Combination of Metformin and Pioglitazone and its Effect in Treatment of Comorbid Pathology

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ABSTRACT

Introduction: The early development and high incidence of cardiovascular lesion in patients with type 2 diabetes mellitus is one of the most serious challenges for the diabetology worldwide.

Aim: The purpose of the paper is to determine the dynamics of the insulin resistance indices in patients with type 2 diabetes mellitus concomitant with coronary heart disease in the combination therapy with metformin and pioglitazone during 3 and 6 months.

Materials and Methods: 95 patients with type 2 diabetes mellitus and coronary heart disease have been treated and randomized into two groups: the comparison group (n=37), treated with metformin and sulfonylureas, and the study group (n=58), treated with metformin in combination with pioglitazone. Prior, after 3 and 6 months of treatment C-peptide was assessed and index of the insulin resistance was calculated.

Results: The resulting data proved the statistically significant lowering of the markers and level of the insulin resistance under the effect of combination treatment with metformin and pioglitazone.

Conclusions: The proposed variant of the combination therapy has a positive effect on the clinical course of the coronary heart disease in patients with type 2 diabetes mellitus, well tolerated by the patients and can be considered as the pathogenetic factor in the treatment of these diseases.

Key words: diabetes mellitus, coronary heart disease, insulin resistance.

INTRODUCTION

The issue on delivery of the medical care for patients with concomitant and combined pathology has been actively discussed in current scientific publications. The early development and high incidence of cardiovascular lesions in patients with type 2 diabetes mellitus (DM2) is one of the most serious challenges for the diabetology worldwide [1]. Therefore, the development of the therapy for type 2 diabetes mellitus, concomitant with coronary heart disease is the relevant issue of the cotemporary medicine, since it is necessary to influence on both the common links of the pathogenesis of the diseases and the specific processes in the cardiovascular and immunoneuroendocrinal systems [2, 3, 4].

Insulin resistance (IR) is the main pathogenetic mechanism of both hidden and apparent DM2 and other components of the metabolic syndrome: dyslipidemia, arterial hypertension, excessive weight [5]. DM2 is considered as the "end point" of the IR development, triggered by hyperinsulinemia.

I. P. Kaidashev [6] and R. DeFronzo [7] report that large doses of insulin accelerate the development of atherosclerosis. Hyperinsulinemia enhances IR, contributes to the formation of triglycerides (TG), LDLs and VLDLs and their transport into the smooth muscle cells of blood vessels [8] and activates the chronic systemic inflammation (CSI). The mechanism of action of the sulphonylurea derivatives is based on the stimulation of insulin secretion from β-cells. Thereafter, concentration of blood insulin increases in patients with DM2, which is the risk factor for hypoglycemia. It is known that hypoglycemia increases the risk for cardiovascular complications, myocardial infarction, stroke and sudden death [9].

Aim. The purpose of the paper is to determine the dynamics of the insulin resistance indices in patients with type 2 diabetes mellitus concomitant with coronary heart disease in the combination therapy with metformin and pioglitazone during 3 and 6 months.

MATERIALS AND METHODS

The study has been carried out at the Research Institute for Genetic and Immunological Grounds of Pathology and Pharmacogenetics of the Higher State Educational Establishment of Ukraine "Ukrainian Medical Stomatological Academy" and at the Endocrynology Unit of the Kremenchuk First Municipal Hospital. 95 patients (39 men and 56 women) with type 2 diabetes mellitus and coronary heart disease have been involved into study. The mean age of the patients was 59.40 ± 8.01 years. Prior to the involvement into study the patients were treated with metformin; a monotherapy-related medium level of NvA1s was 8.90 ± 0.76%. The subjects have been randomized into 2 groups: the comparison group (n=37), treated with 1700-2550 mg/day metformin and sulfonylureas in a day dose of 30 to 60 mg, depending on the body weight; the study group (n=58), treated with metformin in combination with 30 mg/day pioglitazone. The proposed mode of treatment has been patented in Ukraine [11].

The CHD has been diagnosed in the occurrence of typical Class I-II exertional angina pectoris (according to the Canadian Cardiovascular Society grading), using the the WHO criteria. DM2 has been diagnosed according to the Unified clinical protocol of the primary and secondary medical care (approved by the Ministry of Health as of 21.12.2012, No. 1118).

After screening all patients were prescribed with the standard complex of the medicamentous therapy to achieve stabilization of the CHD: 20 mg isosorbide dinitrate twice a day, 75 mg/day acetylsalicylic acid, 10 mg/day amlodipine, 2,5-5 mg/day bisoprolol, 10 mg/day atorvastatin. Patients received conventional treatment during a month. Additionally, recommendations on nutrition and change of the lifestyle have been given to all patients.

Inclusion criteria for clinical trial: men and women aged 45 to 65 years, with confirmed diagnosis of CHD, subcompensated type 2 diabetes mellitus, class I-III obesity, hypertension. The exclusion criteria: patients who, within 6 months, experienced the acute

coronary syndrome, stroke, surgical intervention, serious physical and mental illnesses, as well as patients with poorly controlled hypertension, Class III-IV angina pectoris, stage II B and III heart failure; arrhythmias that required special antiarrythmic treatment; renal and hepatic failure; decompensated diabetes mellitus; patients with intolerance to thiazolidinediones or metformines.

