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FACTORS DETERMINING THE CLINICAL SIGNIFICANCE OF DEPIPTIDYL PEPTIDASE 4 INHIBITORS IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract:

The main components of the treatment of type 2 diabetes mellitus (DM) are hypoglycemic, lipid-lowering and antihypertensive therapy, while endocrinologists traditionally perceive the first of these components as the most important. Based on the results of several large prospective studies, it was concluded that compensation of type 2 diabetes close to normoglycemia is accompanied by an improvement in long-term prognosis in terms of the risk of macrovascular complications and death from cardiovascular diseases.

Keywords: Glycemic component, to normoglycemia, dyslipidemia.

Despite the fact that no clear evidence has yet been obtained, this postulate formed the basis of the concept of a personalized target level of glycemic control indicators, according to which the intensity of hypoglycemic therapy and the target level of glycated hemoglobin are determined individually, depending on factors such as age, compliance, history of cardiovascular events, ability to self-control, etc. [one]. Compensation for the glycemic component of complex therapy for type 2 diabetes is more reflected in the reduction of the risk of microvascular complications and neuropathy [2-4], while the risk of macrovascular complications, in particular heart attack, stroke and death from major cardiovascular events, is more degree is affected by the compensation of arterial hypertension and dyslipidemia, which are detected in most patients with type 2 diabetes [2, 3]. The question of why intensive hypoglycemic control does not reduce the risk of cardiovascular events in type 2 diabetes remains open (Fig. 1). There are at least two groups of reasons for this. Firstly, atherosclerosis and all accompanying systemic vascular and inflammatory changes are triggered much earlier than the formal manifestation of type 2 diabetes, that is, before the development of chronic hyperglycemia, and at the time of diagnosis of type 2 diabetes in a significant proportion of patients, atherosclerotic vascular lesions already reach clinically pronounced stages (ischemic heart disease, damage to the vessels of the brain and lower extremities). Thus, the relationship between atherosclerosis and hyperglycemia itself does not seem to be strong enough, at least when it comes to normoglycemic and somewhat less severe compensation for type 2 diabetes. Microvascular complications, on the contrary, develop only after many years of chronic hyperglycemia, and their pathogenesis is mainly due to long-term decompensation of type 2 diabetes.

The second reason may be hypoglycemic therapy itself, which in an intensive format, especially with the use of secretagogue drugs or insulin itself, is accompanied by potentially unsafe hypoglycemic conditions that increase the risk of developing cardiovascular events [2, 3]. Of the two groups of reasons discussed, the first one seems to be non-modifiable: at the time of diagnosis of type 2 diabetes in a patient with atherogenic changes already developed at the stage of the metabolic syndrome, we can prevent cardiovascular events by prescribing lipid-lowering (usually statins) and antihypertensive therapy to the patient. It is quite possible to modify, that is, reduce the risk of hypoglycemic conditions: for this purpose, it is necessary to intensify the patient's self-control (if he is ready and able to exercise it) and / or use hypoglycemic drugs that, due to their mechanism of action, do not cause hypoglycemia. In other words, from the standpoint of hypoglycemic therapy itself, the prevention of cardiovascular events, according to today's ideas, is largely determined not by the intensification of therapy, but by the prevention of hypoglycemic conditions, especially in patients with clinically pronounced atherosclerosis.

The choice of a hypoglycemic drug is a rather complex and multifactorial process. Based on the characteristics shown in Figure 2, we can conclude that today there is no ideal hypoglycemic drug - each has both advantages and disadvantages. An analysis of the results of studies comparing "head-to-head" various hypoglycemic drugs, in particular a meta-analysis of such studies [5], which included, among other things, studies of long-term prognosis against the background of individual drugs, oddly enough, showed that data indicating the advantage of one group or another in terms of true clinical outcomes (end points) is not so

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much. Metformin has the greatest evidence base in terms of its influence on long-term prognosis; in almost all clinical recommendations, it is recognized as the first-line drug for most patients with type 2 diabetes [1]. The question of the second drug that should be added to the patient in case of unsatisfactory compensation for type 2 diabetes on the background of metformin monotherapy (or prescribed as the first drug if it is impossible to take metformin), by and large remains open. The American College of Physicians (ACP) in 2012 made three recommendations for the treatment of type 2 diabetes, assigning them the status of strict and highly evidence-based [6]:

1. Drug therapy is indicated for patients with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, do not achieve adequate glycemic control.

2. Metformin monotherapy is recommended as the start of medical treatment for type 2 diabetes for most patients.

3. If hyperglycemia persists against the background of metformin monotherapy and lifestyle modification, the patient is recommended to add a second hypoglycemic drug.

