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ANTIHYPERGLYCEMIC THERAPY FOR PATIENTS WITH DIABETES MELLITUS TYPE 2

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The article describes the main classes of oral antihyperglycemic drugs, the mechanism of action, administration details, indications and contraindications. The innovative incretin-directed therapy was also covered. Rational algorithms of patients' treatment with diabetes mellitus type 2 were presented.

KEY WORDS: diabetes mellitus type 2, oral antihyperglycemic drugs, biguanides, sulfonylurea medications, incretin mimetics

ЦУКРОЗНИЖУВАЛЬНА ТЕРАПІЯ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

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У статті розглянуті основні класи пероральних цукрознижувальних препаратів, механізм дії, показання та протипоказання до їх використання, особливості застосування. Висвітлена інноваційна інкретин-спрямована терапія. Наведено раціональні алгоритми лікування пацієнтів з цукровим діабетом 2 типу.

КЛЮЧОВІ СЛОВА: цукровий діабет 2 типу, пероральні цукрознижувальні препарати, бігуаніди, препарати сульфанілсечовини, інкетіноміметики

САХАРОСНИЖАЮЩАЯ ТЕРАПИЯ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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В статье рассмотрены основные классы пероральных сахароснижающих препаратов, механизм действия, показания и противопоказания к их использованию, особенности применения. Освещена инновационная инкретин-направленная терапия. Приведены рациональные алгоритмы лечения пациентов с сахарным диабетом 2 типа.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа, пероральные сахароснижающие препараты, бигуаниды, препараты сульфанилмочевины, инкретиномиметики

According to World Health Organization experts, in economically developed countries about 4 % of the population suffers from diabetes mellitus (DM) [1, 2]. Altogether 5-6 % of the population suffers from DM and every 10-15 years the number of diabetic patients is doubly increased [1, 3]. The epidemiology of diabetes in general is defined by DM type 2 (DM-2), as it is about 90-95 % of all sickness cases [1-4]. The control over the DM progression is a pressing question because DM is one of the most frequent causes of disability and patients' mortality (is ranked third after cancer and atherosclerosis). For patients with DM the life expectancy is reduced by 10-15 % [2, 3]. In the course of DM treatment there should be made some modifications in the patients' lifestyle such as nutritional care and physical activities, smoking cessation, reducing of alcohol ingestion or it renunciation, patient teaching, self-control, psychological support and glycemic control [1-5].

Oral antihyperglycemic drugs (OHGD) are assigned to patients with DM-2 in cases when dietary interventions and increasing of physical activities didn't lead to fasting glucemic goals [1, 3-5].

According to the mechanism of action the OHGD can be divided into main groups [3-6]: drugs that reduce insulin resistance – sensitizers; drugs that stimulate insulin release by B-cells – secretagogues; drugs that reduce intestinal glucose absorption; innovative drugs – innovative incretin-directed therapy (incretin mimetics).

1) Drugs that reduce insulin resistance include biguanides and thiazolidinediones (tab. 1) [3].

Table 1

Drugs that reduce insulin resistance – sensitizers

Drug	Daily dose, mg	Dosage frequency, mg per day	HbA1c Reduction, (%)	Characteristic
Biguanides				
Methylbiguanide (Metformin)	500-3000	1-3	1,0-2,0	Counter-indicative at: GFR < 60 ml/min/1,73m^2; in cases when creatinine >115 mole/l there is a risk of lactic acidosis
Thiazolidinediones (glitazone)				
Pioglitazone	15-45	1	0,5-1,4	Counter-indicative at: hepatic disorders; edema of any origin; HF I-IV FC; in combination with insulin's or nitrate intake; ketoacidosis; pregnancy and lactogenesis

Dimethylbiguanide – metformin is the only biguanide that is used at present.

Basic mechanisms of metformin's antihyperglycemic effect are caused by:

- increasing of peripheral glucose disposal (muscular tissue is in the first flight) by anaerobic glycolysis activation;
- decreasing hepatic glucose output;
- partly – by decreasing of jejunum's glucose absorption.

