ENGLISH VERSION: RESULTS OF A 3 MONTH TREATMENT WITH METFORMIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ASSOCIATED WITH ISCHAEMIC HEART DISEASE*

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The aim of the research was to investigate the effectiveness of mid-term inclusion of Metformin in the complex therapy in patients with diabetes type 2 in combination with IHD for the rational justification of timing, doses of the drug. Materials and methods. 52 man suffering from diabetes type 2 on background of ischaemic heart disease have been observed. An effect of included Metformin at mid-term rate (3 months) was estimated. The blood rates are observed (total cholesterol (TC), HDL-cholesterol, total lipids (TL), triglycerides (TG), β-lipoproteins, glycated hemoglobin, C-peptide) and anti inflammatory markers (IL-1β, IL-6, IL-8 and TNF-α). Results. In patients with diabetes type 2 on background of ischaemic heart disease during 3 months under the action of metformin significant decrease in body weight, waist circumference, BMI, concentration of total cholesterol, C-peptide and insulin resistance index and cytokines level IL-1β, IL-6 and TNF-α were observed. Conclusion. The obtained results indicate the purpose of Metformin prescription in patients with diabetes type 2 and IHD in the continuation of 3 months; it is an effective and safe method of treatment of such patients.

Key words: type 2diabetes mellitus, ischaemic heart disease, insulin resistance, Metformin, systemic inflammation, angina pectoris.

The question about the effectiveness of Metformin in patients with type 2 diabetes mellitus on background of ischaemic heart disease, and pharmacodynamic effects continues to be discussed [1,3,4]. In previous work, we have described the efficacy and safety of Metformin as initial insulin therapy for diabetes type 2 in combination with ischaemic heart disease after 1 month of treatment with Metformin. The clinical trials, anthropometric data, carbohydrate and lipid metabolism and systemic inflammation have been studied. The results showed improvement in clinical condition, reduction of body weight, lower total cholesterol, low-density lipoproteins, glycated hemoglobin, C-peptide, index of insulin resistance, markers of systemic inflammation, increased levels of high-density lipoproteins [2].

The aim of this work was to study the effectiveness of mid-term inclusion of Metformin in the complex therapy of patients with diabetes type 2 in combination with IHD for the rational justification of timing, doses of the drug.

Materials and methods

52 men aged 45-65 years were included in the clinical study, they suffered from ischaemic heart disease in combination with diabetes type 2. The study was conducted in the period from 2008 to 2010 on the basis of the 1st City Clinical Hospital, Poltava and Research Institute of the genetic and immunological basis for the development of pathology and pharmacogenetics of the Ukrainian medical stomatological academy. Before beginning the study an approval from the Commission of bioethics was obtained.

Patients were diagnosed with diabetes type 2 and IHD according to WHO criteria.

All patients underwent a screening examination for verification of diabetes type 2 diagnoses and ischaemic heart disease before the clinical study. There were 52 selected patients after screening who took a standard complex drug therapy within a month: acetylsalicylic acid 75 mg 1 time a day at night, bisoprolol 5-10 mg 1 time a day, atorvastin 10 mg 1 time a day, nitroglycerin 0.5 mg (angina). All patients have got an advice about diet and lifestyle changes.

During the first day of the study all patients were taking blood samples and performed clinical examination. After that, in the combined therapy Metformin at a dose of 500 mg 2 times a day was included (Siofor, Berlin-Chemie), i.e. firstly a drug therapy by oral hypoglycemic drug was assigned. A second survey was carried out after 1 month and 3 months. Anthropometric indicators (height, weight, calculated the body mass index (BMI) were evaluated. All patients were examined clinically including: blood analysis, urine analysis, blood sugar analysis, urine sugar analysis, biochemical blood analysis, total cholesterol, α-cholesterol, triglycerides, lipoprotein, total lipids, ultrasound of kidney, ultrasound of the heart, ECG. All methods were routine and aimed at verifying and determining the severity of the main disease, and identification of comorbidity.

The character of changes of the current disease was assessed by functional class of exertional angina, severity of hypertension, the severity of heart failure.

The study of changes in lipid metabolism in patients was conducted by means of biochemical methods determining the concentrations of total cholesterol, cholesterol high density lipoprotein (HDL), total lipids, triglycerides, lipoproteins in blood serum using reagent kits (Bio-La-Test, Czech Republic).

