Therapy of diabetes mellitus/PGS

Therapy of DM

The main purpose of the diabetes treatment is to achieve the long-term normoglycemia or at least to get as close to its rates as possible (www.diab.cz). The treatment of the every patient with diabetes must always include non-pharmacological measures, such as the selected diet and physical activity considering the age, type of the diabetes, patient's body mass and the presence of the other associated complications. According to the situation, we select the diabetic diets with 175 g, 200 g or 225 g of sugars or the reducing diets (svačina a spol., 2008). Physical activity (for example walking for at least 30 minutes a day) is the essential part of the treatment. Pharmacological treatment differs according to the type of diabetes (Škrha, 2009). Type I diabetes requires insulin treatment from the beginning. Therapy of the type II diabetes immediately begins with metformin treatment together with lifestyle measurements. The further procedures are mentioned below. The self-evident part of the patient's complex treatment is therapy of the associated diseases.

Treatment plan for the type I DM

This includes an individual diet regimen (regulated food consumption) accompanied by the appropriate lifestyle (everyday physical activity and the exclusion of smoking), targeted education of the patient and their family members, insulin treatment and therapy of the related diseases. The physiological basis of insulin treatment is an intensive insulin regimen with insulin application at least three times a day. In these regimens are combined short-acting types of insulin, which are used before the main dishes, and one or two doses of long-acting types of insulin, which at least partially imitate physiological insulin secretion (so-called prandial and basal insulin). In indicated cases it's necessary to think about an insulin pump application.

An Integral part of the diabetes type I treatment is glycemia self-monitoring (self-control), which is accomplished by the patient with help of the glycemic profiles and particular glycemia rates. The treatment of type I diabetes is provided either by a diabetologist or an internal medicine physician with relevant erudition. The treatment plan for type 2 dm is now recommended: immediately after diagnosis simultaneously with non-pharmacological measures to start the metformin treatment and add the others PGS in combination with it.

If the combination of all oral antidiabetics and all measures is not enough to reach the required diabetes compensation, it's necessary to think about an appropriate insulin treatment. The part of the therapy is an individually suggested self-control of the glycemia. Controls of the patient with type II DM take place every 3-6 months, in case if the patient's condition doesn't require the other frequency. The details are mentioned in standards of medical care in type II diabetes (www.diab.cz).

Peroral antidiabetics

• biguanides (metformin) • derivatives of the sulfonylurea (glimepirid, gliklazid, gliquidon, glipizid and glibenclamid) • glinids (repaglinid) • substances with the incretin effect (exenatid, liraglutid, vildagliptin, sitagliptin) • thiazolidinediones (rosiglitazone, pioglitazone) • alpha-glucosidase inhibitors (akarbóza)

The main principle is to begin the treatment with the lower doses. If the effect is insufficient, the dose are increased, however the usage of a combination of antibiotics with different mechanism of action is more prefered than increasing the dose to its maximum. Biguanides (bg) effect particularly the liver insulin resistance, less the peripheral insulin resistance. The only deputy of this group that is used in clinical practice is metformin, which has the lowest risk of lactate acidosis as the treatment complication. It's applicated in one or two doses per day and it doesn't cause the hypoglycemia. There are also fixed combinations su+bG (glibenclamid a metformin). In patients with type II DM it's appropriate to begin the metformin monotherapy with the application of the lowest dose once or twice a day. The chronic maintenance dose usually doesn't exceed 1700–2000 mg per day. If the metmorfin monotherapy doesn't reach the satisfying compensation, it's combinated with an antidiabetic agent of the other type, beginning with the lowest dose. Metmorfin if contraindicated in case of the renal insufficiency (creatinine above 130 umol/l), heart failure, dehydration and hypoxia or shock conditions. There are no age restrictions for contraindication of metformin treatment.

Sulfonylurea derivatives (su) increase the secretion of the insulin. They're added when metformin therapy is not enough for the required effect. In practice are used the second generation medicaments which differ in effect's rapidity, duration of the hypoglycemia, way of the elimination and the side effects. Here belong glimepirid, gliklazid, gliquidon, glipizid and glibenclamid. Su are given in the smallest possible doses once or twice a day. The main risk of the treatment is hypoglycemia, the treatment is also accompanied by the weight gain (less in glimepirid and the most in glibenclamid treatment).