Metformin is a drug of the first-line therapy for patients with DM-2 and with body mass index (BMI) of 30 kg/m^2 or more, i.e. for overweight patients [5]. The metformin's usage for monotherapy is able to reduce HbA1c by 1.5 %. The initial metformin's daily dose is 500 mg (with food in the evening or for a night). Metformin's antihyperglycemic effect is most effective while the dose is 2000-2500 mg/d. Such indices are achieved by dose titration of metformin 500 mg weekly (to minimize adverse effects at intestinal tract) [1, 5-7]. In contrast to the sulfonylurea medications (SUs), metformin does not stimulate pancreas' insulin secretion and that's why doesn't lead to hypoglycemia progression. In other words, the metformin's effect isn't hypoglycemic but antihyperglycemic. Metformin has quite frequent but transient adverse effect such as diarrhea [3, 6-7]. Metformin's contraindications are: pregnancy and lactation, severe renal failure (GFR < 60 ml/ min/1 73 m2), severe hypoxia (heart failure III-IV function classes by NYHA classification, respiratory failure and anemia), alcohol abuse. Although metformin is just slightly lead to lactic acid accumulation (because of anaerobic glycolysis' hyperactivation), but the risk of lactic acidosis increases with renal failure. That's why metformin isn't recommended for patients with serum creatinine level > 115 mmoll/l. If it is necessary to make a radiographic contrast study, metformin should be temporarily put off due to the risk of contrast-media induced nephropathy [3, 5].

Thiazolidinediones (glitazone) have a favorable metabolic profile:

- decrease insulin resistance;
- low risk of hypoglycemia;
- hypolipidemic effect.

Rosiglitazone is forbidden to use and removed from sale because of close relationship between the drug intake and the increased rate of cardiovascular deaths [5, 7]. Pioglitazone – is the only acceptable pioglitazone. Glitazones are able to reduce HbA1c by 1.5 %. Pioglitazone can be added to OHGDs in cases when the OHGDs in the form of monotherapy was ineffective. A daily dose

of pioglitazone in the form of monotherapy is – 15-45 mg, as a part of combined therapy – 15-30 mg. Pioglitazone should be taken as a single dose without regard to timing of food ingestion.

Glitazones' adverse effects such as water retention and edema are more common in patients who receive TZDs with insulin. Patients with HV II – IV FC and those with hepatic impairment should not receive TZDs [3, 5-7].

2) Drugs that stimulate insulin release by B-cells.

This group includes SUs and meglitinids (glinides), which are mainly normalize a postprandial blood glucose. SUs are bind to specific receptors of pancreas' β-cells-surface that leads to closure of ATF-dependent potassium channels and cell membrane's depolarization that causes the calcium channels opening. Calcium inside β-cells causes degranulation and insulin release into the blood [3, 5, 6]. All the SUs are sulphonylurea derivatives and differ from each other by the type of additional conjugations, which were included to the main group, that define the SUs' pharmakokinetics and act habits (tab. 2).

Table 2

Drugs that stimulate insulin release by B cells – secretagogues

Drug	Daily dose, mg	Dosage frequency, mg per day	HbA1c Reduction, (%)	Characteristic
SUs				
Glibenclamid	2,5-20	1-2	1,0-2,0	Has the most pronounced antihyperglycemic effect
Micronized glibenclamid	1,75-14	1-2	«—»	
Glipizide	2,5-30	1-2	«—»	Low risk of hypoglycemia
Glipizide -retard	2,5-30	1	«—»	Drug effect - over a day
Glimepiride	1-8	1	«—»	Drug effect - over a day, wide therapeutic index
Gliclazide	80-240	1-3	«—»	The lowest risk of hypoglycemia, angioprotective effect
Gliclazide MR with modified release	30-120	1	«—»	Drug effect - over a day
Gliquidone	30-120	1-3	«—»	In 95 % of cases is secreted by intestinal tract, that allows to prescribe this drug for patients with early renal failure
Meglitinids (glinides)				
Repaglinide	0,5-16	3-4	0,5–1,5	Risk of weight gain
Nateglinide	120-480	3-4	«—»	Decreasing risk of hypoglycemia

According to the recommendations of International Diabetes Federation 2005, the SUs are drugs of the first-line therapy for patients with DM-2 and with BMI of 30 kg/m^2 or more. The SUs treatment is started with minimum dose and gradually under the glucose profile's control the dose is increasing. Antihyperglycemic therapy isn't recommended to start with SUs that have the highest risk of hypoglycemia progression, i.e. with glibenclamid [5-7]. In cases when chosen SUs are poorly effective it isn't recommended to use it in combination with other SUs or with glinides. SUs reduce HbA1c as effective as biguanides – by 1,5 %. A frequent adverse effect of SUs is hypoglycemia, that occurs in cases of overdose, accumulation (renal failure), carbohydrates' shortfall (meal absence) or

overrun (alcohol ingestion, physical activities). Glinides include repaglinide (a benzoic acid derivative) and nateglinide (a phenylalanine derivative) which stimulate insulin secretion like the SUs, although they bind to a different site within the sulfonylurea receptor. They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. As the result a blood glucose is briefly increasing. Glinides should be taken about 10-20 minutes before meals, 3-4 times per day. A daily dose of repaglinide is – 0,5-16 mg, nateglinide – 120-480 mg. Glinides' contraindications are similar to the SUs. Repaglinide is almost as effective as biguanides and SUs, decreasing HbA1c levels by 1,5 %. The risk of weight gain is similar to that for the SUs, but hypoglycemia may be less frequent, at least with nateglinide [3, 5-7].