As follows from the third recommendation, which particular second drug is in question is not indicated. Most clearly, this contradiction, that is, the problem of the "second drug", has aggravated with the advent of new classes of hypoglycemic agents, in particular, incretin drugs - glucagon-like peptide 1 receptor agonists (GLP-1) and dipeptidyl peptidase type 4 inhibitors (DPP-4). Indeed, the more drugs, the more problems with their choice and discussions about the advantages of a particular group, while it is quite obvious that in addition to medical aspects, this discussion involves numerous arguments related to the pharmaceutical market, primarily the cost of the drug and the ratio of this cost with potential benefits for the patient. Prior to the advent of incretin drugs, the choice of tableted hypoglycemic drugs, predominantly affecting postprandial glycemia, was practically limited to the group of sulfonylurea drugs (PSMs).

In recent years, considerable attention has been paid to the study of the role of two hormones of the gastrointestinal tract, which are actively involved in the regulation of insulin secretion, and, consequently, in the regulation of glucose homeostasis in the human body. These include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). One of the approaches to use the therapeutic effects of GLP-1 and GIP is the inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4), under the influence of which they are rapidly deactivated in the body. The use of DPP-4 inhibitors, against the background of which an increase in the level of incretins is achieved, is a physiological way to restore impaired insulin production and correct glucagon levels - key disorders that are characteristic of T2DM.

The pathogenetically determined mechanism of action of this group of drugs allows them to be successfully used in most patients with DM2 both in monotherapy and in combination with metformin and sulfonylurea drugs. In addition, we are now receiving more and more evidence that the use of DPP-4 inhibitors, such as vildagliptin, is effective even in the late stages of T2DM therapy [4, 5]. Studies have demonstrated high glucose-lowering efficacy of vildagliptin in patients with a relatively long course of the disease [6]. DPP-4 inhibitors significantly reduce basal and postprandial secretion of glucagon by pancreatic α-cells, which can significantly improve glycemic control by reducing glucose production by the liver. Probably, it is due to the effect on glucagon secretion that the hypoglycemic effect of DPP-4 inhibitors is explained, including in patients with relatively low insulin secretion. At the same time, vildagliptin provides glucose-dependent regulation of the function of b- and a-cells, due to which the risk of hypoglycemia is minimal. Among the advantages of gliptins, one should also note their neutral effect on body weight dynamics and the possibility of their use in patients with reduced kidney function. Thus, it is of great interest to study the additional benefits that this group of drugs can provide in patients with long-term diabetes who have not achieved adequate control on insulin therapy.

So far, head-to-head comparisons of various drugs from the group of DPP-4 inhibitors in terms of long-term prognosis have not been carried out (the available studies are devoted to short-term and surrogate indicators, such as the average amplitude of glycemic fluctuations, etc.) [16]. Such studies would be of interest, since the molecules of DPP-4 inhibitors differ somewhat in their selectivity for DPP-4 and a number of other properties [7]. However, we can hardly expect the results of such studies to appear soon: let us recall at least the fact that we have quite a few data on the effect on long-term prognosis even in direct comparison of PSM, which have been used in clinical practice for decades. However, registered and ongoing clinical trials with direct comparisons of various DPP-4 inhibitors can be found at clinicaltrials.gov. If we turn to the data accumulated over 7 years of clinical use of sitagliptin, it becomes obvious that a significant part of the work is devoted to its safety and the risk of complications such as acute pancreatitis and infections,

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as well as the use of the drug in patients with renal and hepatic insufficiency. As shown by the data of the meta-analyses, the risk of complications during therapy with sitagliptin is very low and, in general, the drug is very well tolerated [17]. Sitagliptin can be used in patients with renal insufficiency of all degrees of severity, as well as in mild to moderate hepatic insufficiency [18].

When analyzing numerous studies, it should be borne in mind that in real clinical practice, DPP-4 inhibitors are relatively rarely used as monotherapy. Most often, we are talking about their combination with metformin, which, as indicated, is a first-line drug, and the combined use of metformin and DPP-4 inhibitors makes it possible to influence all the pathogenetic links of type 2 diabetes. In this regard, the popularity of fixed combinations of DPP-4 inhibitors and metformin (for example, Janumet) is natural. In addition, DPP-4 inhibitors can be combined with all other hypoglycemic drugs, including insulin. At the same time, it should be remembered that not all possible combinations are rational from a clinical point of view, especially when it comes to prescribing more than two drugs. Note that in those studies where DPP-4 inhibitors were combined with metformin, the long-term prognosis could be determined by either one or the other drug. All studies that have studied the combination of sitagliptin and metformin have shown its high efficiency, which is apparently due to the fact that the drugs affect different components of the pathogenesis of the disease: metformin reduces insulin resistance and excessive glucose production by the liver, sitagliptin causes glucose-dependent stimulation of insulin production, and also reduces hyperproduction of glucose by the liver by suppressing the release of glucagon by alpha cells. In addition, metformin itself synergistically with the effects of DPP-4 inhibitors increases the production of GLP-1 [19].