In treatment of patients with BMI below 25 kg/m2 are recommended rather short-acting medications (glipizide, gliclazide), which are also added in combination with primarily applicated metformin. Treatments begins with the lowest dose and in case of the insufficient compensation after a couple of weeks the dose increases (usually by two or three times). If patient's condition is not satisfactory, it's possible to choose longer-acting su (for example glibenclamide), but still more preferable are other PGS, particularly glimepiride or gliclazide. In younger DM type II patients with risk of cardiovascular disease is more convenient to use glimepiride, which in addition has lower risk of hypoglycemia and more suitable dosage once a day. Gliclazide is appropriate particularly in younger patients with manifestation of the DM before 55 years of life. In chronic therapy it is not recommended to exceed the moderate doses of PGS!!! (Glibenclamide 10 mg, Glipizide 10 mg, Gliclazide 160 mg, Gliclazide mR 60 mg, Glimepiride 2 mg). In derivative therapy it's important to pay attention to their side effects and drug interactions of su (especially in elder polymorbid patients). Increasement of the peroral antidiabetic dose in patient with glycemia rates about 15 mmol/l won't have any further effect, it's necessary to think of the fundamental change of the therapy. Glinids which affect the prandial glycemia increasement are fast-acting and have relatively short effect on insulin secretion, their effect is also more physiological than sulfonylurea derivatives, because they don't cause protracted hyperinsulinemia. They're applied before the main dishes three times a day, for example repaglinide 0,5 mg, 1 mg a 2 mg pill. Antidiabetics with incretin effect are applicated as derivatives or analogs of the glp-1 (glucagon like peptide-1), here belong exenatide or liraglutide (so-called incretin mimetics), or dipeptidyl peptidase IV inhibitors (dPP iv), which physiologically inactivates GlP-1 (so-called gliptins, for example vildagliptin and sitagliptin). This prospective group of medications improves insulin secretion by the glucose-dependent b-cell and has a lot of other effects (for example slower gastric evacuation, appetite suppression and so on). Medications are applicated in metformin or sulfonylurea derivatives combination therapy. Thiazolidinediones (glitazones) decrease insulin resistance, insulin secretion itself is not affected. Rosiglitazone (4 mg, 8 mg) or pioglitazone (15 mg, 30 mg tbl.) are applicated in combination therapy with metformin or sulfonylurea derivatives. In monotherapy they're not used. In treatment it can cause fluid retention, that's why glitazones are not applicated in patients with heart failure, edema and in pregnancy. This group of medicamentations usually has an amount of effects, many of them haven't been explained yet, and that is the reason why it's recommended to observe the patient consistently while using these medications.

Insulin analogs

insulin analogs have been used more in the treatment of diabetes together with humalog insulins. They are either short-acting (insulin lispro, insulin aspart or glulisine), or long-acting (insulin glargine or insulin detemir). The first group of insulin analogues affects the postprandial glycemia faster and doesn't cause the hyperinsulinemia as much as humalog fast-acting insulin, whereas the second group of insulins leads to the balanced insulin level (no peak time insulin), which is not linked with hypoglycemia like nPH insulins. Both effects are appropriately used in patients with diabetes, whose humalog insulin treatment is not successful enough. Treatment with insulin analogs in type II DM patients has the same rule as humalog insulin treatment - it should be combined with metformin treatment if it's possible. Range of studies proved that using of insulin analogs in treatment doesn't cause the major improvement of HbA1c rates, however it considerably decreases the risk of hypoglycemia at the same compensation level, that has both medical and economic consequences. Insulin analogs make possible the improvement of DM compensation, because almost every DM patient has evident or hidden concern with hypoglycemia, which is the most crucial barrier to the achievement of the target glycemia and glycated hemoglobin rates. The matter of course is the application of both humalog insulins and analogs with help of insulin pump applicators, which is the most accurate and considerate method of insulin application.

Treatment plan for the type II DM

If neither the usual metformin therapy, nor the subsequent combination with sulphonylurea derivatives is not effective enough (or it is not possible to realize the therapy due to the metformin intolerance), it's necessary either to think of the combination with insulin, or to verify the efficacy of combination therapy with thiazolidinedione (glitazone) or newly with incretin mimetic (including the dPP-iv inhibitors). Choice of the insulin medication (humalog insulin or analog, short- or long-acting), its dosage and its distribution during the day depends on the reached resulting rates of DM compensation. Start and the progress of the insulin therapy is determined either by the diabetologist or the internist. Beginning of the insulin treatment is also necessary in acute situations (infection, surgery, injury). In case of the long-term decompensation of the type II DM, when the PGS fail, it's necessary to pick the insulin treatment or to apply insulin analogs in combination with the PGS.