Carbohydrate metabolism was investigated by determining the concentration of glucose and glycosylating hemoglobin (HbA1c) in the blood of patients. Determination of glycosylated hemoglobin was performed using "Glycosylamines hemoglobin" (Bio-La-Test, Czech Republic).

The concentration of C-peptide was determined in serum by ELISA using test system (DRG International, Inc. USA).

For the insulin resistance estimation are used our proposed index of insulin resistance calculated by the formula:

$$\frac{\text{Concentration of C-peptide} \times \text{concentration of HbA1c}}{9{,}71},$$

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which in healthy people should be about 1.

The study of the immune and inflammatory response was performed by determination of the major regulator of interleukin - 1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8). The reagent kits are used for determination of the quantitative determination of human interleukin (IL-1 beta, IL-6, IL-8) in human biological fluids and in culture substrate (Russia, IL-1 beta ELISA-BEST, JSC "Vector-Best).

For estimation of the organism immune status a proinflammatory cytokine has been studied. It is an important molecular mediator of intercellular interactions - alpha TNF (tumor necrosis factor). Quantitative levels of TNF alpha were determined using a set of reagents for the quantitative determination of human alpha TNF in biological fluids of human and cultural environments (Russia, alpha TNF-ELISA-the BEST, JSC "Vector-best").

Statistical analysis of results were performed using the standard STATISTICA 6.0 (StatSoft, USA) with the calculation of the arithmetic mean, standard deviation, probability of the obtained results of T-test for the pair bonded and independent variables (t). For selected indicators, the reliability of differences was calculated by nonparametric methods of Wilcoxon and Van der Waerden. The difference frequency was estimated by calculating χ2.

Research results and discussion

In clinical research, we have formed a group of patients suffering from diabetes type 2 on background of ischaemic heart disease, which has criteria of WHO and ISPAD.

Table 1

Peculiarities of the course of diabetes type 2 in patients with ischaemic heart disease in the dynamics of treatment

Group (n=52)	Angina		Arterial hypertension		Chronic heart failure	
	FC II	FC III	Easy art.	Medium heavy art.	NYHA I	NYHA II
Before treatment Metformin	47	5	14	38	22	30
After 1 month of therapy with Metformin	49	3	24	28	31	21
After 3 months of therapy with Metformin	51	1	28	24	37	15
χ2 Pearson, df=1 (for 1 month)	χ^2 = 0,135; p = 0,713		χ^2 = 3,359; p = 0,067		χ^2 = 2,462; p = 0,117	
χ2 Pearson, df=1 (for 3 months)	χ^2 = 1,592; p = 0,207		χ^2 = 6,750; p = 0,009		χ^2 = 7,678; p = 0,006	

As can be seen from the data oftable. 1, the patients with diabetes type 2 on background of ischaemic heart disease mostly with stable angina of second functional class were represented. The patients with moderate arterial hypertension and 2-stage heart failure are dominated.

These data confirm that included patients with ischemic heart disease who have previously experienced such an important syndrome as hypertension.

The duration of CHD in the group was from 1 to 10 years, obesity from 1 to 5 years, hypertension from 1 to 10 years.

As shown in table. 1, among patients prevailed with angina FC II, mild arterial hypertension - 14, moderate - 38, chronic heart failure of first degree at 22, and II - 30 patients. The inclusion of Metformin in the complex therapy of IHD has resulted in improved clinical course of the disease during the first month of Metformin. But after 3 months there was a reliable decrease in functional class of exertional angina, and a tendency to decrease blood pressure levels and stages of chronic heart failure.

Table 2

Anthropometric data from patients with ischaemic heart disease and diabetes mellitus type 2 in the dynamics of treatment

Patients (n=52)	Weight, kg	Height, cm	Waist circumference, cm	The body mass index, c.u.
Before treatment with Metformin	112,1±7,4	176,0±6,55	118,2±7,1	35,4±4,1
After 1 month of therapy with Metformin	111,7±6,2*		116,6±5,3*	34,1±3,6*
After 3 months of therapy with Metformin	110,8±4,7*		113,6±3,9*	33,8±2,9*

** the reliability of differences between the groups before treatment (p is >0,05)*

After 3 months of Metformin therapy as follows from table 2, anthropometric indicators after 3 months of treatment with Metformin did not differ from the respective figures in 1 month and were significantly lower than before treatmen.