Monitoring the treatment of patients with diabetes mellitus (DM) makes it possible to assess the situation with high reliability in relation to the modern technologies used in the treatment of this chronic disease. According to the IDF (The International Diabetes Federation), in 2021 the number of patients with diabetes was 366 million people and, according to WHO experts, by 2030 their number will reach 552 million people [1]. According to the Ministry of Health of Uzbekistan, in 2020 there were 3.27 million people in Uzbekistan, and by 2030 their number is expected to increase to 5.81 million people. Thus, the epidemiological situation, both throughout the world and in Uzbekistan, is extremely unfavorable. At the same time, if we assume that by 2030 the detection of patients with diabetes will be at least 50% of their real number, and the average life expectancy will remain at the same level, then the actual number of patients in Uzbekistan will exceed 12 million people. It should be taken into account that the introduction of new treatment technologies reduces the mortality rate in patients with DM and significantly increases their life expectancy. These factors are already important prerequisites for an increase in the number of patients with diabetes.

THE AIM OF OUR STUDY WAS TO STUDY

the structure of treatment of patients with type 2 DM (DM2) with such modern drugs as human insulin analogs, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide (GLP-1) agonists. Numerous works have shown their high clinical efficacy, substantiated the economic prerequisites for wider use in the treatment of DM2 [2, 3, 4].

MATERIALS AND METHODS.

The object of the study was the data of 83 regional registries of the Russian Federation as of January 1, 2011. The analysis was carried out using the software of the State Register of Diabetes Register 2002, update 2.039.

RESULTS AND ITS DISCUSSION.

Table 1 presents data on the number of patients with type 2 diabetes receiving drugs from the DPP-4 inhibitor group (Galvus®, GalvusMet®, Januvia® and Ongliza®)

Table 1

Number of patients with type 2 diabetes receiving DPP-4 inhibitors and GLP-1 agonists, according to the GRDM in 2021		
Number of DM2 patients receiving DPP-4 inhibitors		
Name of the drug	**Number of b-x CD2**	**% of the total number of b-x CD2 in Uzbekistan**
1.Galvus®	354	0,0119%
2. GalvusMet®	4104	0,138%
3. Januvia®	167	0,0056%
4. Ongliza®	-	-
TOTAL:	4624	0,1555%
Number of DM2 patients receiving GLP-1 agonists		
1. Victoza®	259	0,0087%
2. Byeta®	892	0,03%
TOTAL:	1150	0,0387%

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It should be noted that drugs purchased at their own expense were not always included in the registry database. However, this does not significantly affect the data on the use of these drugs in patients with type 2 diabetes.

Table 2 presents data on the number of patients with type 2 diabetes who received treatment with human insulin analogues: ultrashort-acting (NovoRapid®, Humalog®, Apidra®), long-acting (Lvemir®, Lantus®) and 2-phase analogues (NovoMix® 30 and HumalogMix® 25). Despite the fact that the pharmacoeconomic efficiency of insulin analogues has been proven [5, 6, 7] and they are well known to practitioners as the most adequate means in the treatment of DM2, their share in the structure of insulin therapy is still insufficiently high and amounts to 2.62 % for short-acting insulin analogs, 4.92% for long-acting and biphasic insulin analogs. Among analogues, Levemir® (1.76%), Lantus® (1.5%) and Novo-Mix® 30 (1.6%) dominate

Table 2

Number of DM2 patients receiving human insulin analogues		
Number of patients with type 2 diabetes receiving ultrashort-acting human insulin analogues		
Name of the drug	**Number of b-x CD2**	**% of the total number of b-x CD2 in Uzbekistan**
1. NovoRapid®	49 996	1,68%
2. Humalog®	23 886	0,80%
3. Apidra®	4284	0,14%
TOTAL:	78 166	2,62%
Number of DM2 patients receiving long-acting and combined-acting human insulin analogues		
1. Levemir®	52 340	1,76%
2. Lantus®	44 608	1,50%
3. NovoMix® 30	47 582	1,60%
4. HumalogMix® 25	1874	0,063%
TOTAL:	146 404	4,923

If we take the total proportion of patients with type 2 diabetes who are on insulin therapy, including combination with an oral hypoglycemic drug (OSSP), as 100%, then therapy with ultrashort-acting human insulin analogues accounts for 16.22%, and long-term and biphasic action - 30.38%. At the same time, it should be borne in mind that in Russia, monotherapy with ultrashort-acting human insulin analogues in patients with type 2 diabetes is rarely used, and the number of such patients is very small. Basically, ultrashort analogs of human insulin are used as part of basal-bolus therapy, and the number of such patients reaches 30.38% of all patients with DM2 on insulin therapy.

