DYNAMICS OF GLYCEMIC VARIABILITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS DURING DEPRESCRIBING THERAPY DEPENDING ON THE PRESENCE OF SEVERE COMORBID PATHOLOGY

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INTRODUCTION

Type 2 diabetes mellitus (DM2) is a complex metabolic disease caused by the interaction of various environmental factors and genetic predisposition. The prevalence of DM2 has reached epidemic proportions and is estimated to affect more than 400 million people worldwide [1]. DM2 has become a prominent global public health problem. An analysis of recent statistical data shows that DM2 has several new epidemiological characteristics. First, diabetes continues to grow steadily in developed countries such as the United States and Japan. Secondly, although old age is a risk factor for DM2, increasing rates of childhood obesity have led to the fact that DM2 is becoming more common among children, adolescents and adolescents, which is a serious manifestation of the epidemic and a new public health problem of significant proportions [2]. According to statistics, about 50% of people with diabetes remain undiagnosed, and about 20-30% of patients usually already develop complications before diagnosis [3]. In the early stages, DM2 is asymptomatic, or the symptoms may be so mild that they go unnoticed. Thus, at the time of diagnosis, many patients already have complications related to DM2.

The standard method for evaluating the effectiveness of DM treatment based on the level of glycated hemoglobin (HbA1c) reflects the average blood glucose level over the previous 3 months, while it does not take into account short-term glycemic variability (HCV) or daily fluctuations in blood glucose levels or hypoglycemic phenomena. Meanwhile, data are accumulating on the value of high blood pressure as an independent predictor of diabetes complications. High blood pressure is fluctuations in blood glucose over a certain period of time. High blood pressure is a more accurate parameter for assessing the risk of developing diabetic complications than traditional parameters for assessing compensation of carbohydrate metabolism. [4]. The lowest risk of developing complications of diabetes, with glycemic variability within 3 mmol/L. Interest in the study of HCV has increased dramatically with the advent of continuous glucose monitoring (HMG) technologies, which made it possible to study in detail the temporal structure of glycemic curves. NMH is a method for recording changes in blood glucose concentration, in which the results are recorded at very short intervals (no more than 5 minutes) for 24 hours a day. It was found that the nature of HCV is more important in predicting the outcomes of cardiovascular diseases compared with the level of HbA1c in patients with DM2. According to a clinical study by Liang et al. a high

amplitude of HCV was associated with a higher risk in cardiovascular diseases (CVD), and minimizing HCV improved insulin resistance and reduced the thickness of the intima media of the carotid arteries, and also led to a decrease in the risk of developing CVD [5]

Hyperglycemia increases the production of free radicals that inactivate nitric oxide (NO), which leads to endothelial dysfunction and vascular complications. In addition, large fluctuations in glucose levels affect changes in endothelial NO synthase, the combination of reduced availability of NO and increased production of vasoconstrictors plays an important role in the development of atherosclerotic vascular changes [16]. Also, high levels of HCV increase the risk of peripheral and cardiac autonomic neuropathy [17]. Cardiovascular diseases are the main cause of mortality and morbidity in both prediabetes and DM2. In numerous epidemiological studies in patients with DM2, a close relationship has been established between the severity of renal dysfunction and the development of various cardiovascular events. In particular, among patients with terminal renal insufficiency, the incidence of cardiovascular mortality is almost 500 times higher than in the general population with normal renal function [6]. The main mechanisms contributing to the formation of cardiorenal syndrome include increased central venous pressure, decreased renal perfusion, intrarenal hypertension, insufficiency of endogenous mechanisms providing effective natriuresis (natriuretic peptide system), endothelial dysfunction, systemic proinflammatory and neurohumoral activation, prooxidant stress and some other factors [7]. Diabetic nephropathy (DN) is one of the most important microvascular complications, the early manifestation of which is the presence of small amounts of protein in urine (microalbumin) [8]. At the same time, the mortality rate in the presence of DN in patients with DM2 was several times higher compared with other complications of DM2.

Traditionally, the goal of drug development has been to selectively target them in order to avoid other interactions that could lead to undesirable side effects. Currently, this approach is considered outdated, and in recent years, most drug development efforts have focused on the development of molecules that affect several links in pathogenesis. For example, the use of incretin effects is an important approach to the successful treatment of diabetes and obesity control. Since they have an effect on the pancreas, including stimulation of insulin secretion and expression of insulin genes, promoting the survival of β cells, improving the sensitivity of β cells to glucose and reducing glucagon secretion. In addition, they have extrapanreatic effects, which are manifested by slowing down gastric emptying, decreased appetite and weight loss [9].

Such drugs have caused some optimism about the possibility of influencing the course of cardiorenal complications of DM2.

iSGLT-2 group drugs have the widest evidence base in terms of efficacy and safety in patients with DM2 with cardiovascular diseases. Effective weight loss without increasing the frequency of hypoglycemic reactions, as well as in reducing systolic blood

pressure, have a beneficial effect on outcomes in patients with CHF. Studies have found that the use of iSGLT-2 drugs was accompanied by a lower frequency of hospitalizations due to CHF compared with placebo. These drugs are very unique not only in terms of positive metabolic effect, cardioprotection, but also have the property of nephroprotection. In turn, patients with DM2 with chronic kidney disease, especially in the presence of albuminuria, increase the risk of developing cardiovascular pathologies [11]. Other mechanisms of the positive effect of iSGLT-2 inhibitors on the course of CHF include osmotic diuresis, a decrease in arterial wall stiffness, a decrease in uric acid levels and a decrease in albuminuria. In current European and Russian guidelines, these drugs are considered as the first line of therapy in patients with CHF and type 2 diabetes.