Table 3

Lipid metabolism in patients with type 2 diabetes mellitus on the background of IHD in the dynamics of treatment

Patients (n=52)	Total cholesterol, mmol/l	The HDL cholesterol, mol/l	Triglycerides mmol/l	The atherogenic index	The LDL-C, mol/l
Before with treatment Metformin	6,58±0,27	1,30±0,04	2,14±0,19*	4,07±1,18	4,31±0,42
After 1 month of therapy with Metformin	5,04±0,21*	1,41±0,03*	1,53±0,11*	2,57±1,08*	2,97±0,20*
After 3 months of therapy with Metformin	4,53±0,19**	1,40±0,01*	1,33±0,09*	2,12±1,05**	2,77±0,16**

*Note: here and after: * - p <0,05 compared to before treatment,*
*** - p <0,05 in comparison with indicators 1 month*

After 3 months of Metformin therapy, reduction in total cholesterol due to HPNP and atherogenic index. continued (compared with 1-month therapy results)

Table 4

Indicators of carbohydrate metabolism, cytokines and cellular factors in patients with metabolic syndrome in the dynamics of treatment

Patients (n=52)	Glycosylated hemoglobin, μmol of fructose/g HB with A1	C-peptide, ng/ml	Index IR	IL-1β, pg/ml	IL-6, pg/ml	IL-8, pg/ml	TNF-α, pg/ml
Before the Metformin prescription	5,23±0,75	13,63±1,52	7,35±0,88	17,92 ± 1,8	41,4±12,8	35,7±8,6	24,92±3,1
After 1 month of therapy with Metformin	4,84±0,45*	8,14±1,74*	4,10±0,82*	7,67±1,8*	19,4±1,8*	18,52±2,2*	18,52±1,9*
After 3 months of therapy with Metformin	4,10±0,27**	8,01±1,57*	4,03±0,72*	7,07±1,4**	19,1±1,5*	18,15±1,9*	18,42±1,8*

*Note: here and after: * - p <0,05 compared with the rates before treatment,*
*** - p <0,05 in comparison with indicators in a 1 month*

As can be seen from the data presented (table. 4), after 3 months of treatment with Metformin the level of $HbA1_c$ and IL1β has decreased. Other indicators remained at the level achieved after treatment during 1 month.

Our results showed that stable process of diabetes type 2 for patients with coronary artery disease treated using modern complex drug therapy is characterized by predominantly overweight, moderate disturbances of lipid metabolism and presence of insulin resistance with pronounced activity of systemic inflammation. These data are grounds for the inclusion of Metform in standard complex therapy.

As can be seen from the table. 2, short-term use of Metformin for the last 1 month has caused a significant decrease in body weight, waist circumference and BMI (p<0,05), but after 3 months has confirmed the reduction of anthropometric indicators. Tendencies towards lower levels of total cholesterol have been observed too. However, reliable applications performance characteristic of lipid metabolism for 1 month have not been identified. But after 3 months there was a tendency to normal lipid metabolism. Similarly, it was not observed a significant decrease of the level of indicators characterizing the level of insulin resistance. However, the index of insulin resistance was decreased by 45,3%.

Very important was a registered significant decrease in the concentrations of IL-1β and IL-6 in serum (table.4) to 8.69±6,94 and 9.33±9,84 pg/ml, respectively . The level of IL-8 was decreased significantly due to individual variability parameters after treatment. The concentration of TNF-α was not changed significantly.

The results show that systemic inflammation plays an important role in the development of diabetes type 2 and IHD. Especially important in practical terms, there is evidence that modern integrated medical therapy of ischaemic heart disease, including nitrates, acetylsalicylic acid, β-blocker and a statin, does not lead to sufficient reduction of the level of systemic inflammation, and in patients with diabetes type 2 and reduce the insulin resistance.