Table 3 shows combinations of NovoRapid® insulin with long-acting and biphasic human insulin analogs (Lvemir®, Lantus®, NovoMix® 30 and HumalogMix® 25). It should be noted that the number of patients who use the NovoRapid® + Levemir® combination is 68.9% compared to the NovoRapid® + Lantus® combination, since when choosing drugs, the doctor prefers analogues of human insulin from one manufacturer. There are a number of other factors that determine the choice of drugs: the individual sensitivity of the patient to certain drugs with which treatment began, the success of achieving compensation for carbohydrate metabolism. The NovoRapid®+NovoMix® 30 combination is used 2.1 times less frequently compared to the first group. With a certain probability, it can be assumed that the treatment of this group of patients began with Novo-Mix® 30 and NovoRapid® was included in the treatment to achieve more complete compensation. It was found that, on average, 1.7 ± 0.04 years after the start of NovoMix® 30 therapy, therapy was intensified with an ultrashort analogue of human insulin — NovoRapid®. The combination of NovoRapid® + Humalog Mix® 25 was extremely rarely used - only in 387 patients with DM2, which amounted to 0.013%.

In general, basal-bolus therapy with human insulin analogs (NovoRapid® + basal human insulin analog) in patients with type 2 diabetes was performed in 35,181 patients, combination therapy with NovoRapid® + 2-phase human insulin analog was performed in 12,223 patients with type 2 diabetes. The combination of NovoRapid® + long-acting human insulin analogue or 2-phase human insulin analogue was used in 47,404 patients with type 2 diabetes, which accounted for 1.59% of all patients with this disease or 9.84% of all patients with type 2 diabetes on insulin therapy.

Thus, the number of patients with the combination Humalog® + - Levemir® amounted to 0.35% of the total number of patients with DM2, in absolute terms - 10,557 people. The proportion of patients with the combination of Humalog® + Lantus® is less in relation to the first group. If all patients on basal bolus therapy with bolus human insulin analog Humalog® are taken as 100%, then the proportion of Humalog® + Levemir® will be 59.5%, and Humalog® + Lantus® - 40.5%. The number of patients on combination therapy Humalog® + NovoMix® 30 was 5234 patients. And just like in the previous group, a small number of patients

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underwent combination therapy Humalog® + HumalogMix® 25 (178 patients), which was 1.67% compared with the 1st group or 0.006% of all patients with DM2.

Overall, the number of patients who received basal bolus therapy with prandial human insulin analog Humalog® in combination with basal human insulin analogs (Lvemir® and Lantus®) or combination therapy with Humalog® + 2-phase human insulin analogs was 23,136 people or 0.78% of the total number of patients with type 2 diabetes. Among all patients with DM2 on insulin therapy, this group was 4.8%

Table 5

Number of DM2 patients receiving Apidra as part of basal bolus therapy with human insulin analogs		
Name of the drug	**Number of b-x CD2**	**% of the total number of b-x CD2 in Uzbekistan**
1. Apidra® + Levemir®	2498	0,084
2. Apidra®+Lantus®	625	0,021
3. Apidra®+NovoMix® 30	327	0,011
4. Apidra®+HumalogMix® 25	60	0,002
TOTAL:	3510	0,118

Table 5 presents data on the number of patients who received basal bolus or combination therapy with the ultrashort insulin analogue Apidra®. In basal bolus therapy for type 2 diabetes, it is most often used in combination with insulin Levemir®. Taking this combination as 100%, we see that in combination with the human insulin analogue Lantus®, its use is 25.0%. Combination therapy with NovoMix® 30 is carried out in 327 patients with DM2, and with the human insulin analogue Humalog Mix® 25 - in 60 patients with DM2.

The total use of insulin Apidra® as a bolus drug in combination with basal or 2-phase human insulin analogs is 0.12%, and in absolute terms - 3510 people. Their proportion among patients with type 2 diabetes on insulin therapy does not reach 1%.

Thus, DPP-4 inhibitors and GLP-1 agonists are gradually taking their place in the structure of treatment of patients with type 2 diabetes [8]. Human insulin analogs are gaining a leading position in the treatment of not only DM1, but also DM2, which is obviously due to a number of their properties that allow faster achievement of target levels of carbohydrate metabolism compensation, avoiding a number of complications and undesirable effects of insulin therapy [9, 10].

CONCLUSIONS

The share of DPP-4 inhibitors and GLP-1 agonists in the treatment of patients with type 2 diabetes remains insignificant and does not exceed 0.2%.

Analogues of human insulin are used much more often and are currently the most promising drugs for the treatment of type 2 diabetes. The share of their use in DM2 patients on insulin therapy reaches 30.38% and continues to grow steadily.

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