Algorithm of the type II DM treatment and dispensarization

(Consensus of the american and european diabetic association 2008)

if Hba1c levels are not under 5 % in three months, we begin the other alternative treatment. We don't use metformin in case of its contraindication or intolerance.

Targets of the DM therapy

1. to normalize glycemia or at least to approximate its physiological rates

2. to prevent the development of the early or late complications

3. at the same time to treat the other related diseases and eventually to prevent them

Indicators of quality of the DM treatment

According to the achieved rates of the particular observed parameters it is possible to assess the compensation level as excellent, acceptable or unsatisfactory.

TABLE

glycemia in the capillary blood excellent acceptable unsatisfactory

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fasting / before food consumption (mmol/l) 4–6,0 6,0–7,0 > 7,0
1–2 hours after food consumption (mmol/l) 5–7,5 7,5–9,0 > 9,0
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Glycated hemoglobin Hba1c (%) * (according to iFcc, od 1. 1. 2004) (according to dcct) <4.5 <6.5 4.5–6.0 6.5–7.5> 6.0> 7 , 5

- according to DCCT (Diabetes Control and Complications Trial) we follow the recommendation of IFCC (International Federation of Clinical Chemistry) used in Czech Republic (watch also www.diab.cz).

the main indicator of the successful DM compensation is either average glycemia assessed by glycated Hb (Hba1c), or postprandial glycemia.

if the target rates of the postprandial glycemia and glycated Hb are not achieved in monotherapy - or PGS combination therapy in 6 months, it's appropriate to consult the patient with diabetologist about further treatment.

Recommendations for levels of compensation

According to the results of the last studies (especially the ACCORD study), experts recommend to distinguish the patients with type II DM by the level of the risk following the intensive diabetes treatment (predisposition to hypoglycemia and presence of the other complications, particularly coronary artery disease) and also by the potential contribution of the compensation to the patient. That's why it's appropriate to adapt the therapy targets according to the patient's profile. DM patients with low risk should achieve the higher compensation level (Hba1c up to 4,5 %), whereas high risk patients can have their target ranks of Hba1c about 5,3–6,0 % according to ifCC!

Therapy of the related diseases in type II DM

1. treatment of arterial hypertension: achievement of the target rates of the blood pressure < 130/80 mmHg by the monotherapy or more often by the combination of the antihypertensive medications with different mechanism of action. The most preferable are acei and sartans, Ca channel blockers, then centrally-acting antihypertensive drugs, beta-blockers and diuretics. The most preferable antihypertensive medications are positive or neutral inotropic ones, here belong particularly the first three mentioned types of the aH.

2. treatment of dyslipidemia: In case of predominant hypercholesterolemia use statins, in hypertriglyceridemia - application of the fibrates. To achieve dyslipidemia compensation it is necessary to combine statin and fibrates therapy though.

3. treatment of obesity: in patients with bmi > 30,0 kg/m2 can be indicated sibutramine or lipase inhibitors (orlistat) in combination with regimen measures (diet and physical activity) and other combined pharmacotherapies.

4. treatment and prevention of the diabetic nephropathy (Ras inhibitors [angiotensin converting enzyme], sartans and aCei), consistent hypertension examination.

Check-up of the type II DM patient

Glycemia every check-up

Hba1c once in three months until the compensation of the DM, then once in six months

Blood pressure every check-up

serum lipids once in 6 months in treatment, once in two years in case of the normal rates

Weight or BMI every check-up

Na, K ,Cl , creatinine, uric acid once a year

tsH in case of suspected thyroid disease

urea chemical tests + sediment once a year

microalbuminuria/proteinuria once a year (repeat twice in case of positive result)

bacteriological tests of urea once every six months

lower extremities inspection every check-up

eye examination once a year

- the internal investigation is provided by the physician in preventive care examination once a year

ECG once a year

orientational neurological examination once a year

Internal examination is aimed at the great blood vessels damage and signs of ischemic heart disease, lower extremities and CNS (targeted anamnesis and the objective examination including the auscultation of the carotid arteries, femoral arteries and the palpation of the peripheral arteries). This finding during internal examination indicates of the need for further laboratory investigation (the complete blood count, enzymes and so on).

Damage of the target organs Poškození cílových orgánů respektive SOP

Subclinical organ damage and an interpretation of the results:

The finding of the borderline or mildly abnormal rates related to the kidney function should lead to more intensive diabetes and arterial hypertension treatment in order to reach as good level of compensation as it's possible.

