ejpmr, 2017,4(2), 175-178

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

THE ROLE OF INFLAMMATORY MEDIATORS IN THE PATHOGENESIS OF PROGRESSIVE ANGINA PECTORIS COMBINED WITH DIABETES MELLITUS TYPE 2.

Kasimova M.S.*[1], Ismailova A.A.[2], Shek A.B.[3], Akhmedova Sh.S.[4] and Khoshimov Sh.U.[4]

[1]PhD Student of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.
[2]MD., Head of the Laboratory of Immunopathology and Immunopharmacology of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.
[3]MD., Chief of Department of Coronary Coronary Heart Disease of the Republican Specialized Center of Cardiology.
[4]PhD of Department of Coronary Coronary Heart Disease of the Republican Specialized Center of Cardiology.

***Corresponding Author: Dr. Kasimova M.S.**

PhD Student of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.

Article Received on 01/12/2016 **Article Revised on 21/12/2016** **Article Accepted on 11/01/2017**

ABSTRACT

The article presents the results of the study of serum levels of IL-6, TNF-α and C-reactive protein (CRP) in patients with unstable angina with the presence of diabetes mellitus type 2 (DM T2) and without it. **Materials:** We examined 34 patients with unstable angina of II B class in accordance with E. Braunwald (2000), all patients were divided into groups: the first group - was represented by 15 patients with unstable angina and DM T2, the second group was represented by 19 patients with unstable angina without DM T2. The average age of patients was 56,8 ± 1,7 years. The cytokines IL-6 and TNF-α were determined in serum by ELISA using kits produced by "Vector-Best" LTD (Novosibirsk, Russia) on the enzyme immunoassay analyzer «StatFax - 2100" (USA). **Results:** In patients with DM T2 have high values of CRP and fibrinogen, in excess of 2 ($p<0,05$) and 1,3 ($p<0,01$) times, than those without DM T2. When comparing the values of cytokines in patients with persons of the control group in patients with DM T2 was an increase in the level of IL - 6 to 12,3 times ($p<0,01$) and TNF-α in the 4,6 ($p<0,05$) times. In the group of patients with unstable angina and DM T2 revealed correlation between the IL-6 and TNF-α ($r=0,84$ $p<0,001$), TNF-α and fibrinogen ($r=0,2$), TNF-α and CRP ($r=0,3$; $p<0,05$), between the values of the level of fasting plasma glucose and HbA1c with CRP level ($r=0,56$; $p<0,001$ and $r=0,31$; $p<0,05$, respectively). **Conclusions:** In patients with unstable angina in combination with DM T2 a history of hypertension were more frequent ($p<0.05$) and the PICS ($p<0.01$). In patients with DM T2 the presence of inflammatory mediators values significantly higher relatively to patients with unstable angina without DM T2. Therefore, in patients with progressive angina absence of diabetes determines a more favorable course of the disease.

KEYWORDS: unstable angina, diabetes mellitus type 2, cytokines, inflammation.

INTRODUCTION

Cardiovascular complications are the leading cause of morbidity and mortality in patients with diabetes mellitus type 2 (DM T2).[1,2] In view of the close relationship between diabetes and cardiovascular disease in the epidemiological and pathophysiological level the National program of dissemination of knowledge about cholesterol in adults (NCEP ANP-III) defines diabetes as a cardiovascular risk equivalent.[14] Diabetes accelerates the development of atherosclerosis, which often begins before the appearance of clinical signs and the establishment of hyperglycemia. At the time of detection of diabetes in half of the patients already have coronary heart disease, which demonstrates the importance of early diagnosis and aggressive treatment of hyperglycemia and related disorders. Progress also the plaque formation and atherosclerotic changes in the coronary arteries, the brain and peripheral vessels.[8,15] A number of studies with an equal increase in the content of glucose in the blood in patients with insulin-dependent and non-insulin dependent diabetes carotid arteries were more characteristic of people with insulin-dependent diabetes and only in combination with hypercholesterolemia and which is regarded as the leading factor in atherogenesis.[3,5,11]

Pro-atherogenic effect of diabetes is largely determined by the ability to inhibit hyperglycemia macrophage apoptosis, provoke the development of oxidative stress and support the inflammatory process in the vessel wall. To date, cytokines are the most promising markers of disorders of immune processes in inflammatory diseases. Feature cytokinemia in diabetes is that patients as the disease increases the number of cell structures with a

high production of cytokines.[6] Research on the role of pro-inflammatory cytokines and CRP, suggesting a role of induced cytokine subclinical inflammation in the pathogenesis of diabetes type 2.[16,17] Given these factors, we have an interest to explore the role of the indicators of the level of proinflammatory cytokines and lipid metabolism in patients with progressive angina in combination with DM T2.