3) Drugs that reduce intestinal glucose absorption – α-glucosidase inhibitors.

This group includes acarbose, which reversibly blocks α-glycosidase of jejunum. As the result, the polysaccharides' absorption slows down , the rate of resorption and glucose admission in the jejunum decreases and the postprandial blood glucose level reduces. The drug has no systemic effects, does not cause hypoglycemia and mainly reduces postprandial blood glucose. The drug is taken immediately before the meal. The initial daily dose is 150 mg and it should be taken three times per day. In the future it is possible to increase the dose up to 300 mg per day. In comparison with biguanides and SUs, acarbose is less effective in reducing blood glucose level. It is able to reduce the level of NbA1s by 0.5-0.8 %. The flatulence and diarrhea are the main adverse effects of acarbose. The main reason of such effects is admission of not absorbed carbohydrates to the colon. [3, 5-7].

4) Incretin mimetics.

Searching for the DM's optimum treatment, based on the study of a new regulating mechanism of glucose homeostasis, led to the creation of drugs with the incretin effect [5-8]. After a meal incretin-hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide (GLP) are synthesized in intestinal mucosa. Such hormones are easily destroyed (about 2-7 minutes) by dipeptidyl peptidase-4 enzyme (DPP-4) [8-10]. Incretins exert multiple effects on the exocrine pancreas, but their main mechanism is connected with potentiation of insulin release by B cells. The fundamental point is that the insulinotropic effect of GLP-1 is glucose-dependent. In other words, GLP-1 stimulates insulin secretion only with hyperglycemia, insulin stimulating effect is leveled down during the normalization of blood glucose level at least less than 6,0 mmol/l. Whereas, GIP with a glucose level above 7,8 mmol/l has a little effect on insulin secretion and doesn't suppress the glucagon synthesis [11]. In turn, GLP-1 is also suppressed glucagon secretion according to the blood glucose level. The physiological mechanism of insulin secretion «on demand» and glucose-dependent suppression of glucagon secretion under the action of GLP-1 prevents the progression of hypoglycemic states [10, 11]. One of the positive properties of GLP-1 is the fact that it affects the regulation of postprandial hyperglycemia by lowering the motor and secretory activity of the stomach and intestines. Moreover, in cases, when GLP-1 has an effect on nuclei in the hypothalamus, it promotes rapid saturation and, as a consequence, reduces body weight. The additional effects of GLP-1 are shown in the suppression of hepatic gluconeogenesis and glucose escape in muscle and adipose tissue (resolves insulin resistance of peripheral tissues). The experiments demonstrated that GLP-1 prevents the progression of osteoporosis and osteopenia [11]. Presumably GLP-1 has an additional advantage in terms of conservation mass of β-cells pancreas [8].

The effective investigation of incretin metabolic approach led to the creation of two drug groups (tab. 3):

1. Agonists of GLP-1 (aGLP-1);
2. Medications, that prevent the destruction of GLP-1, DPP-4 inhibitors (iDPP-4).

Incretin-mimetics took a worthy place in the treatment of patients with DM- 2 due to the following advantages: physiological mechanism of insulin secretion «on demand» with a low risk of hypoglycemia, glucose-dependent suppression of glucagon hypersecretion, the improving of beta-cell function, the ability to control body weight [11].

Table 3

Incretin-mimetics

Drug	Daily dose, mg	Dosage frequency	HbA1c reduction, (%)	Characteristic
aGLP-1				
Exenatide	0,5 – 1,0	1 – 2	1,5	Injected subdermally, there is no information on long-term efficacy and safety
Liraglutide	0,6 – 1,8	1	1,1 – 2,5	
iDPP-4				
Vildagliptin	100	1 – 2	0,5 – 1,4	Is not recommended in the cases when the activity of ALT or AST is increasing > 2,5 times; Dosage modification in moderate and severe renal failure
Sitagliptin	100	1	0,6 – 1,4	
Saxagliptin	5	1	0,7 – 0,8	
Linagliptin	5	1	0,4 – 1,2	Excreted mainly via the intestine, that's why there is no need of dosage modification according to the renal function

GLP-1 receptor agonists are injected subdermally the abdominal zone, femora or antibrachium. Exenatide is recommended to inject 2 times a day within 60 minutes, prior to breakfast and dinner. After a month of therapy the dose can be increased to 1,0 mg two times a day [5, 7, 11].