Data concerning the concentration of proinflammatory cytokines in patients with diabetes type 2 on background of ischaemic heart disease co-ordinate with the results of M. Mamedov [5] derived from patients with different clinical IHD and various risk factors. The authors rightly conclude that the presence of systemic inflammation in patients destabilization of the atherosclerotic process and its increasing in unstable (progressive) angina process. As you know, as a primary molecular mechanism of action of Metformin is considered the inhibition of complex 1 of the respiratory chain, which leads to decreased production of ATP, the increase in the ratio of AMP/ADP/ATP and inhibition of gluconeogenesis [11]. Our findings emphasize the simultaneous reduction in the activity of immune system cells that produce cytokines inflammation, which can also be a result of the above process, but plays an independent role as a factor in the reduction of insulin resistance.

Conclusions: after 3 months of treatment with Metformin patients with diabetes type 2 on background of ischaemic heart disease, compared with the results obtained after 1 month of treatment displayed:

1. Patients have a tendency towards improvements of clinical rates, reduction in the functional class of exertional angina, the severity of heart failure, blood pressure, and also saved the achieved reduction of body mass index.
2. The further improvement in lipid metabolism was noted: the reduction of total cholesterol, triglycerides, and atherogenic index.
3. Saving of a level of glycated hemoglobin C-peptide, index of insulin resistance and systemic inflammation was achieved in 1 month,.
4. Obtained results indicate that Metformin prescription for the patients with diabetes type 2 and IHD during 3 months is an effective and safe method of treatment of such patients.

References

1. Volkov V.I. Ischaemic heart disease and diabetes / V. I. Volkov, S. A. Serik // Zdorov'ya Ukraini. - 2007. No. 1. - P. 7-8.
2. Lavrenko A. V. Effectiveness of Metformin as initial insulin therapy in patients with ischaemic heart disease and diabetes type 2 / Lavrenko, A. V., Kutsenko L. A. Solokhina I. L. [and others] // Likars'ka sprava. - 2011. - № 1-2 (1108). - P. 89-95.
3. Lutay M. I. Atherosclerosis: a modern view of the pathogenesis / Ukr. cardol. mag. - 2003. No. 1. - P. 12-16.
4. Lutay M. I., I. Golikov I. P., Deak S. I., Slobodskoy V. A. Systemic inflammation in patients with ischaemic heart disease: correlation with clinical course and risk factors / Ukrainskiy medichniy chasopis. - 2006. - №2 (52). - P. 80-83.
5. Mamedov M. N. The significance of the metabolic syndrome in clinical practice: diagnostic principles and ways of correct medication / M. Mamedov // News of medicine and pharmacy. - 2007. No. 10. - P. 16-17.
6. Mankovsky B. M. Effectiveness of treatment of patients with diabetes type 2: results of a prospective study TAR-

GET-CONTROL / Liki Ukraini. - 2009. - № 10 (136). - P. 13-16.
7. Medical treatment of stable angina. Methodical Recommendation of working groups about problems of atherosclerosis and chronic forms of IHD/ Association of cardiologists of Ukraine. - Kyiv, 2008. – P. 62 .
8. Talaeva T. V. Insulin resistance: pathogenetic significance and possibilities of pharmacological correction / Ukrainian cardiological mag. - 2009. No. 1. - P. 64-82.
9. Unique effects of Metformin in the treatment of metabolic syndrome / Mkrtumyan A. M., Biryukov,E. V., N. Markina N.V., Garbuzova M. A. // Russian medical mag. - 2009. T. 17, No. 10. - P. 692-698.
10. Anselmino M., Bartnik M., Malmberg K., Ryden L. Management of coronary artery disease in patients with and without diabetes mellitus. Acute management reasonable but secondary prevention unacceptably poor: a report from the Euro Heart Survey on Diabetes and the heart / Eur. J. Cardiovasc. Prev. Reh. - 2007. – Vol. 14 (1). – P. 28-36.
11. Graham Rena, Ewan R.Pearson, and KeiSakamoto. Molecular mechanism faction of metformin: old or new insights Diabetologia.-2013.-Vol. 56.-P. 1898–1906.
12. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) / Eur. Heart J. – 2007. – Vol. 28. – P.88-136.
13. Guidelines on the management of stable angina pectoris: executive summary. The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology / Eur. Heart J. – 2006. - Vol. 27. - P. 1345-1381.
14. UKPDS Group. Effect of blood glucosae control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34) / Lancet. – 1998. – Vol. 352 (9131). – P. 854-865.

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