The Review of DIABETIC STUDIES

RESEARCH

Assessment of the Dynamics of Hormonal and Metabolic Parameters in Diabetes Mellitus During Treatment with Glimepiride, Repaglinide and Metformin

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■ Abstract

Introduction: Despite the availability of various medications for type 2 diabetes (T2DM), treatment quality remains inadequate, leading to increased complications. Therefore, the introduction into health care practice of optimal methods of strategy and tactics of glucose-lowering therapy at the present stage, as a measure to prevent the development of its complications, is one of the pressing problems of diabetology. The purpose of the study was to evaluate the dynamics of hormonal and metabolic parameters in patients with type 2 diabetes during treatment with glimepiride, repaglinide and metformin from 4.5 years to 5 years. **Materials and Methods:** The conducted study belongs to a randomized controlled clinical trial. Patients with type 2 diabetes (T2DM) were divided into groups (n=280) based on treatment with glimepiride, repaglinide, metformin, or gliclazide (control). The study assessed hormonal and metabolic parameters over 3 months to 5 years. The nature of the study is clinical, comparative and prospective. The effectiveness of various drugs (glimepiride, repaglinide, metformin) in the treatment of type 2 diabetes mellitus was compared, tracking the dynamics of various indicators over a long period. **Results:** Glimepiride demonstrated superior glycemic control and lipid management compared to gliclazide. Only a small percentage of patients achieved optimal HbA1c levels, while many experienced suboptimal or decompensated control. Glimepiride was associated with a lower risk of decompensation compared to other sulfonylurea drugs. **Conclusion:** Glimepiride, repaglinide, and metformin each demonstrated distinct advantages in managing type 2 diabetes. Glimepiride and repaglinide effectively reduced blood sugar levels and glycosylated hemoglobin, while metformin was particularly effective in early-stage disease. Individualized treatment plans, including combination therapies, can improve patient outcomes and quality of life.

Keywords: Type 2 Diabetes Mellitus (T2DM), T2DM with Coronary Heart Disease (CHD), Glimepiride, Repaglinide, Metformin, Gliclazide.

1. Introduction

Diabetes is one of the costliest health problems in the world [1-3]. Globally, diabetes is likely to be the fourth leading cause of death. Approximately 90% of people with diabetes have type 2 diabetes. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly [4-7]. As the need for insulin rises; the pancreas gradually loses its ability to produce insulin. Combination therapy has been shown to achieve greater blood glucose lowering than monotherapy because different classes have different and complimentary mechanisms of action [8, 9]. Therefore, it is more logical to add another drug than replace the existing drug.

According to WHO, there are currently 285 million people with diabetes in the world, and by 2025 their number will be 380 million and 435 million in 2030 [10, 11]. The modern algorithm for the treatment of type 2 diabetes mellitus includes dietary therapy, lifestyle changes (regular physical activity, smoking cessation, patient education, self-monitoring), and in most cases, the prescription of oral hypoglycemic drugs [12, 13]. If obesity is present, anorectics may be recommended [14, 15]. In case of insufficient effect from sulfonylurea derivatives (SUD) in case of excess body weight (BMI = 30 kg/m2 or more), combination treatment with metformin (Siofor) is prescribed [16]. These drugs can be used as monotherapy or in combination. If the effect of the treatment is unsatisfactory, insulin therapy is indicated in the future. The criterias for prescribing insulin therapy for T2DM are the absence of compensation for

diabetes mellitus during diet therapy in combination with glucosidase inhibitors, biguanides or SUD drugs and in case of secondary insulin resistance to oral drugs [17]. Resistance to sulfonylureas occurs in 5-20% of patients with diabetes and is associated with a decrease in residual insulin secretion.

Research question: to evaluate the effectiveness of various groups of oral hypoglycemic drugs (glimepiride, repaglinide, metformin) in achieving and maintaining carbohydrate metabolism compensation in patients with type 2 diabetes mellitus, as well as to determine which of them have the best safety and tolerability profile.

2. Materials and Methods

A total of 280 patients were enrolled in this 3-3.5-year study. Participants included 140 with type 2 diabetes mellitus (T2DM) and 140 with T2DM and coronary artery disease. The average age of T2DM patients was 53.74 ± 2.48 years, with an average disease duration of 9.2 ± 0.61 years. T2DM patients with coronary artery disease had an average age of 60.1 ± 2.98 years, and their disease duration ranged from 6 to 15 years.