The aim of the research

Assess the role of inflammatory markers in patients with progressive angina depending on the availability of a history of diabetes.

MATERIALS AND METHODS

The study involved 34 patients with unstable (progressive) angina class II B corresponding to E. Braunwald classification (2000). The average age of patients was 56,8 ± 1,7 years. 23 (67.6%) of these were men (mean age 55.7 ± 2.1 years) and 11 (32.4%) were women (mean age 59.3 ± 2.8 years). Prescription of CHD disease ranged from 2 to 17 years (mean 7,27 ± 0,48 years). The indications of myocardial infarction were 17 (50%) patients. The CHD was diagnosed on the background of arterial hypertension in 25 (73.5%) patients.

Based on clinical data, patients were divided into groups: the first group consisted of 15 patients with unstable angina and DM T2, mean age was 57,3 ± 2,8 years. The second group consisted of 19 patients with unstable angina without DM T2, mean age - 56,5 ± 2,2 years. Gathering patients was carried out on the basis of RSCC in office in 2012-13., who were hospitalized. The control group consisted of healthy people of similar age 25 (56,2 ± 1,53 years) and gender.

The study included face up to 70 years with typical manifestations of new-onset or progressive angina corresponding ESC guidelines[10]; the presence of documented diabetes type 2(WHO, 1999.). Exclusion criteria were: the development of acute myocardial infarction (MI) in a given period of hospitalization or transferred in less than 3 months ago; severe heart failure (HF) III-IV FC; DM T2 in the stage of severe decompensation; the use of insulin as glucose-lowering therapy; complex cardiac arrhythmias; severe liver and kidneys.

All patients received standard and hypoglycemic therapy may be needed. From biochemical assays to determination of the level of C-reactive protein (CRP) and fibrinogen at a biochemical autoanalyzer «Randox» (United Kingdom). The evaluation of carbohydrate metabolism was carried out by determining the level of fasting blood glucose and in terms of glycosylated hemoglobin (HbA1c).

The Immunological studies were performed in the laboratory of immunopathology and immunopharmacology of Institute of immunology, Academy of Sciences of Uzbekistan. The cytokines IL-6 and TNF- α were determined in serum by ELISA using kits of "Vector-Best" LTD (Novosibirsk, Russia) on the enzyme immunoassay analyzer «StatFax - 2100" (USA).

Statistical processing of the results was carried out with the use of software applications for statistical processing of data Statistica® version 6.0. The significance of differences between treatment groups was evaluated by Student's t test. Differences compared values recognized statistically significant at $p<0,05$. The correlation analysis was held with the help of calculation of the Spearman's coefficient. To find the difference between the quality indicators used $\chi 2$ method and Fisher's exact test for small samples.

RESULTS AND DISCUSSION

Patients in both groups were comparable in age, blood pressure level, duration and clinical course of the underlying disease. However, the analyzed groups significantly differed in magnitude BMI, SBP and DBP. Also in the group of unstable angina patients in combination with DM T2, a history of hypertension were more frequent ($p <0.05$) and the PICS ($p <0.01$), indicating an increase in plasma glucose, accompanied by a permanent increase of cardiovascular morbidity in DM T2[1] (Table. 1).

Table 1. Clinical and medical history of patients with progressive angina with and without DM T2 (M ± SD)

Indicators	With DM T2 (n = 15)	Without DM T2 (n = 19)	P
Age, years	57,3±2,77	56,5±2,2	ns
Men, n (%) **Women, n (%)**	10 (66,7%) 5 (33,3%)	13 (68,4%) 6 (31,6%)	
BMI, kg / m2	33,1±1,05	29,2±1,07	<0,05
Duration CHD years	7,4±1,0	6,55±0,78	ns
The prevalence of hypertension, n (%)	14 (93,3%)	11 (57,9%)	<0,05
Have PICS, n (%)	11 (73,3%)	6 (31,6%)	<0,01
SBP, mm. hg. art.	143,3±5,2	123,7±4,9	<0,01
DBP, mm. hg. art.	87,3±2,8	76,6±2,36	<0,01
Fasting Glucose, mmol / l	10,16±1,3	5,5±2,8	<0,01
HbA1c, %	12,44±2,1	87,3±2,8	<0,01