Liraglutide is a first analog of human GLP-1, is injected once a day. It does not cause hypoglycemia, reduces body weight (in overweight patients) and blood pressure. The initial dose of Liraglutide is 0,6 mg per day and can be increased to 1,2 mg in a week, but the excess more than 1.8 mg is not recommended. Patient's body weight is reduced to 4 kg during the aGLP-1's chronic administration. The most common adverse effects (30-40 % of patients) of this drugs group are nausea and vomiting, that have transient effect. It is contraindicated in case of renal failure (GFR less than 30 ml/min/1.73 m^2); liver function abnormality; cardiac failure of III-IV functional class. This drug should be carefully prescribed to patients with relapsing pancreatitis [7, 11].

The iDPP-4 ' medications are gaining popularity in the DM-2 treatment. Published research results shows the efficacy and safety of the iDPP-4, both as the monotherapy and in the combination with other antihyperglycemic drugs [5, 7, 9, 12, 13].

The iDPP- 4 class, in view of its efficacy and safety, was included to all current recommendations of the DM-2 treatment [5, 12-14]. Besides the proved antihyperglycemic effect, indisputable advantage of the iDPP-4, compared to the traditional drugs, is a minimum hypoglycemia's risk, lack of weight gain, that is especially important for patients with particular risk group. So, the iDPP-4 should be prescribed for overweight patients, patients with excess body weight and for elderly people with high hypoglycemia's risk. Upper respiratory infections (6,8 %), nasopharyngitis (4,5 %) and diarrhea(3,0 %) are the most frequent adverse effects during a chronic administration of DPP-4 inhibitors [5, 13, 14].

Drugs are not recommended for patients with severe renal (GFR less than 30 ml/min/1,73 m^2) and hepatic failure. The drug should be carefully prescribed for patients with anamnestic indications of relapsing pancreatitis. In general, the inhibitor therapy is assessed as a safe one, but the greatest benefits are for patients with high cardiovascular risk factors [5, 13-16]. The concept of the target achievements in the DM-2 treatment is changing with the rise of new antihyperglycemic drugs, their introduction into clinical practice and the data capture of formerly used medicines. As the result, there are regular renewals of international and national hypoglycemic therapy algorithms [5, 7, 13-17].

A joint algorithm of American Diabetic Association (ADA) and the European Association for the Study of Diabetes (EASD) is one of the most recognized international algorithms of DM-2 treatment, which was first proposed in 2006 and amended in 2009 [6, 7]. Due to this algorithm the DM-2 therapy is represented as two tiers: well-validated core therapies (tier 1) and less well-validated

therapies (tier 2). The aim of hypoglycemic therapy is to achieve and maintain the level of glycosylated hemoglobin (HbA1c) <7,0 % in all patients.

Tier 1: well-validated core therapies

Metformin and lifestyle interventions are recommended as the initial pharmacological therapy for patients with DM-2. If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve HbA1c >7 %, another antihyperglycemic medication (the SUs or basal insulin) should be added within 2–3 months of the initiation of therapy. Insulin is the more effective glycemia-lowering agent for patients with HbA1c >8.5 % or with symptoms to hyperglycemia. If glycaemic targets aren't achieved, the next step should be to start, or intensify insulin therapy.

Tier 2: less well-validated therapies

To a basis metformin therapy and lifestyle interventions may be added aGLP-1 or glitazone. If these interventions, after 3 months therapy, are not effective in achieving HbA1c target, the insulin therapy or addition of a sulfonylurea could be considered.

Weaknesses of ADA/EASD algorithm (2006, 2009) [5, 6, 7]:

1. One target level of HbA1c for all patients (< 7,0 %);
2. Basal control value of carbohydrate metabolism with a limited choice of initial therapy isn't taken into account;
3. High rate of therapy' s intensification;
4. There are no modern incretin-mimetics – iDPP-4.

