The association of interleukin-6 gene with obesity in patients with coronary artery disease

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The aim of this study was to estimate value of a polymorphic locus C-174G of interleukin-6 gene in obesity development in patients with coronary artery disease.

Materials and methods. 222 patients with coronary artery disease and obesity were included in this study. The research of an allelic C-174G polymorphism of interleukin-6 gene was conducted by PCR method with electrophoretic detection of results with use of reagents SNP-EKSPRESS (“Sintol”, Russian Federation).

Results. Development of obesity in patients with coronary artery disease has been connected with G gene (odds ratio = 1.58, 95 % confidence interval = [1.12–2.24], \( \chi^2 = 6.9, p < 0.05 \)) and G/G genotype (odds ratio = 1.98, 95 % confidence interval = [1.25–3.16], \( \chi^2 = 8.4; p < 0.05 \)) polymorphic locus of C-174G of interleukin-6 gene. The genotype G/G was reliably more frequent in patients with coronary artery disease and stage III of obesity by 15.26 % and 8.45 %, than in patients with the accompanying I and II stages of obesity (p < 0.05). In it's turn, C/G genotype in patients with coronary artery disease and the III stage of obesity occurred 11.21 % less, than in patients with the I stages of obesity (p < 0.05). Allele C, G and genotype C/C had unreliable distribution in patients with coronary artery disease depending on obesity degree (p < 0.05).

Conclusions. This study has shown that the allele of G and G/G genotype of polymorphic locus C-174G of interleukin-6 gene is associated with development and progress of obesity in patients with coronary artery disease.
Introduction

There is little data on association of genes coding pro-inflammatory cytokines polymorphism with cardiovascular diseases (CD) development in the literature, and these only few researches devoted to interrelation between polymorphisms with risk of development and origin of chronic heart failure (CHF) progression in patients with coronary artery disease (CAD).

So, S. N. Shilov and coworkers showed in their work that polymorphic options of interleukin (IL)-1β (C + 3953T) genes, tumor necrosis factor (TNF-α) (G-308A), endothelial nitric oxide synthase (eNOS) (Glu298Asp) not only are the determinants of the increased risk of CHF development in ischemic heart disease patients, but are also associated with severity and characteristic of heart failure course in this category of patients. Besides, it has been proved that polymorphic loci of IL-1β (C + 3953T) gene are associated with expression of heart inotropic function disturbances and left ventricle remodelling. It is necessary to notice that the research was carried out with participation of Caucasian race patients, the Novosibirsk population. In total 226 ischemic heart disease patients with CHF I–IV functional class (FC) were examined, among them – 149 men and 77 women aged from 45 up to 65 years. Control group consisted of 136 people, among them – 63 men and 73 women aged from 45 up to 65 years without cardiovascular pathology and serious chronic illness [1]. 266 patients with CHF and EF lower than 40 % have been included in other research, no associations between TNF-α plasma concentration and TNF-α (308 A/G, 238 A/G, TNF beta Ncol and 3TACE) gene polymorphism have been observed [2].

L. Spinarova et al. [3] studied a polymorphism of G8002A and gene of endothelin-1 (EDN1) 3A/4A, and also TNF-α – A308G, A238G, FNO-β Ncol and 3TACE genes polymorphism in patients with CHF of ischemic genesis and diabetes mellitus. The research included 224 patients of Caucasian race (176 men and 48 women, the average age was 55 years), with CHF II–IV FC and proved reduction of left ventricle ejection fraction less than 40 %. Authors didn’t find relationship between plasma concentration of endothelin-1 and G8002A (p = 0.87, p = 0.81) and 3A/4A (p = 0.871, p = 0.749) EDN1 gene polymorphism. Also interrelations between TNF-α plasma concentration and polymorphic options of TNF-α, β and TNF-α-turning enzyme genes haven’t been observed. However it has been established that an allele A of G8002A polymorphism in comparison with G gene was reliably more frequent in the patients after MI and/or had ischemic disease of the lower extremities. In patients with dilatation cardiomyopathy the prevalence of this or that EDN1 gene polymorphic option hasn’t been revealed. It has been concluded that EDN1 and TNF-α gene polymorphic options aren’t important genetic determinants in patients with CHF, and their plasma concentration depends rather on the HF severity.

Wang et al. [4] suggested a correlation between – 174 G > C and coronary artery disease, whereas Ghazouani et al. [5] and Tong et al. [6] did not find this correlation, although all 3 studies were aimed to assess coronary artery disease. Discrepancy of the obtained data is probably connected with lack of the large randomized researches devoted to this problem, once again confirms need of further studying of genes coding pro-inflammatory cytokines polymorphism and also their influence on CD and CHF formation and progression.

The purpose – to estimate the value of interleukin-6 gene C-174T polymorphic locus in the development of obesity in patients with coronary artery disease.

Materials and methods

For investigation a comprehensive examination of 222 patients with CAD and obesity treated in cardiologic unit of the Kharkiv City Hospital № 27 which is the basic medical institution of Department of Internal Medicine № 2 and Clinical Immunology and Allergy of Kharkiv National Medical University HM of Ukraine was carried out. The comparison group included 115 CAD patients with normal body weight. 35 almost healthy people formed the control group.

