CHRONIC SYSTEMIC INFLAMMATION IN THE PATHOGENESIS OF COMORBID PATHOLOGY AND ITS CORRECTION

Zlatoslava O. Shaienko, Nataliia I. Vynnyk, Lyudmila Ye. Bobyreva, Alla O. Popruga

«Ukrainian Medical Stomatological Academy»

Abstract. The paper presents the findings of our own study on the changes of the systemic inflammation in patients with type 2 diabetes mellitus (DM2) and ischemic heart disease (IHD) during the combination treatment with metformin and pioglitazone. 95 patients with IHD concomitant with DM2 have been treated. Patients, enrolled into study, have been randomized into 2 groups: the comparison group (n=37) treated with metformin and sulphonylureas, and the study group (n=58) treated with metformin and pioglitazone. The proposed course of therapy lasted 6 months. Before, after 3 and 6 months of treatment the control over the state of inflammatory responses was made and C-reactive protein, tumor necrosis factor-alpha, Interleukin-6 was assessed. The resulting data confirmed a statistically significant reduction under the effect of the combined treatment with the proposed combination of marker drugs and the degree of chronic systemic inflammation that is specific for IHD and DM2, which has a positive impact on the development and progress of IHD in DM2 patients, is well tolerated and can be considered as a pathogenic factor in the therapy of the presented comorbid nosologies.

Keywords: diabetes mellitus, ischemic heart disease, chronic systemic inflammation.

ХРОНІЧНЕ СИСТЕМНЕ ЗАПАЛЕННЯ В ПАТОГЕНЕЗІ КОМОРБІДНОЇ ПАТОЛОГІЇ ТА ЙОГО КОРЕКЦІЯ

Шаєнко З.О., Винник Н.І., Бобирьова Л.Є., Попруга А.О.

Резюме. У статті представлені результати власних досліджень про динаміку зміни системного запалення у хворих на цукровий діабет 2 типу (ЦД) та ішемічну хворобу

серця (ІХС) при комбінованому лікуванні метформіном та піоглітазоном. Проліковано 95 хворих з ІХС у поєднанні з ЦД 2 типу. Пацієнти, включені у дослідження, були рандомізовані на 2 групи: група порівняння (37 чоловік), які отримували метформін та препарати сульфонілсечовини та група спостереження (58 пацієнтів), яким до метформіну в терапію був включений піоглітазон**.** Запропонований курс терапії тривав 6 місяців. Через 3 та 6 місяців лікування проводили контроль стану запальної відповіді – визначали С-реактивний білок, фактор некрозу пухлин-альфа, інтерлейкін 6. Отримані нами дані підтверджують статистично значиме зниження маркерів та рівня хронічного системного запалення, яке характерне для ІХС та ЦД 2 типу, під дією комбінованого лікування, що має позитивний вплив на розвиток та перебіг ІХС у хворих з ЦД 2 типу, добре переноситься пацієнтами та може розглядатися як патогенетичний чинник в терапії даних коморбідних нозологій.

Ключові слова: цукровий діабет, ішемічна хвороба серця, хронічне системне запалення.

INTRODUCRION

It has been recognized that chronic retarded inflammatory process (CSI) and CSI-induced insulin resistance (IR) underlies the pathogenesis of multiple chronic diseases, in particular, type 2 diabetes mellitus, atherosclerosis and its complications in the form of coronary heart disease [1,2]. The CSI is activated by various stressors, namely, infections, intoxications, injuries, oxidative stress, metabolic disorders that lead to the disorder of the immune system, primarily its monocytic-macrophage link, accompanied by hyperproduction of proinflammatory cytokines [4,6,7]. Nuclear transcription factors of both proinflammatory (for example, NFkB) and inflammatory (for example, PPARγ -activated receptors) nature are crucial in these processes [3,5,10].