Patients were divided into three groups: T2DM (120 patients), DM2IHD (120 patients), and a control group (40 patients). Each group was further divided into three subgroups (30 patients each): T2d, Tdr, T2m, DM3g, DM3r, DM3m, K1, and K2.

Drug doses were individualized based on glycemic profile and daily glucosuria. Effectiveness was assessed by normoglycemia, aglucosuria, and drug tolerability.

Glimepiride, repaglinide, metformin, and gliclazide were used in the study.

Laboratory-biochemical methods were employed to evaluate lipid, protein, and hormone metabolism.

Data collection was carried out at the base visit (at the time of inclusion in the study) and at subsequent visits (6, 12 months).

Statistical analysis included the Student's t-test for comparing means and correlation analysis for assessing relationships between variables.

3. Results

First of all in all patients with diabetes decompensation of diabetes should be eliminated regardless of age and other associated causes. This state means the need to achieve a fasting glycemic level of <7.8 mmol/l, and after a meal - <10.0 mmol/l. Long term maintaining glycemia within these limits will lead to a decrease in HbA_{1c} levels < 7.5%.

Fasting hyperglycemia is associated with a relative deficiency of insulin in the liver at night, hepatocyte IR, increased lipolysis of visceral fat, and lipotoxicity. Our studies confirm the involvement of morning hyperglycemia in the maintenance of dyslipidemia (Figure 1).

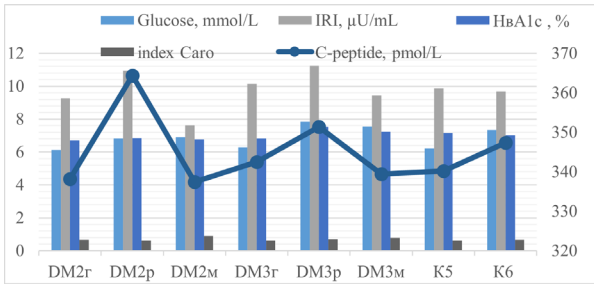

Figure 1: Biochemical Blood Parameters in Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin.

Considering the importance of normalizing postprandial glycemia, we set a goal to develop optimal approaches to ensure satisfactory blood sugar levels during the night and in the morning.

Treatment with sulfonylurea derivatives: glimepiride and gliclazide. SUD are the most common antihyperglycemic drugs used in the treatment of patients with T2DM and T3DM.

First of all, it became obvious that, regardless of the type of drug, it is possible to achieve compensation for carbohydrate metabolism with SUD monotherapy only in 40% of patients (110 patients out of 275). All other patients required combination therapy with the addition of metformin or insulin to achieve this goal.

We compared the main SUD drugs used in the treatment of patients with type 2 diabetes [18], glimepiride and gliclazide. A study of the ratio of insulin and blood glucose levels when using various sulfonylurea drugs glimepiride and gliclazide showed that this ratio (increase in plasma insulin/decrease in blood glucose) was 0.03 for glimepiride and 0.07 for gliclazide [19]. The least stimulating effect of amaryl on insulin secretion provides a lower risk of hypoglycemia.

When studying the secretion of IRI and C-peptide, the most physiological insulin secretion was also achieved with the use of glimepiride. Thus, minimal glycemia is observed while taking glimepiride, and maximum glycemia is observed with gliclazide. In the patients we observed, there was more likely a correlation between the degree of compensation of carbohydrate metabolism and a tendency toward a decrease or normalization of blood lipids, rather than with the influence of one or another (SUD) on this process. All compared sulfonylurea derivatives did not have a negative effect on liver and kidney function (Figure 2).

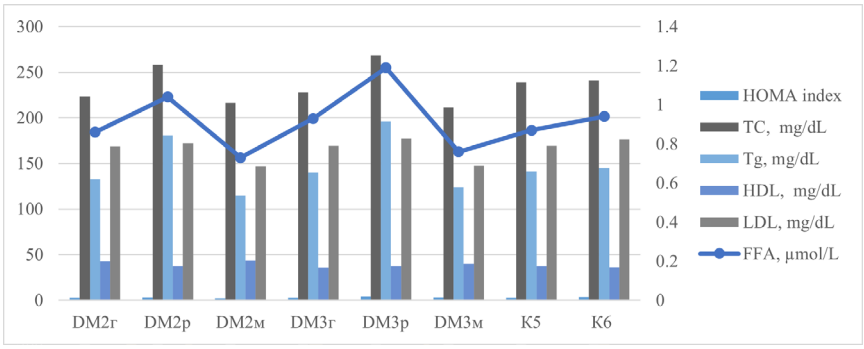

Figure 2: Biochemical Blood Parameters in Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin.

