ROLE OF IMMUNO-INFLAMMATORY REACTIONS IN THE PATHOGENESIS OF CLINICAL VARIANTS OF CORONARY HEART DISEASE

Tashkenbaeva Eleonora,
MD, PhD, Head of the therapeutic block, Samarkand branch of the Republican Research Center of Emergency Care, e-mail: eleonora.B86@mail.ru.

Ziyadullaev Shukhrat,
MD, PhD, Scientific Secretary, Institute of Immunology and Human Genomics of the Academy of Sciences of Uzbekistan

Nasirova Zarina,
PhD researcher, Department of Internal Medicine №2, Samarkand State Medical Institute

Kadirova Farzona,
MBBS, Department of Internal Medicine №3, Tashkent medical academy

Yusupov Shokhrul,
PhD researcher, Department of otolaryngology and dentistry of Tashkent medical academy, e-mail: farzona.kadirova88@gmail.com

Kamalov Zaynittin,
MD, PhD, Professor, Head of the Laboratory of Immunoregulation, Institute of Immunology and Human Genomics of the Academy of Sciences of Uzbekistan

Received: 19.11.2019
Revised: 22.12.2019
Accepted: 02.01.2020

Abstract:
The role of inflammation in the pathogenesis of atherosclerotic lesion in CHD is widely discussed. In the study the relationship between the production of cytokines IL1, IL4, IL10, TNFs and clinical variations of ischemic heart disease has been studied. Patients with ischemic heart disease with stable and unstable angina were examined. The level of production of cytokines in blood serum was determined by immunoenzyme analysis. Studies show strong evidence for the participation of cytokines in immune inflammation mechanisms in coronary heart disease. The high functional class of angina accompanied by hyperproduction of pro-inflammatory cytokines dictates the need to develop new therapeutic approaches to reduce the production of proinflammatory cytokines in order to reduce the progressive inflammatory process and prevent the transition to an unstable form of the disease.

Keywords: Ischemic heart disease, proinflammatory cytokines, anti-inflammatory cytokines

© 2019 by Advance Scientific Research. This is an open-access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
DOI: http://dx.doi.org/10.31838/jcr.07.01.33

Introduction
Coronary heart disease (CHD) is the leading cause of morbidity, primary disability and mortality in the vast majority of the world’s countries [Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R., & Lucia, A. (2016). Epidemiology of coronary heart disease and acute coronary syndrome. Annals of translational medicine, 4(13).]. Cytokines of the immune system are key inflammatory factors that control all stages of the atherosclerotic process, participate in the formation of CHD and its complications [Kilik, T., Ural, D., Ural, E., Yumuk, Z., Agacikien, A., Sahin, T., ... & Komsuoglu, B. (2006). Relation between proinflammatory to anti-inflammatory cytokine ratios and long-term prognosis in patients with non-ST elevation acute coronary syndrome. Heart, 92(8), 1041-1046.]. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. The Lancet, 379(9822), 1214-1224, Tashkenbaeva, E.N., Ziyadullayev Sh.H., Togaev D.H., F.Sh. Kadyrova. The role of regulatory cytokines in the formation and progression of coronary heart disease associated with asymptomatic hyperuricemia. Journal of biomedicine and practice 2018, vol. 1, issue 1, pp. 30-35.]. Thus, anti-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNFα) cause or enhance the synthesis of cell adhesion molecules ICAM-1 and VCAM-1 by endothelial cells. Expression of the last endothelial cells on the membrane leads to the appearance of microthrombosis, development of tissue and cellular hypoxia, excessive vascular permeability and hyperproduction of free radicals, which contributes to the progression of inflammation and, as a result, leads to tissue damage [Simon, A. D., Yazdani, S., Wang, W., Schwartz, A., & Rabbani, L. E. (2000). Circulating levels of IL-1β, a prothrombotic cytokine, are elevated in unstable angina versus stable angina. Journal of thrombosis and thrombolysis, 9(3), 217-222.]. In turn, anti-inflammatory cytokines - IL-4, -10, -13, -17 - are involved in limiting the activity of inflammatory response by inhibiting the secretion of proinflammatory cytokines such as IL1, IL6 and TNFs and regulate the severity of tissue damage [Mosser, D. M., & Zhang, X. (2008). Interleukin-10: new perspectives on an old cytokine. Immunological reviews, 226(1), 205-218, Gordeeva, E.K., & Cade, A.H. (2016). Change of cytokine status at stable voltage angina. Medical Journal of the South of Russia, 1(1)]. The aim of this study was to study the relationship between the production levels of cytokines IL1, IL4, IL10, TNFs and clinical variations of ischemic heart disease.
ROLE OF IMMUNO-INFLAMMATORY REACTIONS IN THE PATHOGENESIS OF CLINICAL VARIANTS OF CORONARY HEART DISEASE

Material and methods

Patient information

106 patients with coronary heart disease were examined, 48 (45%) of them were patients with stable angina and 58 (55%) patients with unstable angina. Diagnosis of CHD with different angina course was made according to ESC recommendations for chronic stable angina (CSAP), unstable angina or myocardial infarction without ST segment elevation (UA/NSTEMI) and myocardial infarction with ST segment elevation (STEMI).