We analyzed the differences in the rates of subclinical inflammation between groups of patients with progressive angina with and without disorders of carbohydrate metabolism (Table 2). This is due to have emerged in recent years, the data on the important role of inflammation in the occurrence and development of atherosclerosis and its clinical manifestations.[4] The degree of increase of CRP level and hence, the intensity of the inflammatory process are combined with an increased risk of coronary events.[12] It was found that the group of patients with DM T2 had significantly higher levels of inflammatory markers CRP and fibrinogen, in excess of 2 ($p < 0,05$) and 1,3 ($p < 0,01$) fold, respectively, than those without diabetes. Reliably significant indicators were observed when comparing the level of CRP in the control group in the presence of coronary artery disease in patients with DM T2 and without exceeding in 9,8 ($p < 0,001$) and 4,8 ($p < 0,001$) times, respectively.

Table 2. The level of the biomarkers of inflammation in patients with progressive angina with and without DM T2 (M ± SD)

Indicators	With DM T2 (n = 15)	Without DM T2 (n = 19)	Control group (n=20)	P		
				With DM T2 and without DM T2	With DM T2, and a control group	Without DM T2 and control group.
CRP, mg / l	8,8±1,82	4,31±0,71	0,9±0,2	<0,05	<0,001	<0,001
Fibrinogen, g / l	3,56±0,17	2,82±0,15	2,5±0,6	<0,01	ns	ns
TNF - α, pg / ml	20,95±8,29	10,41±1,93	4,58±0,81	ns	<0,05	<0,01
IL - 6, pg / ml	42,1±13,24	18,15±6,1	3,42±0,28	ns	<0,01	<0,05

When analyzing the detected increase in pro-inflammatory cytokines IL-6 and TNF-α in patients with DM T2 is 2.3 times and 2 times, respectively, than in those without diabetes, but they were not significantly significant. Although they observed a significant increase when compared with the control group of individuals: in patients with diabetes was an increase in the level of IL - 6 to 12.3 times ($p < 0,01$) and TNF-α in the 4,6 ($p < 0,05$) fold and in patients without diabetes IL-6 increased 5.3-fold ($p < 0,05$) and the level of TNF-alpha in 2.3 times ($p < 0,01$). Increasing evidence of the presence of chronic inflammation in patients with angina pectoris, and in the group with a combination of angina and DM T2 observed their overexpression. Increased TNF-α content in blood serum is combined with the presence of insulin resistance and compensatory hyperinsulinemia, increase in concentration CRP, IL-6, as well as indirect acceleration of apoptosis.[8,13] These results are consistent with a number of studies that have confirmed elevated levels of inflammatory markers in patients with diabetes, contributing to the development and progression of atherosclerosis.[3] According Alexandraki K. increase in blood markers of inflammation in healthy people can act predictor of the future, not only CVD but also diabetes. Thus subclinical inflammation activity correlated with the biochemical markers of insulin resistance.[9]

The last 10 years' studies show that inflammation in particular pro-inflammatory cytokines are predictors of vascular complications of diabetes.[6] Thus, patients with progressive angina with concomitant DM T2 differ from patients without DM T2, higher values of inflammatory markers. It is important to note that this is confirmed by the direct correlation between the values of the clinical and immunological markers of inflammation. In the group of patients with unstable angina and DM T2 showed significant relationship between indicators of IL-6 and TNF-a ($r = 0,84$ $p < 0,001$), TNF-alpha and fibrinogen ($r = 0,2$), TNF-alpha and CRP ($r = 0,3$; $p < 0,05$). In the group of patients with unstable angina without DM T2 found significant positive correlation relationship between indicators of IL-6 and CRP ($r = 0,3$; $p < 0,05$). Also it should be noted that the group of patients with DM T2 has found a direct correlation between the values of the level of fasting blood glucose and HbA1c c CRP ($r = 0,56$; $p < 0,001$ and $r = 0,31$; $p < 0,05$ respectively), which is extremely important and is consistent with studies in which inflammation contributes to the development and progression of atherosclerosis in diabetes type 2.[3,9] Consequently, the absence of diabetes type 2 in patients with progressive angina predetermines a more favorable course of the disease, which is also associated with lower activity of subclinical inflammation processes.

