5 – 2,5	3 – 4
Short-acting	Humodar R Actrapid HM Monodar R Actrapid MC Iletin	0,5 – 1,0	1 – 4	5 – 8
Intermediate-acting	Humodar B Protaphan HM Humulin L NPH Monotard MC	1 – 3	6 – 12	18 – 26
Long-acting	Ultratard HM Ultralong	4 – 8	14 – 20	20 – 36
	Glargine (Lantus) Levemir	24 h		
Combined preparations	Humodar C-15 Mixtard 30 HM Monodar C-30	0,5	Depends on quantity of components	

Basal secretion

It using three or four shots of short-acting insulin (1/3 of total daily dose) plus intermediate-acting(2/3 of total daily dose) insulin daily is started as soon as possible in an attempt to "rest" the damaged islet cells and help to "induce" a remission ("honey moon" phase).

Other advantages include the following:

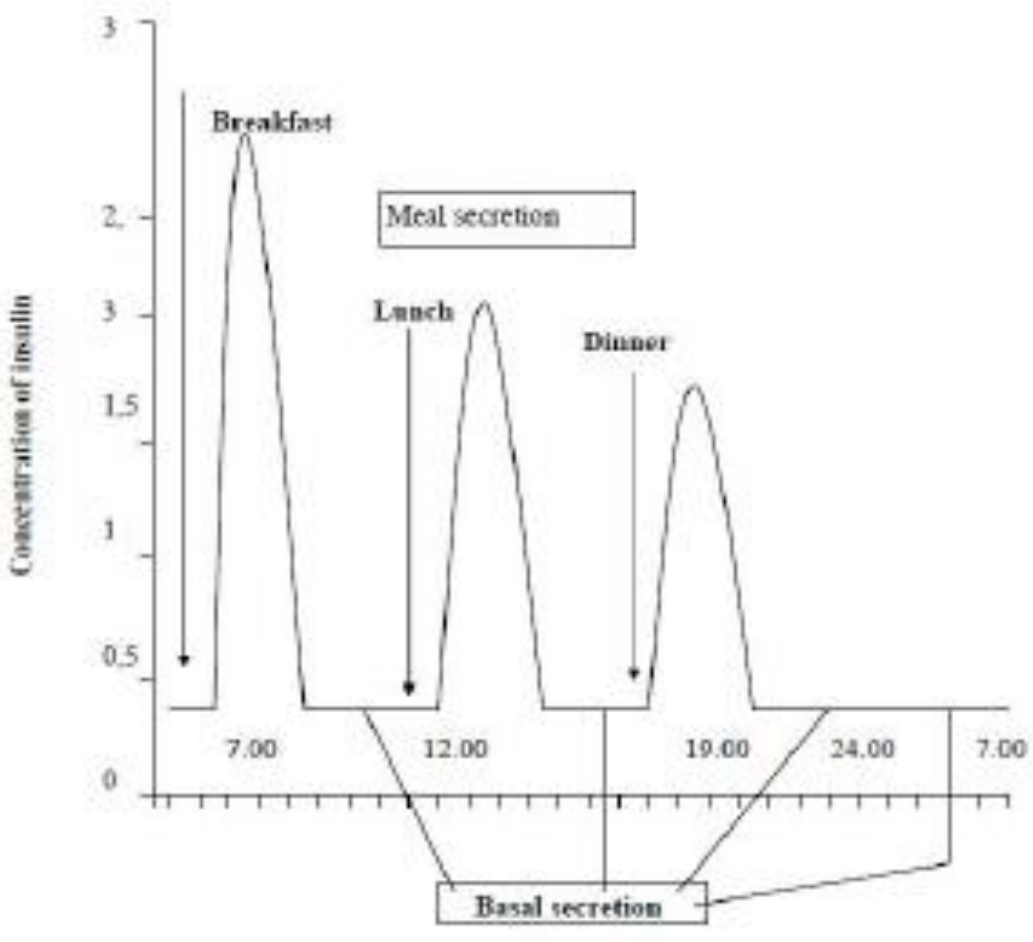
- hypoglycemic reactions may be decreased or prevented because smaller doses of insulin areneeded;
- more physiologic match of insulin to meals is achieved.

2/3 of the total daily dose we give before lunch, 1/3 in the evening and then make correction due to the glucose blood level. Insulin doses should be given 30 minutes before meal to allow for adequate absorption of regular insulin.

Other commonly used insulin treatment algorithms:

1. Single pre breakfast injection of intermediate-acting insulin.
2. Intermediate-acting insulin: pre breakfast injection of 2/3 total daily dose, 1/3 of daily dose before dinner.
3. Combination of intermediate- and short-acting insulin:
   - single pre breakfast injection of 2/3 intermediate-acting + 1/3 of short-acting;
   - 2/3 – before breakfast, 1/3 – before dinner; 2/3 – intermediate-acting, 1/3 – short-acting.
4. Short-acting insulin 30 min before each meal and small dose of intermediate-acting insulin at bedtime.
5. Combination of long-acting (in pre breakfast time) and short-acting insulin (1/2 hour beforeeach meal.)

Secretion of insulin in health people



Some words about “honey moon” stage. It results from a partial recovery of islet-cell function (as measured by C-peptide). It occurs within 1 - 3 month after diagnosis and can last from weeks to few months during which time insulin requirements fall drastically to less than 0,3 units/kg/day and in some, to no requirement for insulin at all. Insulin administration, however, is not discontinued

during this time because of potential development of insulin allergy, as well as the need to reinforce the concept that IDDM is a lifelong illness without potential for true remission.