Finally, the logical question of how certain advantages of various (SUD) affect compensation for type 2 diabetes is the greatest interest. We compared HbA1c levels 6 months after patients were registered and whether they achieved satisfactory levels of carbohydrate metabolism upon discharge from the hospital. First of all, it should be noted that after 6 months of treatment, the HbAlc level was not below 6.5% in any of the observed groups. However, in all groups, with the exception of those receiving gliclazide, subcompensation of carbohydrate metabolism was achieved.

In patients receiving gliclazide therapy, HbA_{lc} exceeded 7.5%, although during the observation period this figure decreased by 16% ($p < 0.05$). Thus, our data indicates that at the first stage of treatment, with rationally selected hypoglycemic therapy, the use of any modern 3rd generation PSM can eliminate decompensation of diabetes or significantly improve the state of carbohydrate metabolism.

Analysis of a specific number of T2g patients in varying degrees of compensation for carbohydrate metabolism showed the following: HbA_{lc} was below 6.5% (compensation) in only 23.3% (7 out of 30) of patients. In the majority of patients, 76.6% (23 out of 30), this figure ranged from 6.5-7.5% (subcompensation). In 13.3% (4 out of 30) patients with T3g, HbA_{lc} exceeded 7.5%, that is, they were in a state of decompensation of carbohydrate metabolism. We were unable to identify a correlation between the level of HbA_{lc} and the type of PSM obtained, since the distribution of patients with varying degrees of compensation for carbohydrate metabolism in the compared groups was approximately the same. The only fact that drew attention to itself was that among those receiving glimepiride and any form of glipizide, there was not one in a state of decompensation.

All patients receiving glimepiride and glipizide were satisfied with a single dose of the drug per day, which excluded skipping a drug dose. None of them noted even mild hypoglycemic conditions and no one gained weight. The improvement in the quality of life affected their vital activity and increased productivity. A summary table of symptoms indicatng the level of quality of life of patients during the treatment of PSM is presented in Figure 2. When treated with glimepiride, cortisol levels decreased significantly ($p<0.05$) by 22.5% in patients with diabetes mellitus and the glucagon level ($p<0.001$) by 33.1%; the GH level ($p<0.01$) increased to 34.8 %, and when treating patients in the T3g group, there was a decrease in norepinephrine levels by 20.8% and an increase in STH ($p < 0.05$) to 29.7% (Figure 3).

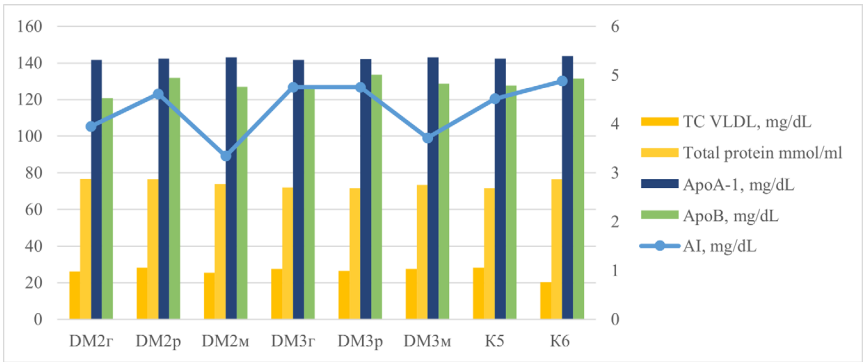

Figure 3: Biochemical Blood Parameters in Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin.

After treatment with glimepiride for 6 months, the BMI indicator decreased in women in the T3g group with obesity by 9.42% and in men by 5.67%, waist size in men in the T2g group significantly ($p < 0.05$) decreased by 11.45 % (Figure 4-5).