The results of ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease-Preterax and Dimicron Modified Released Controlled Evaluation) and VADT (Veteran Affairs Diabetes Trial) study are demonstrated that factors such as age, risk of hypoglycemia and the presence of concomitant diseases need to be considered for every patient before choosing the individual HbA1c target level [5, 7]. The algorithm of the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE, 2009) takes into account the above disadvantages [7].

New AACE/ACE-2009 recommendations:

- choosing initial therapy, the HbA1c target level is taken into the account;
- there are modern incretin mimetics – iDPP-4;
- there noted that taking sulfonylureas is associated with a high risk of hypoglycaemia and during a long-term treatment its effectiveness decreases.

Due to AACE/ACE-2009 recommendations, the experts of the Russian Association of Endocrinologists (RAE) built up a Consensus for therapy optimization of DM-2 [5]. In the RAE recommendations the emphasis laid on individualization, safety and efficacy of treatment.

General provisions of RAE Consensus for initiation and intensification of DM-2 antihyperglycemic therapy [5]:

The individual glycemic control target's determination on HbA1c level (tab. 4).

Table 4

The individualized choice's algorithm of the HbA1c target level

Severe complicationsand/or risk of severehypoglycemia	**Age**		
	Juvenile	**Median**	**Elderly and/or LE* < 5 years**
Present	<6,5%	<7,0%	<7,5%
Epsent	<7,0	<7,5%	<8,0%

* life expectancy

In addition the doctor should pay attention the motivation and treatment compliance, interaction with already obtained drugs.

1. The stratification of treatment strategy depending on the HbA1c initial level.

Regardless of the HbA1c initial level, the first main recommendation is a lifestyle modification. But taking into account the low compliance to the non-drug treatment, it is necessary to prescribe the hypoglycemic therapy at the beginning of the disease.

If the initial HbAlc level is about 6,5-7,5 %, it is recommended to start with the monotherapy. But if HbA1c targets are not

achieved, it is necessary to prescribe the combined therapy, which includes 2 or 3 drugs.

If the initial HbAlc level is 7,6–9,0 % it is recommended to start with the combined therapy. If the treatment is not effective it is possible to combine three OHGDs or to conduct insulin therapy.

If the the initial HbAlc level is more than 9,0 % it is necessary to prescribe insulin as a monotherapy or in the combination with OHGDs. In the case of reaching HbA1c targets it is possible to start the treatment with tableted antihyperglycemic drug.

2. The ability to make allowances to previously prescribed therapy schemes.

It is recommended to measure therapy outcomes every 3 month, and, if it is necessary, to intensify therapy not later than 6 months, or in cases of patient's deterioration.

Therapeutic management with the initial HbA1c level 6.5-7.5%.

Before choosing the clinical management of the patient it is necessary to determine the individual target level of HbA1c (Table 4). If it is below the initial level for a particular patient, it is necessary to recommend the diet therapy and regular doctor's following up. In the case when the initial level of HbA1c is above the target, it is recommended to start with OHGD therapy.

Step 1 –therapy initiation.

First-line drugs: biguanides, the iDPP -4 or aGPP-1.

Metformin is the most studied in terms of efficiency and safety drug in monotherapy. It does not cause hypoglycaemia and weight gain. Therefore its prescribing to the overweight patients is justified. The drugs from iDPP-4 and aGPP-1 group also should be prescribed to the patients who need weight reducing, and individuals with a high risk of hypoglycaemia. The choice between first-line drugs depends on the risk of possible adverse effects of a particular patient.

Alternative medications for therapy initiating are: OHGD, glinides, glitazones, alpha-glucosidase inhibitors.

If the initial HbA1c level is 6,5–7,5 % OHGD , glinides are not considered as a first-line agents, because of hypoglycemia's risk. The OHGD and glinids' prescribing is justified in case when there are contraindications to first-line drugs. It can be prescribed to patients with normal body weight (lack of insulin secretion dominates). Pioglitazone can also be recommended to individuals with normal body weight without cardiovascular diseases, if taking the first-line drug is contraindicated.

If the initial HbA1c level is 6,5–7,5 %, insulin therapy is not prescribed as starting treatment. It is possible only in cases of suspected latent autoimmune diabetes in adults (LADA), when the insulin secretion deficiency symptoms are expressed (massive weight loss, thirst, polyuria).

If individual HbA1c targets are achieved or there is a decrease of HbA1c to more than 0.5 % for 6 months, it is necessary to follow the monotherapy option.

Step 2 - therapy intensification.