CONCLUSIONS

1. The coronary artery disease combined with type 2 diabetes, says a more severe course of the disease characterized by elevated SBP, DBP, BMI and they have a history of hypertension were more frequent ($p < 0.05$) and the PICS ($p < 0.01$). Regardless of the duration of the ischemic heart disease, diabetes exacerbates the clinical course of unstable angina.
2. The levels of CRP and fibrinogen in patients with diabetes type 2 is significantly higher than in patients without diabetes, indicating the involvement in the pathogenesis of coronary artery disease progression of subclinical inflammation.
3. Patients with progressive angina in combination with diabetes type 2 are different from patients without diabetes high values of proinflammatory cytokines IL-6 and TNF-α, which is a diagnostic and prognostic character in the development of cardiovascular complications in coronary artery disease.

4. In patients with progressive angina absence of diabetes type 2 predetermines a more favorable course of the disease, which is associated with lower activity of subclinical inflammation processes.

REFERENCES

1. Dedov I.I., Melnichenko G.A. Endocrinology: national guide. M.: GEOTAR Media, 2012; 373-400.
2. Janashiya P.Kh., Mirina E.Y. Possible correction of lipid metabolism in patients with diabetes mellitus type 2. Russian Medical Journal, 2008; 16(11): 1561-66.
3. Kulikova A.N. The role of inflammation in atherogenesis in diabetes. Cytokines infl., 2007; 6(3): 14-19.
4. Oganov R.G, Zakirova A.D., Zakirova A.N. The Immunological response in acute coronary syndrome. Rational pharmacotherapy in cardiology, 2007; 5: 15-19.
5. Fushtey I.M., Podsevakhina S.L., Tkachenko O.V., Palamarchuk A.I. Immunological aspects of the development of endothelial dysfunction in patients with coronary artery disease and the role of risk factors in their formation. Domestic meditsina, 2007; 4(4): 38-44.
6. Hasanov Y., Galkina A.B., Nelayeva A.A., Medvedev I.V. The features of lipid metabolism and levels of proinflammatory cytokines in patients with diabetes type 2 with diabetic nephropathy, depending on the chronic kidney disease stage. Obesity and Metabolism, 2012; 2: 53-56.
7. Shestakova M.V. The comments of endocrinologist to the Recommendation on diabetes, pre-diabetes and cardiovascular disease ESC-EASD 2007. Diabetes, 2008; 1: 97-99.
8. Al-Dokhi L.M. Adipokines and etiopathology of metabolic disorders. Saudi. Med. J., 2009; 30(9): 1123-1132.
9. Alexandraki K., Piperi C., Kalofoutis C., Singh J. et al Inflammatory process in type 2 diabetes: the role of cytokines. Ann. N.Y. Acad Sci., 2006; 1084: 89-117.
10. Anderson J.L., Adams C.D., Antman E.M. et al. ACC / AHA 2007 Guidelines for the Management of Patients With Unstable Angina / Non-ST-Elevation Myocardial Infarction. A Report of American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelinesfor the Management of Patients With Unstable Angine / Non-ST-Elevation Myocardial Infarction). JACC, 2007; 50(7): el-e157.
11. Enderie M.D., Benda N., Schmuelling R.M. Preserved endothelial function in IDDM patients, but not in NIDDM patients, compared with healthy subjects. Diabet Care, 1998; 21(2): 271-280.
12. Goldberg R. Cytokine and Cytokine-like inflammation markers, endothelial dysfunction and imbalanced coagulation in development of diabetes and its complications. J. Clin. Endocrinol. Metab., 2009; 94(9): 3171-3182.
13. Hotamisligil G.S. Inflammation and metabolic disorders. Nature, 2006; 444(7121): 860-867.
14. National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Third Report of the Expert Panel on Detection, Evaluation and Teatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). http://nhlbi.nih.gov/guedelines/cholesterol/ atp3full.pdf.
15. Rodbard H.W. Dyslipidemias in diabetes. J of Diabetes, 2004; l.2: 20-22.
16. Schet G. Diabetes is an independent predictor for severe osteoarthritis. Diabetes Care, 2013; 36(2): 403-409.
17. Volpe C., Abreu L. The production of nitric oxide, IL-6 and TFN-α in Palmitate-Stimulated PBMNCs is Enhanced through Hyperglycemia in Diabetes. Oxydative Med. And Cellular Longevity, 2014; ID 479587: 12.