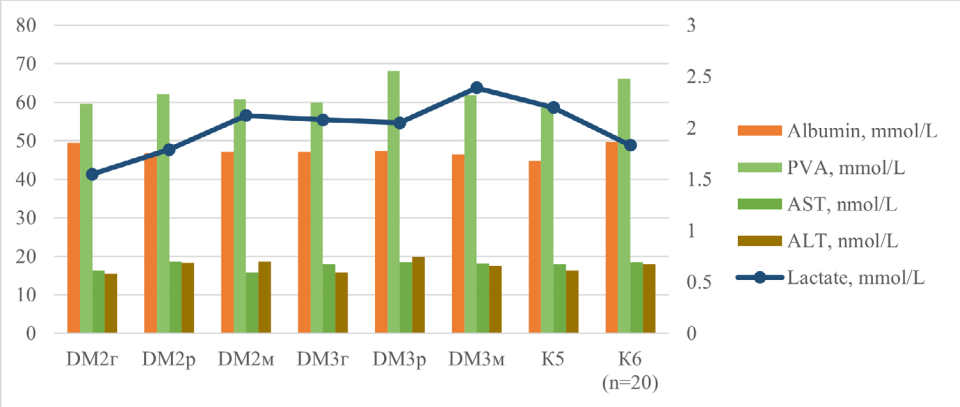

Figure 4: Biochemical Blood Parameters in Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin.

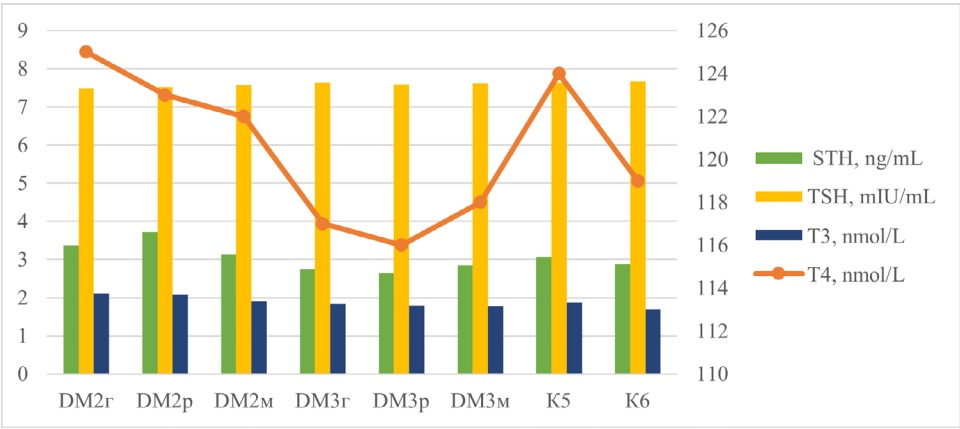

Figure 5: The Hormone Levels in the Blood of Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin (M±m).

Thus, there is a certain correlation between the characteristics of the hypoglycemic effect of (SUD) and the quality of life of patients. Glimepiride provides more physiological insulin secretion, which allows for more flexible correction of glycemia and is subjectively better tolerated by patients.

Repaglinide: Patients (n=30) were selected in each subgroup of T2DM2r and T3DM3r, whom we treated with repaglinide, since they very often experienced hypoglycemic conditions when taking SUD. The maximum concentration of repaglinide in the blood is 0.6 hours. The level of insulin in the blood serum of patients with the subgroup DM2r and DM3r after taking repaglinide increased after 60 minutes for a short time (90 minutes), which is combined with its hypoglycemic effect. Treatment with repaglinide for 6 months allowed a significant reduction in the content of glycosylated hemoglobin by 29.7%, and with treatment with gliclazide, the figure decreased to 26.4% in the 1st K5 group (Figure 1). Fasting glucose levels in patients with T2D also decreased significantly ($p < 0.001$) by 33.5% in DM2r and 33.3% in DM3r. A decrease in glycemia and glycosylated hemoglobin was observed in all patients, regardless of whether they ate food 2, 3 or 4 times a day. Episodes of hypoglycemia were observed in 2% of patients receiving repaglinide.

Analysis of the assessment of tolerability of drugs and symptoms, indicating the level of quality of life of patients, showed that they are subjectively better tolerated by patients. Their use reduces the risk of developing latent and overt hypoglycemic conditions, both during physical activity and when skipping meals. All patients were satisfied with taking the drug once a day, which excluded skipping a dose.