Recently, the pharmacological therapy has been tending to use the combination of blood glucose-lowering drugs with different mechanism of action that affect the IR and CSI [4, 7, 8,14]. Pioglitazone (PG) and metformin (MF) has an effect on the leading links of DM2 pathogenesis, acting through different mechanisms and different affinity to the target tissues. MF acts mainly in the liver, inhibiting gluconeogenesis and reducing the activity of the nuclear proinflammatory transcription factor (NFkB) [5,9,13]. The effect of PG is focused in the adipose tissue, muscle and macrophages and overcomes the insulin resistance by nuclear transcription factors-receptors which activate proliferation bythe peroxisome-gamma (PPARγ) [3,10,11, 12]. This combination reduces the risk of weight gain, which is typical for monotherapy by glitazones, is well tolerated by patients and, as current publications report, effectively reduces all macrovascular diabetes complications [4, 8,14].

Many publications report on investigation of the effect of glitazones and biguanides, given separately, on glycemic control in patients with type 2 diabetes mellitus [9,11,12,13]; however, their combination, used in treatment of patients with DM2 concomitant with IHD is still not completely studied.

PURPOSE

The aim of the paper is to define the dynamics of the systemic inflammation in patients with type 2 diabetes mellitus and ischemic heart disease in combination treatment with metformin and pioglitazone.

MATERIAL 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 O.T. Bogaievskii Kremenchuk First Municipal Hospital. 95 patients (39 men and 56 women) with ischemic heart disease and type 2 diabetes mellitus and have been treated. The mean age of the patients was 59.40 ± 8.01

years. The mean duration of DM2 was 5,3±07. Prior to the involvement into study the patients received metformin; the mean level of the monotherapy-related HвA1was 8,90±0,76%. The patients, enrolled into study, have been randomized into 2 groups: the comparison group (n=37), treated with metformin (Siofor®, *Berlin-Chemie Menarini*) at a dose of 1700-2550 mg/day and sulfonylureas at a daily dose of 30 to 60 mg according to the body weight and glycemia index; the study group (n=58), who received 30 mg/day pioglitazone (Pioglar®, *Ranbaxy Laboratories Ltd, Ind. Area*), an insulin sensitizer (a thiazolidinedione), in association with metformin. The proposed mode of treatment has been patented in Ukraine [8].

The IHD has been diagnosed in compliance with the WHO's 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).

Once the screening was made, all patients received the standard comprehensive medicamentous therapy to achieve stabilization of the IHD indices: 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. The patients received conventional treatment during a month. Additionally, the recommendations on healthier nutrition and lifestyle have been given to all patients.

Inclusion criteria for clinical study are: men and women aged 45 to 65 years, with confirmed diagnosis of IHD, subcompensated type 2 diabetes mellitus, class I-III obesity and hypertension.

The proposed course of treatment [8] lasted for 6 months. Before, after 3 and 6 months of treatment the control over the state of inflammatory response was made. The level of C-reactive protein was assessed in both groups, whereas the tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) was assessed in 36 patients of the study group, using the test-

system set (ZAO „Vektor-Best”, Russia). The statistical analysis of the results 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 test.

The drug tolerance has been evaluated by the incidence of undesirable events and side effects. The 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 study of the degree of systemic inflammation in the groups of patients has established that after 3 months of treatment the level of TNF-α and IL-6 reduced by 29,6% and 44,1%, respectively, in patients treated with MF and sulfonylureas as compared with 56,34% (p=0,027) and 56,4% (p=0,035), respectively, in patients treated with MF in combination with PG. After 6 months of treatment in the comparison group the level of TNF-α and IL-6 reduced by 54,4% and 61%, respectively, whereas in the study group it reduced by 76,8% (p<0,001) and 68,1% (p=0,013), respectively (Table 1).