C-peptide was determined by the immunoenzyme method using the test-systems (DRG, United States) and insulin resistance index (IRI) was calculated. The assessment of the insulin resistance level has been made using the formula, developed by I.P. Kaidashev, et al. [17]: IRI = ($Hв_{A1c}$ concentration) x (C-peptide concentration): 9.71; (the norm is about 1.0, limits of range from 0.66 to 17.6). The higher the index, the lower is the insulin sensitivity and, consequently, the higher is the insulin resistance. Statistical analysis of the findings was made by the BioStat software (Analyst Soft Inc, ver. 2009 for Windows), using the Mann–Whitney U test (for independent samples) and the Wilcoxon test (for dependent samples) and χ^2.

Tolerance of drugs has been assessed by the incidence of undesirable events and adverse reactions. Safety was determined by the incidence of episodes of hypoglycemia, allergic reactions, as well as by the results of biochemical blood examination, complete blood count and urinalysis.

RESULTS AND DISCUSSION

The comparison of the IR indices has shown that prior to starting the therapy no statistically significant difference was found between the study groups (Table I).

Table I

Insulin resistance indices in patients with DM2 and CHD before and after treatment (M±σ)

Index,	Clinical study groups

units of measure	Before treatment		3 months following the treatment		6 months following the treatment	
	Study group (n=58)	Comparison group (n=37)	Study group (n=58)	Comparison group (n=37)	Study group (n=58)	Comparison group (n=37)
C-peptide, ng/mL	8,48±1,88	8,20±2,05	7,04±1,62	7,91±2,02	6,08±1,52	7,64±1,93
P*	0,416		0,045		<0,001	
IPI	7,71±1,71	7,41±1,76	5,61±1,34	6,47±1,61	4,42±1,17	5,65±1,43
P*	0,42		0,008		<0,001	

Following the 3 months after treatment the level of C-peptide and insulin resistance index statistically significantly decreased in both groups of patients. However, the comparison of the indices between the study groups showed that the level of C-peptide in the blood serum of patients treated with MF and sulfonylureas lowered from 8.20 ± 2.05 ng/mL to 7.91 ± 2.02 ng/mL, whereas in patients who received combination treatment with MF and PG it decreased from 8.48 ± 1.88 ng/mL to 7.04 ± 1.62 ng/mL (p = 0,045). The IRI level in the comparison group and study group decreased from 7.41 ± 1.76 to 6.47 ± 1.61 and from 7.71 ± 1,71 to 5.6 ± 1,34, respectively (p = 0.008).

Following the 6 months after treatment the level of C-peptide and insulin resistance index was tending to decrease in both groups of patients. The comparison of the indices between the study groups showed that the C-peptide level in the blood serum of patients treated with MF and sulfonylureas lowered to 7.64±1.93 ng/mL, whereas in patients who received combination treatment with MF and PG it decreased to 6.08±1.52 ng/mL (p<0,001).

The IRI level in the comparison group and study group lowered to 5,65±1,43 and 4,42±1,17, respectively ($p<0,001$).

Thus, the resulting data showed more positive effect on the IR indices in patients with comorbid pathology, treated with MF in combination with PG, in contrast to the comparison group. It has a positive impact on the development and course of the present nosologies and can be considered as a pathogenetic factor in the therapy of the above nosologies.

Optimization of treatment of CHD in patients with DM2 is associated rather with the progress of hypoglycemia therapy, then with the measures aimed at reducing the CSI and IR [10, 11, 12]. Pioglitazone (PG) and metformin (MF) affects the major links of DM2 pathogenesis with different mechanisms of action and different affinity with regard to the target tissues. The effect of MF is focused mainly in the liver, inhibiting gluconeogenesis and reducing the activity of the nuclear proinflammatory transcription factor (NFkB) [13, 14]. PG is the agonist of the nuclear transcription factors (NTF), peroxisome proliferator-activated receptors gamma (PPARγ). The study of N.I. Vynnyk has proved the positive effect of PG on reduction of IR level in patients with CHD combined with metabolic syndrome [15, 16]. However, the present combination of drugs reduces the risk of weight gain, which is typical for the monotherapy with glitazones, well tolerated by patients, and, according to current publications, effectively reduces all macrovascular complications of DM [11].

No negative interaction of MF and PG with antianginals has been recorded. Side effects were observed in 2 patients (3.63%), not requiring drug discontinuation. No case of the marked, clinically manifested edemas has been recorded. The complete blood count and urinalysis results showed no negative dynamics. Biochemical indices of the liver and kidney functioning were within the normal range. No cases of hypoglycemic reactions, drug withdrawal, or discharge of patients from the clinical study due to adverse or allergic reactions to the therapy have been reordered during observation. All the above data indicate

about good tolerability and safety of PG and MF in patients with DM2 combined with CHD.

CONCLUSION

1. The IR correction is crucial in prevention of cardiovascular diseases, which must be done well in advance of the DM2 onset as the end point of the IR development.
2. Combination therapy with metformin and pioglitazone provided for patients with DM2 and CHD leads to statistically significant improvement of the insuline resistance indices: lowering of the C-peptide and insulin resistance index by 28.3% and 42.7%, respectively.
3. Metformin and pioglitazone therapy is well tolerated by patients, improving the quality of life, and can be recommended to patients with this pathology.
4. The prophylactic prescribing of drugs, reducing the IR, to individuals who, due to various reasons, cannot adjust the IR through a diet and exercise should be considered.

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