When treated with repaglinide, cortisol levels decreased significantly ($p<0.001$) by 37.1% in patients with type 2 diabetes mellitus and by 37.7% in patients with type 2 diabetes mellitus, the level of glucagon decreased ($p<0.01$) by 32.8% in patients with type 2 diabetes mellitus, and the level of growth hormone ($p<0.01$) increased by 48.8% during treatment of patients in the T2DM2r group and 24.5% in DM3r ($p<0.05$) (Figure 3). After treatment with repaglinide for 6 months, the WC) indicator decreased in men in the T2D group by 21.66% and in women by 18.18%; in the group T3D with IHD, WC decreased in men by 11.3%, in women 19.5% and BMI by 13.93% (Figure 6).

Thus, nowadays, repaglinide is a short and rapid-acting oral hypoglycemic drug that is a prandial glucose regulator in patients with T2DM.

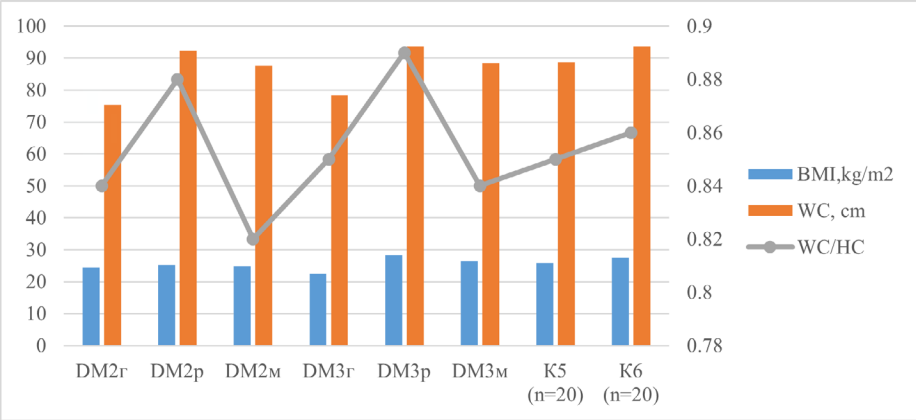

Figure 6: The Mean Values of BMI, WC, WHR, and BP in Patients with Diabetes Mellitus Receiving Treatment with Glimepiride, Repaglinide, and Metformin (M±m).

Metformin: Among the patients with DM2m and DM3m we observed, 30 patients in each subgroup received metformin as monotherapy. Despite the well-known advantages of this drug, compensation for carbohydrate metabolism with metformin is less compared to glimepiride. Thus, the glycemic level significantly ($p<0.05$) decreased by 32.7%, the HbA_{lc} level decreased ($p<0.001$) to 30.2% in the DM2m group and 32.0% in the DM3m group (Figure 1). The positive dynamics of IRI stood out especially, which decreased in the DM3m group to 53.5%. However, the effectiveness of metformin monotherapy in them decreased to 10.0% a year after the onset of the disease. Such differences in the effectiveness of metformin monotherapy at different stages of the disease are explained by the gradual worsening of impaired insulin secretion. Achievement of compensation of carbohydrate metabolism when taking metformin was observed in patients with T2DMm2 and T3DMm3 with insulin resistance. In this regard, in the presence of clinical signs, metformin is the drug of choice: on the one hand, it reduces the manifestations of IR, and on the other, it suppresses the production of glucose by the liver.

An analysis of the assessment of drug tolerability and symptoms indicating the level of quality of life of patients showed that the risk of developing hidden and overt hypoglycemic conditions decreases, both during physical activity and when skipping meals. None of them noted even mild hypoglycemic conditions and no one gained weight. The improvement in the quality of life affected their vital activity and increased productivity (Figure 2).

While metformin treatment, cortisol levels decreased significantly ($p<0.001$) by 28.9% in patients with DM2m and 22.1% in patients with DM3m, glucagon levels decreased ($p<0.01$) by 33.01% in DM2m, and the level of growth hormone increased by 25.6% in the treatment of patients in the DM2m group and significantly ($p<0.01$) 33.9% in DM3m. There was a decrease in norepinephrine by 20.4% in patients with DM3m (Figure 3).

Among all observed patients who were planned to be prescribed metformin, 12 had contraindications to its use. The actual percentage of refusal to use metformin due to such serious reasons as impaired renal function, liver function, circulatory and respiratory failure was 2-3 times lower compared to alcohol abuse.