Paradoxically, strict glycemic control is ineffective in relation to cardiovascular risk in those patients with DM2 who have the highest risk of developing cardiovascular events in the future. Finally, strict glycemic control, especially in elderly patients with multiple diseases, is associated with an increased risk of hypoglycemia, which may further increase the risk of cardiovascular diseases [12].

In general, early detection of DM2 patients, the appointment of combination therapy using innovative drugs from the moment of diagnosis, in order to achieve early glycemic control, reduce the risk of long-term complications and reduce disease progression, as well as monitoring the effectiveness of therapy not only based on the results of HbA1c and also using the level of fluctuation in blood pressure, remain relevant.

Thus, the determination of HCV using the NMH method allows for a more thorough assessment of the effects of therapy, is a more accurate parameter for assessing the risk of diabetic complications than traditional parameters for assessing compensation of carbohydrate metabolism. It also helps to identify hidden hypo- and hyperglycemic events, which in turn are the main predictors of severe complications.

Materials and methods. A prospective analysis of 40 patients (28 men and 12 women) who were hospitalized at the V.P. Demikhov State Clinical Hospital was carried out. To assess HCV, patients were divided into several groups: group I included patients with DM2 without a history of severe comorbid pathology (n=22), group II - with DM2 and with the presence of diseases such as ACC, CHF or CKD (n=18). Further, they were divided into groups III and IV, depending on the presence of either only cardiac (n=10) or cardiorenal pathology (n=8), respectively. The third stage of our study was to assess the effect of preferential drugs (iSGLT-type 2, arGPP-type 1) on lowering hypertension, estimated by the level of MAGE (Mean amplitude of glycemic excursion, average amplitude of glycemic fluctuations). All patients of group II during the study were transferred from traditional hypoglycemic drugs (SSPs) to innovative ones, respectively, patients of group II were further divided into groups V and VI in order to assess HYPERTENSION during deprescribing therapy. The glycemic level in all patients was

assessed using the FreeStyle Library flash monitoring. The collected data were analyzed using Jamovi, Excel 2016 software.

RESULTS

The average age of the patients was 66 [54;79] years, the median BMI was 36.4 [27.7; 44.1] kg/m2. Patients with DM2 with complications from the cardiorenal systems, compared with patients without complications, had higher levels of HA (group I 6.15 [5.68; 6.62] vs group II - 8.4 [7.54; 9.26], $p<0.001$) and more pronounced GW (Group I - 3.0 vs group II - 5.76, $p<0.001$) (see chart No. 1). Patients with cardiorenal pathology had lower The levels of G. K. (group III-9.11 [7.95; 10.3] vs. group IV - 6.89 [6.72; 7.47], $p<0.01$) and mag (group III - 6.32 vs. group IV - 4.50, $p<0.038$) were compared with a patient with a pathological pathology. When evaluating the dominant sugar-free drugs, the predominant cardio and nephroprotection were not satisfied with the differences in the excretion of the average HA (group V - 8.49(7.19-9.79) vs. group VI - 8.16[6.9-9.23], Rh 0.58, 6.58, 6.79), a pronounced decrease in the mag index (Group V – 5.18 vs. group VI - 3.9, $P<0.001$). When analyzing the VG indices, distributors in Group 1 could not determine BC by comparison with the comparison categories: MAGE (3.0 & 5.76 ($R<0.01$)), LI (2.81 and 4.83 ($R<0.05$))), HBGI (1.78 and 7.42 ($R<0.06$), CONGA (4.67 6.91 ($P<0.05$).

DISCUSSION

The epidemic of DM2 requires the development of new therapeutic and preventive strategies to reduce the spread of this debilitating disease. The correlation between the level of HCV and the risk of developing new cases of cardiovascular events in patients with DM2 is linear [13]. For decades, HbA1c levels have been the main indicator in assessing glycemic control. The HbA1c level is used by doctors and patients to evaluate treatment outcomes and optimize diabetes therapy, and in clinical studies of DM2 it is the main indicator of effectiveness. At the same time, HbA1c has certain disadvantages, the most noticeable of which is its limited sensitivity to fluctuations in blood glucose levels.

Our study proves once again that the level of fluctuation in blood pressure depends on the received hypoglycemic therapy, while innovative drugs have shown their advantage over traditional ones when comparing the results that we received after deprescribing therapy. And also in our study, the negative effect of concomitant comorbid pathologies on GW was demonstrated, regardless of the therapy received.

Preferred hypoglycemic drugs are ideal for the treatment of DM2 due to their effectiveness, positive effect on the severity of hypertension, low risk of hypoglycemia and weight loss. It is important to note that sulfonylureas have been associated with significant hypertension and can lead to increased hypoglycemia and mortality[15]. Studies have reported that when several CVD risk factors were influenced in people with DM2, the risk of CVD and microvascular events decreased by about 50% [14]. Therefore, a multifactorial approach to the treatment of DM2 is currently relevant, in

which, along with glycemic control, special attention is paid to reducing cardiovascular risk factors.

CONCLUSIONS

Therapeutic interventions aimed only at reducing HbA1c may lead to unbalanced treatment adjustments, potentially increasing the risk of hypoglycemia. Fluctuations in blood glucose levels, represented by high blood pressure indicators, may provide a better predictor of such complications. In turn, our results showed that the presence of comorbid pathology in patients with DM2 was associated with high GW and high GC levels. In patients with severe comorbid pathology, when prescribing preferential SSPs, there was a significant decrease in HCV, despite comparable values of GC indicators. The relative low rates of HB and average GC levels in the group of patients with cardiorenal syndrome, apparently, could be associated with sparing CTT, which they received taking into account CKD. Further large randomized trials using NMH devices are required to assess the role of HCV in the development of isolated complications in patients with DM2.

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