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REVIEW ARTICLE

Glycemic control in diabetes mellitus: review of international studies of glucose-lowering drugs cardiological safety

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Summary

This review article observes the data about social and medical significance and dynamic prognosis for the next decade. It analyzes modern glucose-lowering drugs, their mechanism of action, efficacy and side effects. Big part of this article is concentrated on the review of clinical studies of lipid-lowering drugs cardiological safety. It demonstrates the results of 5 major international clinical studies dedicated to investigation of cardiological consequences of modern glucose-lowering drugs therapy. In general, not only efficacy but also safety of glucose-lowering drugs is important for their wide use

Keywords

Diabetes mellitus, cardiological safety, glucose-lowering drugs

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Diabetes mellitus: bases of social and medical significance

Diabetes mellitus(DM) is one of serious social and medical problems in developed and developing countries, that can be explained with its high occurrence, significance of complications and high costs of treatment and rehabilitation.

According with the World Health Organization (WHO), in 2014 there were 387 millions of people suffering from diabetes (8,3% of adult population), in 20 years this number is predicted to increase up to 600 millions. The biggest increase of diabetes mellitus frequency is expected for the countries of the South America, Africa, the Middle East, the South-East Asia, Russia and several CIS countries [1]. It is necessary to mention also the increase of risk factors (obesity, metabolic syndrome) that are the predictors of DM.

According with the results of Federal target program "Prevention and management of socially significant diseases in 2007-2012", 3,549 millions of patients with DM have been registered during this period. In 2014 this number had increased up to 3 964 889 persons, 91,4% of whom had DM 2 type [2]. The highest morbidity rate was detected in the Central and Volga federal districts: 224,6 and 227,0 per 100 000 of adult population. The lowest morbidity rate was registered in the North-Caucasian federal districts: 139,9 and 187,8 per 100 000 of adult population, respectively.

The data included in the Atlas of International Diabetes Federation indicate that 13% of total healthcare budged of the Russian Federation are used for the treatment of DM and its complications. In future it would be necessary to increase the costs of DM treatment in case of predicted growth of DM frequency [1].

It is known that the prognosis for the life of patients with DM 2 type depends on their gender, age and the presence of complications and correlates with the degree of disease's control. Cardiovascular diseases are the main cause of disability and mortality in DM patients. In particular, myocardial infarction (MI) is the cause of death of 50% of patients with DM 2 type [3]. frequent development of MI atypical forms like painless or syncopal ones is an important feature of MI course in DM, and it complicates its opportune diagnosis and considerably impairs the prognosis.

Constant growth of DM morbidity and its "rejuvenation" together with the high risk of complications development including the fatal ones highlight the significance of this problem and predetermine the necessity of multilateral approach in treatment and prevention.

Glycemic control: the review of glucose-lowering drugs

According with the results of prospective studies, glycemic control is one of important methods that reduce progression of DM and its complications. During the last years the spectrum of glucose-lowering drugs has significantly widened. Glycemic control drugs can be divided into four groups: 1) drugs stimulating insulin secretion – secretagogues (sulfonylurea derivatives, meglitinides, glucagone-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors); 2) drugs increasing the sensitivity to insulin – insulin sensitizers (biguanides, thiazolidinediones); 3) drugs inhibiting intestinal absorption of glucose (alpha-glucosidases inhibitors); 4) drugs decreasing glucose reabsorption in kidney - Sodium-glucose cotransporter 2 (SGLT2) inhibitors [4].

Sulfonylurea drugs, meglitinides and incretin mimetics (GLP-1 agonists and DPP-4 inhibitors) directly or indirectly increase endogenous insulin secretion. GLP-1 receptor agonists and DPP-4 inhibitors also have additional effects in gastrointestinal tract and brain that affects the sense of satiation (DPP-4 inhibitors have no effect on body weight, GLP-1 receptor agonists promote weight loss). Unlike sulfonylurea and meglitinides administration, in this case stimulation of insulin secretion has distinct glucose-dependent effect that doesn't increase the risk of hypoglycemia development [5].