Table 1

Indices of systemic inflammation (study group) in patients with IHD and DM2 before and after treatment (M±σ)

Index, units of measure	Study group (n=36)			p
	Before treatment	After 3 months of treatment	After 6 months of treatment	
TNF-α, pg/ml	6,3±1,91	2,05±1,53	1,17±0,68	< 0,001
IL-6, pg/ml	5,11±2,38	2,67±1,67	1,31±0,67	< 0,001

We have established that index of blood plasma C-reactive protein before treatment was positive in both groups of patients (Table 2). After 3 months of treatment the C-reactive protein was detected in 50 (86,2%) patients treated with MF in combination with PG and in 34 (91,9%) of patients who received MF and sulfonylureas (p=0,007). After 6 months of treatment it was found in 43 (74%) patients of study group and in 33 (89,2%) patients of the comparison group (p=0,033) (Table 2).

Table 2

The level of C-reactive protein in patients with IHD and DM2 before and after treatment (M±σ)

Clinical study groups							
Before treatment				After 6 months of treatment			
Study group (n=58)		Comparison group (n=37)		Study group (n=58)		Comparison group (n=37)	
+	-	+	-	+	-	+	-
58 (100%)	-	37 100%	-	43 (74,13%)	15 (25,87%)	33 (89,2%)	4 (10,8%)
p=1,0				p=0,033			

Consequently, the MF/PG combination treatment of patients with DMA concomitant with IHD leads to a statistically significant reduction of the TNF-α, IL-6 and C-reactive protein compared with MF/sulfonylureas therapy, indicating a powerful anti-inflammatory action of their combined use and has a positive impact on the IHD progress in patients with DM2.

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.

Noteworthy, even patients' keeping to the diet and healthy life-style recommendations, as well as comprehensive therapy of IHD with statin add-on therapy leads to a significant reduction of the CSI markers, and pioglitazone in association with metformin provides with additional anti-inflammatory effect.

The study of N.I.Vynnyk [11, 12] has shown that in IHD patients with the events of metabolic syndrome 30 mg pioglitazone during 6 months significantly reduced the degree of systemic inflammation, namely, the level of ceruloplasmin (by 1,24 times, $p < 0{,}001$), C-reactive protein (by 2,75 times, $p < 0{,}001$) and TNF-α (by 2,23 times, $p < 0{,}01$). The observation showed that in the comparison group the level of ceruloplasmin was tending to increase ($p < 0{,}05$). No significant changes in TNF-α level was observed, and the level of hypersensitized C-reactive protein reduced by 2,5 times ($p < 0{,}001$). The author indicates that comparison between the groups shows that within 12 months the significant difference in the level of ceruloplasmin ($p < 0{,}01$) and TNF-α ($p < 0{,}01$) was preserved. In the group of patients who received PG these indices was lower.

A.V. Lavrenko [13] has reported about the significant decline of inflammation indices in patients with IHD and DM2 in the short-term (1 month) therapy with MF at a dose of 1 g/day. The level of the IL-1, IL-6 and TNF-α reduced by 51%, 53% and 43%, respectively. The patients with metabolic syndrome without DM2 showed significant reduce in these indices within 30-40%, except for the TNF-α level that remain without changes. This indicates the marked anti-inflammatory effect of MF in both of DM2 individuals and patients with metabolic syndrome without DM2.

The comparison of the resulting data obtained by these authors of the effect of the separate use of pioglitazone and metformin on the indicators of inflammation generally

coincides with the data of our study. However, it should be noted that quantitatively, combination therapy is much more effective. In this way, pioglitazone reduces the level of TNF-α by 2.23 times, and metformin by 43%, whereas its combination reduces TNF-α by 5 times. The above data indicate a high anti-inflammatory activity of both MF and PG, and especially their combination, in patients with MD2 and IHD.

CONCLUSIONS

1. The combination of metformin and pioglitazone in the comprehensive treatment of patients with DM2 and IHD leads to statistically significant improvement of the indices of systemic inflammation, i.e., the reduce in level of TNF-α, IL-6 and C-reactive protein by 81,4%,74,4% and 25,87%, respectively.
2. The metformin and pioglitazone combination therapy is well tolerated by patients, improving the quality of life.

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