• slight increase of the creatinine serum concentration (m 115–133, Ž 107–124 μmol/l) • low glomerular filtration rate (< 60 ml/min/1,73m2, ≤ 1,0 ml/s/1,73 m2) • microalbuminuria (30–300 mg/24 h or albumin/creatinine ratio m 2,5–25, Ž 3,0–30 g/mol creat.)

Target rates of lipids in patients with diabetes

(According to the common recommendations of nine czech expert associations for prevention of the coronary artery disease in adulthood, years 2005-2008)

Lipids target rates in DM patients

Total cholesterol < 4,5 mmol/l

LDL-cholesterol < 2,5 mmol/l

Triglycerides < 2,0 mmol/l

HDL-cholesterol > 1,0 mmol/l

In patients with high risk (diabetes + manifesting cardiovascular disease) is desirable to reach LDL-cholesterol rate < 2,0 mmol/l.

Pharmacotherapy of diabetic dyslipidemia

Hypercholesterolemia (↑ ldl-cholesterol) => Hgm Coa reductase inhibitors (statins) third generation fibrates biliary tract sequestrants.

Combined hyperlipidemia (↑ ldl + ↑ vldl) => Hmg Coa reductase inhibitors (statins) (in case of persisting hypertriglyceridemia fibrates in combination with statins) acipimox

Isolated hypertriglyceridemia =>(↑ vldl ± chylomicrons) fibrates acipimox omega 3 fish oils

- LDL – low-density lipoprotein; VLDL – very low-density lipoproteins

The prognosis is serious for all age groups. There is no "mild" diabetes. It's impossible to prevent macrovascular complications in DM II patients without medical intervention. Prognosis of the each patient with DM is worsen in case of kidney diseases (albuminuria, dysfunction, infection, renal insufficiency), which accelerate the development of the cardiovascular stroke. Proliferative retinopathy progressively decreases visual perception.

Preventive measures

High level of physical activity, weight reduction at least by 5–10 % and maintenance of this body mass, restriction of the animal fats consumption, restriction of the consumption of secondary processed meat (smoked meat, pastes, minced meat, fast food), dand reduction of juice intake also has a certain effect. Manifestation of DM is not connected with consumption of sugars. Risk of type II DM can be decreased by higher consumption of plant fats, nuts, fibres, coffee and fish meat. Pharmacotherapy plays a significant role in reducing the incidence of type 2 diabetes. DM manifestation is about 30 % lower in hypertonic patients treated with ace inhibitors and about 10–25 % lower in hypertonic patients treated with sartans and ace inhibitors. In obese non-diabetic patients or patients with glycemia disorder while fasting or with glucose tolerance disorder were accomplished the preventative medication tests with metformin, acarbose, orlistat, rosiglitazone amd pioglitazone. All these substances significantly decreased the manifestation of the type II DM. Type II DM is a disease which can be prevented; it's important to pay attention to the obese patients with diabetes in their family history. The best results in the prevention of DM in obese patients were achieved by the bariatric surgery, when DM risk decreases by 40 times. In patients with type II DM the disease can disappear in 90 % of the cases.

Qualification requirements

Treatment of the patients with an uncomplicated type II DM is provided by a general practitioner, internist or diabetologist in ordination with the required equipment and the ensured laboratory biochemical tests of blood and urea parametres in the accredited laboratory. The general practitioner must have the ensured connection with diabetes ordination. Patients with type I DM or complicated type II DM are treated by the diabetologist. Cooperation with neurology, eye, cardiac and angiosurgical department is self-evident.

Links

Related articles

- Diabetic coma / PGS (VPL)
- Diabetes mellitus / PGS (VPL)
- Diabetes mellitus / PGS therapy (VPL)
- Complications of diabetes mellitus / PGS (VPL)
- Diabetic foot / PGS (VPL)
- Prediabetes / PGS (VPL)

External links

- DP Diabetes mellitus novelizace 2009 (na www.svl.cz) (https://www.svl.cz/Files/nastenka/page_4771/Version1/Diabetes-meliitus.pdf)

Bibliography

- KAREN, Igor, et al. *Diabetes mellitus : doporučený diagnostický a léčebný postup pro všeobecné praktické lékaře* [online] . 1. edition. Praha : Společnost všeobecného lékařství ČLS JEP, 2009. Available from <https://www.svl.cz/Files/nastenka/page_4771/Version1/Diabetes-meliitus.pdf>. ISBN 978-80-86998-30-5.