Some particularities of insulin therapy:

1. insulin acts faster when is administrated intravenously;
2) subcutaneous and intramuscular absorption of insulin is decreased in the dehydrated or hypotensive patients;
3) it is necessary to change the insulin injection site (because the absorption is more rapid from the new sites);
4) the most rapid absorption from the abdomen;
5) exercises accelerate insulin absorption (before planned exercise program patient has to decrease insulin dose or take more caloric diet).

Insulin is stable at room temperature, but refrigeration of the vial is recommended until it is used.

Future directions in improving glycemic control:

- nasal insulin preparations;
  pancreatic transplantation;
- islet replacement therapy;
- genetically engineered pseudo-beta-cells.

Side effects (complications) of insulin therapy.

1. Hypoglycemia.

This complication represents insulin excess and it can occur at any time-frequently at night (common symptom: early-morning headache).

Precipitating factors:

- irregular ingesting of food;
- extreme activity;
- alcohol ingestion;
- drug interaction;
- liver or renal disease;
- hypopituitarism;
- adrenal insufficiency.

Treatment (preventing coma):

- to eat candy or to drink sweet orange juice (when the symptoms develop);
- to receive intravenous glucose;
- 1 mg of glucagon administrated subcutaneously;
- gradual reduction of insulin dose in future.

Somogyi effect (Somogyi phenomenon, rebound effect). It is caused by overinsulinization: hyperglycemia proceeded by insulin – induced hypoglycemia. Hypoglycemia is the cause of increases secretion of antagonists of insulin (glucagon,

epinephrine, cortisol, growth hormone), which inhibit insulin secretion and increase glucose output by the liver (as a result of the stimulation of glucogenolysis and glucogenesis).

Treatment: gradual reduction of insulin dose.
Dawn phenomenon. Many patients with Type I DM demonstrate an early morning (4 – 8 a.m.) rise in glucose level, because of activation of insulin antagonists hormones. It may be confused with the Somogyi phenomenon. Sampling of glucose level throughout at night might help differentiate these two conditions.

Treatment: some have recommended an earlier injection in the morning (5 – 6 a.m.), and most suggest a late evening (before bedtime) injection of intermediate-acting insulin.

2. Allergic reactions.
These include burning and itching at the site of insulin injection; skin rash; purpura and anaphylactic reactions.

Treatment:
- antihistamines;
- changing of standard insulin to pure pork insulin or to human insulin;
- at extreme cases – glucocorticoids.

3. Insulin resistance.
Clinical status characterized by insulin resistance:
- obesity;
- therapy with oral contraceptives;
- glucocorticoid therapy;
- acromegaly;
- Cushing's syndrome;
- acanthosis nigricans;
- chronic liver or renal disease.

Non-true insulin resistance may be caused by long-time injections of insulin into the one site.

4. Lipodystrophy.
It is atrophy or hypertrophy of the adipose tissue, which occurs at the site of insulin injection.

Treatment:
- changing the site of injection;
- usage of human insulin.

Exercise program.

Exercise is an excellent adjunct to diet therapy, but it is very ineffective when used as the sole weight-reducing modality.
Exercises must be clearly planned and depend on patient's abilities and the physical condition,exclusion of the competition's elements.
Exercises may be valuable adjunct to the management of the DM by:

- lowering blood glucose concentration;
- decreasing insulin requirements;
- potentiation the beneficial effects of diet and other therapy.

To prevent hypoglycemia, patients should carefully monitor glucose level and taking of insulin. Mostly they need to reduce the insulin dosage by 20 – 25 % on the day that strenuous exercises are planned.

Plant's therapy (phytotherapy).

1) hypoglycemic action;
2) treatment of chronic diabetic complications;
3) influence on the immune reactivity.

Patient's education.

1. the nature of DM and importance of metabolic control;
2. the principles and importance of good nutrition and reasonable exercise program;
3. the principles of adequate foot, dental and skin care;
4. treatment of DM during the periods of illness;
5. techniques of insulin administration and measurement of urine and blood glucose level (if taking insulin);
6. recognition of hypoglycemia, its causes and methods of prevention;
7. an importance of general and specific measures to minimize diabetic complications and maintain of good overall health.

Treatment of long-term complications.

The main principle: adequate metabolic control.

<u>Diabetic retinopathy.</u>

1) careful ophthalmologic examination (at least yearly) by ophthalmologist experienced with diabetes;
2) non-proliferative retinopathy:
   - anabolic agents (nerabol 5 mg, nerabolil 1mg/week 1,5 – 2 month, retabolil 1ml/3 weeks 3 – 6times);
   - hypocholesterol agents (atorvastatin, rosuvastatin);
   - antioxydative therapy (emoxipin, trental);
   - vitamins A,B,E,PP;
   - anticoagulants;
3) pre-proliferative or proliferative retinopathy: treatment by photocoagulation.

Diabetic nephropathy.

1) low-protein diet (less than 40 g of protein daily);
2) inhibitors of ACF (lizinopril);
3) hypotensive therapy;
4) hemodyalisis, kidney's transplantation.

Diabetic angiopathy of lower extremities.

1) patient education in foot care; early detection of risk factors, ulcers, infections, calluses,exposed nails, diminished pulses, deformities;
2) anticoagulants;
3) preparations for improvement blood circulation.

Diabetic neuropathy.

1) inhibitors of aldose reductase (sorbinil), multivitamins, phenytoin, anticonvulsants (carbamazepin, gabapentin),antidepressants(amitriptyline);
2) physiotherapy (inductotermia, magnetic-laser therapy and others).

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