Pioglitazone (thiazolidinediones group) is PPARg (Peroxisome proliferator activated receptor gamma type) agonist with the effect on PPARa (Peroxisome proliferator activated receptor alpha type) that decreases glucose concentration in blood reducing its production in liver and suppressing insulin-resistance, whereas metformin is a biguanide which reaches the same effects activating AMP-kinase.

Acarbose reduces glucose absorption in gastrointestinal tract (GIT), and SGLT2 inhibitors decrease glucose absorption in kidney's proximal tubules.

In DM 2 type metformin is the drug of the first line, particularly in case of obesity. The main problem of metformin treatment is lactate-acidosis, especially in case of impaired liver or kidney function. But several studies which involved particular cohorts of patients had comparably low frequency of lactate-acidosis [6]. Nevertheless, metformin is not recommended for patients with glomerular filtration rate (GFR) less than 50 ml/min [7]. Still there is no consent about this value that is considered extremely high. Guidelines of British National Institute for Clinical Excellence are

less restricted: it is allowed to use metformin if GFR is higher than 30 ml/min with the reduction of dose starting from GFR 45 ml/min.

Decrease of HbA1c levels is expected to be in the range of 0,5-1% after treatment with each peroral drug or subcutaneous administration of GLP-1 agonists as monotherapy, although it depends on DM duration and other individual factors. Combination of two and three drugs: metformin with one or two drugs that can be chosen from pioglitazone, sulfonylurea, incretin mimetics, meglitinide and glucose absorption inhibitors , is commonly recommended in case of disease progression [8]. In order to reach target glycemic levels, combined use of glucose-lowering drugs is recommended soon after the diagnosis is set. Early aggressive therapy seems to play some role in cardiovascular outcomes decrease, but it is still not investigated enough in prospective protocols.

Cardiovascular safety of glucose-lowering drugs

The question of glucose-lowering drugs safety is actively discussed since the appearance of information about adverse effects of rosiglitazone, especially in combination with other drugs. In general, 10-years observation after the end of the UKPDS study demonstrated that patients who received sulfonylurea drugs and insulin had decrease of MI risk down to 0,85 (95% confidence interval (CI) 0,74–0,97, p=0,01) and mortality risk down to 0,87 (95% CI 0,59–0,89, p=0,002). Although the UKPDS study demonstrated that metformin has advantages from the point of view of cardiovascular outcomes (because of this it obtained the recognition as the first line medicine for obesity and DM 2 type), it is important to notice generally insufficient evidence base of this opinion. There is a possibility that combination of metformin and sulfonylurea can provoke the development of severe consequences influencing morbidity and mortality. Nevertheless, the results of this meta-analysis consider advantages of long-term treatment with this drug in young patients [10].

Pioglitazone reduced the frequency of secondary composite endpoint for general mortality, fatal MI and stroke in the PROActive study (Relative risk (RR) 0,84, 95% CI 0,72–0,98; p=0,027) in patients with DM 2 type and high risk of macrovascular complications [11]. Since the primary outcomes in the PROActive study hadn't reached statistical significance, the interpretation of these results cannot be fully correct. Pioglitazone administration is linked with liquid retention due to indirect effect on kidney, that leads to edema and the worsening of heart failure (HF) functional class in predisposed patients. It is possible to use diuretic therapy to reduce this impact.

In the STOP-NIDDM study acarbose that is prescribed to patients with impaired glucose tolerance (IGT) reduced the number of cardiovascular events, including cardiovascular mortality. Meglitinide have not been studied formally in DM 2 type, but in patients with IGT and high risk nateglinide did not reduce the risk of fatal and non-fatal cardiovascular events [12]. Up to recent time there was no information about outcomes for GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors. Comparative efficacy and safety profile of main peroral glucose-lowering drugs sis present in the Table 1.