Among the patients we observed treated with metformin, there were 26 patients who had suffered a myocardial infarction, but had no signs of circulatory failure. All of them had good tolerability of the drug and normal blood lactate levels. However, it should be emphasized that these patients, in addition to training in the principles of treatment of type 2 diabetes, require special vigilance regarding the possibility of an increase in lactate against the background of the development of circulatory failure [20]. With strict adherence to all contraindications to the use of metformin, after a year of observation, the lactate content in the blood was practically no different from the baseline (1.4 ± 0.1 mmol/l and 1.5 ± 0.03 mmol/l, respectively).

A study of the effect of metformin on basic biochemical parameters did not reveal any negative effects of taking the drug on liver and kidney function [21]. Moreover, during the period of taking metformin, there was an obvious trend towards a decrease in lipids. The clearly positive dynamics in the lipid profile are noteworthy. Thus, the levels of total cholesterol, triglycerides, and LDL-C decreased statistically significantly. At the same time, the level of HDL-C increased statistically significantly.

So, the data we obtained during our work allows us to assert that metformin monotherapy, with a disease duration of more than one year, is effective in only 6.6% of patients with pronounced clinical manifestations of IR. The remaining patients require combination therapy for (SUD), which is due to increasing impairment of insulin secretion. The most effective is combination therapy with metformin and SUD, which is explained by the different effects of these drugs on all currently known links in the pathogenesis of type 2 diabetes.

For the majority of patients - 91 out of 95 (95.7%), to achieve compensation for carbohydrate metabolism, SUD during the day and metformin before bed are enough. In patients with severe IR (BMI>30 and ITB>0.95), long-term use of metformin in combination with SUD helps reduce cholesterol, LDL-C ($p<0.05$), triglycerides ($p>0.05$) and increase cholesterol- HDL ($p<0.05$) (Figure 3).

Analysis of the degree of compensation of carbohydrate metabolism at the time of registration has showed that 74.6% of patients were in a state of decompensation. 93.3% of patients had arterial hypertension, which is the most important risk factor for the development of not only atherosclerosis and premature death, but also microvascular complications (UKPDS 38.39). In the observed patients at the time of registration, the systolic pressure was 155.9 ± 3.8 mm Hg, and the diastolic pressure was 89.0 ± 2.3 mm Hg. The combination of two unfavorable risk factors for the development of complications of diabetes, such as chronic hyperglycemia and arterial hypertension, affected the presence of late complications of this disease in the observed patients [22, 23].

Thus, over a five-year observation period, the number of patients with diabetic polyneuropathy decreased (by 8.8%), with fatty liver (by 45.0%), and diabetic ulcers of the lower extremities were completely cured. The number of patients diagnosed with diabetic retinopathy and nephropathy increased slightly (by 3.8% and 3.9%). None of the observed patients developed diabetic foot syndrome.

Thus, these data indicate that careful control of glycemia and blood pressure is quite achievable and slows the rate of progression of late complications of diabetes mellitus and prevents the occurrence of acute macrovascular complications.

4. Discussion

Analysis of the degree of compensation of carbohydrate metabolism at the time of registration showed that 74.6% of patients were in a state of decompensation. In 93.3% of patients, arterial hypertension occurred, which is the most important risk factor for the development of not only atherosclerosis and premature death, but also microvascular complications (UKPDS 38.39). In the observed patients, at the time of registration, systolic pressure was 155.9 ±3.8 mmHg, and diastolic pressure was 89.0±2.3 mmHg. The combination of two such adverse risk factors for the development of diabetes complications as chronic hyperglycemia and arterial hypertension affected the presence of late complications of this disease in the observed patients.

Considering the main and final goal of the study, the group of patients with DM in combination, which was under our constant strict control, is of the greatest interest. When studying the secretion of IRI and C-peptide, the most physiological insulin secretion is achieved with the use of glimepiride. So, the minimum glycemia is observed against the background of taking glimepiride, and the maximum is gliclazide. In the patients we observed, there was a correlation between the degree of compensation of carbohydrate metabolism and the tendency to decrease and normalize blood lipids. An analysis of the specific number of patients with ADhd who are in varying degrees of carbohydrate metabolism compensation showed the following: HbA_{1c} was below 6.5% (compensation) in only 23.3% (7 out of 30) patients. In the majority of patients 76.6% (23 out of 30), this indicator ranged from 6.5-7.5% (subcompensation). In 13.3% (4 out of 30) patients with ADhd, NIA1c exceeded 7.5%, that is, they were in a state of decompensation of carbohydrate metabolism. An analysis of the assessment of drug tolerance and symptoms indicating the level of quality of life of patients showed that glimepiride and glipizide are subjectively better tolerated by patients. None of them reported even mild hypoglycemic conditions, and none gained weight. The improvement in the quality of life affected their vital activity and increased efficiency.