The step of therapy intensification can be started within 6 months from the monotherapy beginning, if the HbA1c target isn't achieved or it's decreasing is less than 0.5 %. At this step the combination of two complementary medicines is prescribed.

Rational combination of antihyperglycemic drugs:

- Metformin + the iDPP-4;
- Metformin + aGPP-1;
- Metformin + SUs or glinides.

These combinations reduce insulin resistance and at the same time stimulate the secretion of insulin. At the same time a combination of metformin + iDPP-4/aGPP-1 has a minimal risk of hypoglycemia and lack of weight gain, and the combination with aGPP-1 decreases its level. The prescribing of two fixed different drug combinations is a possible variant. If the targets of glycemic control are achieved, the chosen combination scheme of 2 antihyperglycemic drugs should be continued.

Step 3 - further therapy intensification.

If the double scheme proved to be ineffective, even using the most effective doses of both components, than it is necessary to start taking the triple combination, or adopt the insulin therapy. The decision on further intensification must be taken not later than 6 months from the start of step 2 beginning. Meformin continues to be a major component of any combination, even during the insulin therapy. At the triple combination, the second and third components can be incretin mimetics or SUs/glinides, in some cases, glitazones, except irrational schemes.

The list of irrational and/or unauthorized combinations of antihyperglycemic drugs:

1. SUs + glinides,

2. iDPP+ aGPP-1,
3. Two representatives of SUs,
4. Glitazones + insulin,
5. aGPP-1/iDPP-4 + glinides,
6. Short-acting insulin + SUs/aGPP-1/iDPP-4/glinides.

It is necessary to carry out the insulin therapy, if the three-part treatment is ineffective. If there are no metformin contraindications, the combination of metformin with insulin is quite safely. The iDDP-4 and aGPP-1 drugs can be taken only in combination with basal insulin. Taking glitazones in combination with insulin increases the risks of: edema, weight gain, and cardiac decompensation. So, the combination of these drugs isn't recommended. The combination of insulin with SUs or glinides is dangerous and can become a cause of hypoglycemia.

Therapeutic management with the initial HbA1c level 7,6–9,0 %.

Step 1 – therapy initiation.

If the target level of HbA1c is above the initial level, it is recommended to prescribe a minimum dose of medications with low risk of hypoglycemia (metformin and iDPP-4), in addition to diet therapy.

If the target level is below the initial HbA1c level, it is recommended to start therapy with a combination of two drugs, which act on various links of the DM-2 pathogenesis (insulin secretion and its sensitivity to peripheral tissues).

The combination of basic drug (Metformin) with iDPP-4 or aGPP is more appropriate For overweight patients, patients with excess body weight and high hypoglycemia's risk. For patients with more than 8.5 % NbA1c, that indicates the presence of serious decompensation of carbohydrate metabolism, the metformin combination with SUs or insulin is more appropriate. The other combinations are possible, but it depends on the individual drug tolerance profile, adverse effect and contra indications.

The chosen scheme of hypoglycemic therapy should be continued in case when the target level of HbA1c was achieved or decreased at more than 1,0 % from the initial level within six-month period.

Step 2 - therapy intensification

In case when HbA1c is<1,0%, the obtained therapy can be intensified after 6 months from its beginning or in case of the patient's deterioration it can be intensified even earlier. In such case it is recommended the 3 drugs' combination with the main component (metformin) and with possible insulin taking.

Step 3 - further therapy intensification.

It is recommended to start insulin therapy in case when within 6 months triple therapy the level of HbA1c wasn't decreased to the target level.

Therapeutic management with the initial HbA1c level more than 9,0 %.

Step 1 – therapy initiation.

If the patient has not previously received glucose-lowering therapy and has the initial HbA1c> 9 %, the glucose toxicity should be urgently removed by insulin treatment. If the level of HbA1c within 6 month insulin therapy decreases by more than 5 %, it is possible to start a 2-3 antidiabetic drugs combination.

If there are any strong indications of decompensation (progressive weight loss, polyuria, polydipsia), the alternative 2-3 components scheme can be prescribed even at onset of disease. The basis of such combinations should be the drug with a maximum insulin secretory capacity (DMC) and metformin (if there are no contraindications). The insulin should be prescribed, if the HbA1c target level is not reached. If within 6 months of insulin therapy the HbA1c level decreases less than 1.5 % or its targets will not be reached, insulin therapy should be intensified (steps 2, 3).

Thus, the RAE Consensus encourages to individualize the treatment of patients with DM-2, starting out from the initial state of metabolic control, choosing safe and effective therapy [5, 17].

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