Table 1. **Efficacy and adverse effects of glucose-lowering drugs**

Class of drugs	Effects	Body weight change	Hypoglycemia (in case of monotherapy)	Comments
Metformin	Insulin sensitivity	No/loss	No	Side gastrointestinal effects, lactate-acidosis, GFR reduction, hypoxia, dehydration.
Sulfonylurea	Increase of insulin concentration	Increase	Yes	Allergy, hypoglycemia risk, weight gain
Meglitinides	Increase of insulin concentration	Increase	Yes	Frequent administration, hypoglycemia risk
Alpha-glucosidase inhibitors	Inhibition of glucose absorption	No	No	Side gastrointestinal effects, frequent administration
Pioglitazone	Insulin sensitivity	Increase	No	HF, edema, fractures, bladder cancer (?)
GLP-1 agonists	Increase of insulin concentration	Loss	No	Side gastrointestinal effects, pancreatitis, parenteral administration
DPP-4 inhibitors	Increase of insulin concentration	No	No	Pancreatitis
Insulin	Increase of insulin concentration	Increase	Yes	Parenteral administration? risk of weight gain and hypoglycemia
SGLT2 inhibitors	Glucose reabsorption block in proximal convoluted tubules	Loss	No	Urinary tract infections

Analysis of latest clinical studies dedicated to cardiological safety of glucose-lowering drugs

Previously performed large-scale studies of DPP-4 inhibitor (saxagliptin, alogliptin) in patients with DM type 2 demonstrated increased risk of HF that brought anxiety to endocrinogists and cardiologists. The TECOS [13] study estimated cardiovascular safety of another representative of this class – sitagliptin (n=7332) comparing with placebo (n=7339) that had been added to standard therapy of DM 2 type with concomitant cardiovascular diseases (CVD). Sitagliptin did not increase the frequency of combined primary endpoint (cardiovascular death, non-fatal MI, non-fatal stroke, admission to hospital because of unstable angina) in case of 2,9 years observation median (RR 0,98 for 95% CI 0,88–1,09; p<0,001 for "not worse" statement). The frequency of admission to hospital due to HF was 3,1% in groups of sitagliptin and placebo (RR 1,00 for 95% CI from 0,84–1,20; p=0,95), and sum of hospitalization events because of HF or cardiovascular death was 7,3% and 7,2%, respectively (p=0,81). Analysis of subgroup with 2643 patients with previously present HF did not reveal increased risk of cardiovascular events during sitagliptin treatment. These results demonstrated cardiovascular safety of sitagliptin therapy in patients with DM 2 type, including HF.

Mineralocorticoid receptor antagonists spironolactone and eplerenone decrease morbidity and mortality of patients with chronic heart failure (CHF), but their wide use is restricted by the risk of hyperkalemia. Finerenone excels spironolactone in selectivity and eplerenon in the degree of affinity to mineralocorticoid receptors. The ARTS-HF study involved 1055 patients with DM 2 type and/or chronic kidney disease who had been admitted to hospital due to deterioration of systolic HF [14]. Patients were randomized either into 6 groups for treatment with eplerenone, titrating its dose from 25 mg once per 2 days to 50 mg per day or into 5 groups for treatment with finerenone, titrating its dose from 2,5mg to 20 mg per day and trying not to achieve hyperkalemia. Reduction of N-terminal pro-brain natriuretic peptide levels by 30% and more in respect to its initial levels before 90 days of treatment (primary endpoint) was detected with similar frequency in eplerenone and finerenone groups. At the same time finerenone therapy was linked with significant decrease of the frequency of admission to hospital because of cardiovascular reasons (p=0,0229), death because of any cause (p=0,0262) and cardiovascular death (p=0,0108). The biggest reduction of summated unfavorable cardiovascular events was achieved with starting dose of finerenone 10 mg/day (RR 0,56, p=0,0157). Increased potassium plasma levels up to 5,6 mmol/L and more have been registered only for finerenone dose 15-20 mg/day, and if it was safer than eplerenone if it was administered in dose 2,5-15 mg per day.