Repaglinide therapy for 6 months significantly reduced the content of glycosylated hemoglobin by 1.14%, which is 0.99% lower than in the control group. Fasting glucose levels in patients with DM2r also significantly decreased by 1.8 mmol/l. A decrease in glycemia and NIA1c was observed in all patients, regardless of whether they ate 2, 3 or 4 times a day. Episodes of hypoglycemia were observed in 2% of patients receiving repaglinide. Repaglinide therapy makes it possible to maintain compensation of carbohydrate metabolism in patients with DM2 for a long time, improving their quality of life and allowing for a more flexible dietary regime. Repaglinide is a postprandial stimulator of insulin secretion. Repaglinide had no direct effect on lipid metabolism and no patient showed a tendency to decrease or normalize blood lipids.

In most cases, they achieved compensation or subcompensation of carbohydrate metabolism and maintained the desired blood pressure level. These patients, who were under constant supervision, were compensated for carbohydrate metabolism and blood pressure levels. Dieting led to a decrease in body weight, despite the fact that many of them received insulin therapy. Compensation of carbohydrate metabolism excluded the toxic effect of glucose on β-cells, which was manifested by a completely preserved residual secretion of insulin, despite the long duration of the disease.

A comparison of the frequency of late complications at the beginning and at the end of treatment showed that within five years, the manifestations of diabetic polyneuropathy decreased in patients, and the number of patients with retinopathy and nephropathy practically did not increase. It is important to emphasize that none of the patients had problems with the lower extremities (diabetic foot syndrome), no one suffered either acute myocardial infarction or acute cerebrovascular accident.

Thus, during the follow-up period, the number of patients with diabetic polyneuropathy decreased (by 8.8%), with fatty liver dystrophy (by 45.0%) and diabetic ulcers of the lower extremities were completely cured. The number of patients diagnosed with diabetic retinopathy and nephropathy increased slightly (by 3.8% and 3.9%). None of the observed patients developed diabetic foot syndrome.

Thus, the data obtained indicate that careful control of glycemia and blood pressure is quite achievable and slows down the rate of progression of late complications

of diabetes mellitus and prevents the occurrence of acute macrovascular complications.

Based on the conducted research, the following practical conclusions can be drawn: the results of the study emphasize the importance of an individual approach to the treatment of patients with type 2 diabetes mellitus. It is necessary to take into account not only the type of drug, but also factors such as the stage of the disease, the presence of concomitant diseases, and the patient's lifestyle. Combination therapy with metformin and sulfonylurea has shown high efficiency in achieving compensation of carbohydrate metabolism in many patients.

It must be recognized that this study has a number of limitations: a limited sample size and a set of drugs. The study covered a limited number of drugs, which does not allow us to draw conclusions about the effectiveness of other medicines.

In the future, it is necessary to study the efficacy and safety of new classes of hypoglycemic drugs (SGLT2 inhibitors, DPP-4 inhibitors, etc.) in comparison with traditional drugs; to study the role of genetic factors in the effectiveness of various treatment regimens.

Thus, this study is an important step in studying the effectiveness of various drugs in the treatment of type 2 diabetes mellitus. However, in order to obtain more complete and reliable data, further research is needed, taking into account these limitations.

5. Conclusion

1. The use of oral hypoglycemic drugs glimepiride and metformin leads to positive dynamics of carbohydrate-lipid metabolism, a significant decrease in insulin levels by 22.6% and glucagon as in patients with type 2 diabetes.
2. Repaglinide is a postprandial stimulator of insulin secretion and its implementation to patients with T2DM combined with coronary artery disease leads to normalization of carbohydrate balance by reducing corticotropin and cortisol in the blood by 28%.
3. Long-term use of metformin in combination with PSM helps reduce cholesterol, LDL-C ($p<0.05$), triglycerides ($p>0.05$) and increase HDL-C ($p<0.05$).

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