Basic therapy for CHD included anti-agregants, β-adrenoblockers, calcium antagonists, nitrates, statins, ACE inhibitors. A total of 64 healthy individuals were examined as a control group, including 31 men and 33 women with an average age of 63 years. Individuals in the control group were physically healthy, without cardiovascular disease. In order to characterize immunoinflammatory reactions, the content of proinflammatory (IL-1β, TNFα) and anti-inflammatory (IL4, IL10) cytokines in blood serum was studied.

The increased level of proinflammatory production in CHD revealed in the studies testifies to the strengthening of proinflammatory blood potential with a change in the balance of the immune response in the direction of Th1-mediated cellular reactions, which generally reflects the instability of the immunological phenotype and the likelihood of association with the severity of the disease course and phase.

Therefore, we analyzed the obtained results of the level of proinflammatory and anti-inflammatory serum cytokines of cro-41 patients of CHD depending on the FC stable angina tension and the phase of the disease course. In the group of patients of CHD CVA II PC's increased indices of proinflammatory cytokines (IL-1β 98,5±1,68 pg/ml; TNFα 68,4±1,6 pg/ml) and decreased indices of anti-inflammatory cytokines (IL-4 22,5±1,52 pg/ml; IL-10 11,9±0,60 pg/ml) were revealed (Table 2). The average level of proinflammatory cytokines IL-1β and TNFα concentration was the highest in patients with CHD CVA IV FC, the lowest average level of anti-inflammatory cytokine IL-10 concentration was also registered in the group of patients with CHD CVA IV FC. The level of anti-inflammatory cytokine IL-4 did not differ significantly in the comparison groups.

Table 2. Results of proinflammatory and anti-inflammatory cytokines depending on PCI patients

<table>
<thead>
<tr>
<th>The indicator</th>
<th>KG</th>
<th>II FC</th>
<th>III FC</th>
<th>IV FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β pg/ml</td>
<td>26,6±0,93</td>
<td>98,5±1,68*</td>
<td>101,0±1,34**</td>
<td>109,1±2,23***</td>
</tr>
<tr>
<td>TNFα pg/ml</td>
<td>21,2±0,60</td>
<td>68,4±1,6*</td>
<td>74,0±1,34**</td>
<td>74,8±2,11***</td>
</tr>
<tr>
<td>IL-4 pg/ml</td>
<td>24,1±0,82</td>
<td>22,5±1,52</td>
<td>27,4±1,57*</td>
<td>22,4±1,05</td>
</tr>
<tr>
<td>IL-10 pg/ml</td>
<td>15,2±1,02</td>
<td>11,9±0,60**</td>
<td>14,0±0,71</td>
<td>11,4±0,31**</td>
</tr>
</tbody>
</table>

Note: * - p<0.05 - reliability of the difference with the control group; ** - p<0.05 - reliability of the difference between the groups; *** - p<0.05 - reliability of the difference between the groups and the control group.

In the course of our study of cytokine parameters depending on the phase of CHD flow (Table 3), an increase in the content of proinflammatory cytokines was found in both clinical variants of IBS. The concentration of proinflammatory IL-1β and TNFα cytokines in the HC group was statistically significantly increased in comparison with both the group of patients with SS and the control group. The levels of anti-inflammatory cytokines IL-4 and IL-10 tended to decrease in the group of patients with NS.
Table 3. Indexes of cytokines depending on the flow phase of CHD

<table>
<thead>
<tr>
<th>The indicator</th>
<th>KG</th>
<th>CC</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β pg/ml</td>
<td>26.6±0.93</td>
<td>98.8±1.90*</td>
<td>116.7±1.18**</td>
</tr>
<tr>
<td>TNFα pg/ml</td>
<td>21.2±0.60</td>
<td>68.5±0.93**</td>
<td>74.5±1.16***</td>
</tr>
<tr>
<td>IL-4 pg/ml</td>
<td>24.1±0.82</td>
<td>23.9±0.42</td>
<td>23.8±0.97</td>
</tr>
<tr>
<td>IL-10 pg/ml</td>
<td>15.2±1.02</td>
<td>12.4±0.18*</td>
<td>12.1±0.33*</td>
</tr>
</tbody>
</table>

Note: * - p<0.05 - reliability of the difference with the control group; ** - p<0.05 - reliability of the difference between the groups; *** - p<0.05 - reliability of the difference between the groups and the control group.

Conclusion

The results of the present study indicate a reliable connection between cytokines and CHD and its clinical forms. High functional class of angina is accompanied by hyperproduction of proinflammatory cytokines that testifies to the presence of progressive inflammatory process at the stage of stable angina, which, in its turn, increases the risk of transformation from stable to unstable form of the disease. From the point of view of possible definition of long-term clinical effect of ischemic heart disease course stabilization, the development of new therapeutic approaches to decrease proinflammatory cytokines production is very actual.