The ELIXA study involved patients with DM 2 type who survived MI (83% of cases) or admission to hospital due to unstable angina during last 6 months [15]. After randomization subcutaneous injections of GLP-1 receptor agonist lixisenatide (n=3034) or placebo (n=3034) have been added to standard therapy . Primary composite endpoint (cardiovascular death, MI, stroke, unstable angina) has been registered in 13,4% and 13,2% of cases (RR 1,02 for 95% CI 0,89-1,17) of lixisenatide and placebo groups, respectively. Lixisenatide has been considered safe in this category of patients, including HF, but it did not reduce the risk of cardiovascular complications in patients with DM 2 type.

The SCOT study [16] included 7297 patients without cardiovascular diseases who received selective cyclooxygenase-2 inhibitor celecoxib or non-selective nonsteroidal anti-inflammatory drugs (NSAID) (diclofenac, ibuprofen) for the treatment of osteoarthritis or rheumatoid arthritis. Composite primary endpoint included admission to hospital due to non-fatal acute coronary syndrome with elevated levels of myocardial necrosis biomarkers, non-fatal stroke, cardiovascular death and it had been registered during 3,2 years averagely in 1,8% and 2,2% of cases in celecoxib and other NSAID (RR 1,12; p=0,50). The differences in frequency of severe adverse reactions (5,2% in celecoxib group versus 5,8% in other NSAID group) were insignificant. But total number of adverse reactions was higher in patients who received celecoxib (22% versus 16,1% of cases; p<0,001), and its cancellation had been required more frequently than other NSAID (50,9% versus 30,2%; p<0,0001). In general, use of NSAID in patients without severe CVD has not been associated with high risk of cardiovascular complications.

The OPTIDUAL [17] project involved 1799 patients with stable coronary heart disease or acute coronary syndrome, who were implanted with 1 or more drug-eluting stents. After 12 months of double antiplatelet therapy (aspirin and clopidogrel) 1385 patients who did not have severe cardiovascular/cerebrovascular complications or bleedings were randomized for prolonged administration of clopidogrel 75 mg per day (double antiplatelet therapy prolonged for 36 months, n=695) or termination of clopidogrel

treatment (aspirin group, n=690). After a median observation time after stent implanting of 33,4 months the primary composite endpoint (death, MI, stroke or bleeding) had been registered in 5,8% and 7,5% of patients (RR 0,75 for 95% CI 0,50-1,28, p=0,17), death had been registered in 2,0% and 3,5% of cases (RR 0,65, 95% CI 0,34-1,22; p=0,18), bleeding had been registered in 2,0% and 2,0% of cases (p=0,95) in the groups of prolonged double antiplatelet therapy and aspirin, respectively. Although the tendency seems to be promising, it is still impossible to make a categorical statement about efficacy and safety of prolonged double antiplatelet therapy because of insufficient statistical power of the study.

Conclusion

Diabetes mellitus is one of severe and socially significant diseases of XXI century. Primary and secondary prevention of DM significantly increases patients' quality of life and lifespan. Glycemic control is one of important aspects of treatment of patients with DM. Use of new glucose-lowering drugs as monotherapy or combined therapy give new possibilities for glycemic control. But it is necessary to mention that the safety of new drugs is an important aspect of long-term therapy of patients with DM and comorbid diseases. At the same time, there is an opinion that in case of lack of financing there is no need to study precisely cardiologic safety of new glucose-lowering drugs and spend big amount of recourses. In our opinion, it is necessary to reach consensus for this question, since both efficacy and safety of glucose-lowering drugs are important for wide use.

Conflict of interest: None declared

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