In addition CAD patients and obesity patients had been divided into subgroups depending on degree of obesity: the first subgroup was composed of 80 patients with obesity I stage, the second included 71 patients with obesity II stage, the third – 71 patients with obesity III stage. Groups were comparable in age and sex. The research didn’t include patients with the serious accompanying pathology of respiratory organs, digestive system, kidneys and persons with oncologic diseases.

The diagnosis was established according to the existing orders of HM of Ukraine.

General clinical and instrumental examinations were carried out for all patients. The body weight index (BWI) (Quetelet’s index) was used to characterize obesity and was calculated on the basis of the following formula:

\[
\text{weight (kg) / body height (sq. m)}
\]

The research of interleukin-6 C-174T gene allelic polymorphism was carried out by PCR method with electrophoretic detection of results using “SNP-EKSPRESS” sets of reagents produced by CJSC “Sintol” (Russian Federation). Correctness of genotypes frequencies distribution was defined by compliance with G. Hardy–V. Weinberg equilibrium (\(p^2 + 2pq + q^2 = 1\)). According to the Helsinki Declaration all patients were informed of the clinical trial and have given their consent for studied gene polymorphism identification.

Statistical data processing was realized by means of Statistic software application, version 6.0. For comparison of alleles and genotypes frequencies distribution between groups criteria \(x^2\) of Pearson and Fischer was used. Odds ratio (OR) for determination of diseases development...
risk was calculated. OR = 1 was regarded as absence of associations; OR > 1 – as the positive association; OR < 1 – as the negative association of allele or genotype with disease (low risk of disease development). The confidence interval (CI) represented the interval of values within which was 95 % probability of OR prognostic value. Statistically significant differences have been considered in case of p < 0.05.

**Results**

Development of obesity in patients with CAD has been connected with G gene (OR = 1.58, 95 % CI = [1.12–2.24], χ² = 6.9; p < 0.05) and G/G genotype (OR = 1.98, 95 % CI = [1.25–3.16], χ² = 8.4; p < 0.05) polymorphic locus C-174G of IL-6 gene (Table 1).

The study of alleles and genotypes of IL-6 gene C-174G polymorphic locus frequency distribution in patients with CAD depending on BMI showed reliable increase in frequency of genotype G/G detection according to increase in body weight (Table 2).

The genotype G/G was reliably more frequent in patients with coronary artery disease and stage III of obesity by 15.26 % and 8.45 %, than in patients with the accompanying I and II stages of obesity (p < 0.05). In its turn, C/G genotype in patients with coronary artery disease and the III stage of obesity occurred 11.21 % less, than in patients with the I stages of obesity (p < 0.05). Allele G, and genotype C/C had unreliable distribution in patients with coronary artery disease depending on obesity degree (p < 0.05).

**Discussion**

Inflammation plays a very important role in atherosclerosis and cardiovascular diseases development. IL-6 is primarily secreted into serum and binds to receptor alpha (IL-6R-α) to mediate a transcripational inflammatory response during acute or chronic inflammatory process. Second, IL-6 stimulates the migration and proliferation of vascular smooth muscle cells and reconstructs vessels. Third, IL-6 regulates blood pressure by stimulating the sympathetic nervous system and controlling the angiotensinogen expression, resulting in a high angiotensin II concentration and its receptor. Fourth, IL-6 increases the concentration of Ca²⁺ in vascular smooth muscle cells and causes vasoconstriction. Last, despite the direct effect on blood pressure, IL-6 is associated with obesity, CAD, diabetes mellitus, [7] and catecholamine release, all of them can cooperate to promote the occurrence and development of hypertension. Thus, the progress of CAD may be affected by anything that interferes with the copy, transcription and translation of the IL-6 gene or secretion, migration, and proliferation of IL-6 protein. CAD is a major cause of morbidity and mortality, much international effort has been expended to detect risk factors, both heritable and environmental [8]. One of these, obesity, is associated with CAD. Genetic factors play an important role in the primary obesity development. Recent studies concentrate on IL-6 gene polymorphisms influence on certain medical conditions development. The relation between some genetic variant and obesity development seems to be more and more precisely documented.

A small number of works are devoted to studying of IL-6 gene polymorphic locus C-174G role in obesity development and their results show contradictory data. Our results, unlike what was reported in Finland [9], can be compounded with results which were received after carrying out researches among Americans and Spaniards [10], which showed that homozygotes with G/G-gaplotype bound to insulin resistance, type 2 diabetes mellitus and obesity.

Confusing data obtained by authors studying the influence of G 174C polymorphism on the incidence of diabetes and obesity might be explained by difficulties in selection of control and experimental groups. As there are so many divergences and uncertainties, there is an urgent need to study associations between polymorphisms of genes encoding proinflammatory cytokine genes and various obesity risk factors.

**Conclusions**

The allele of G and G/G genotype of polymorphic locus C-174G of interleukin-6 gene is associated with development and progression of obesity in patients with coronary artery disease.

The perspectives of further scientific research in this direction is to study the best ways of pharmacological therapy in patients with CAD and obesity.

**References**


**Table 1.** Value allele G and IL-6 gene G/G genotype polymorphic locus C-174G in obesity development in patients with CHD

<table>
<thead>
<tr>
<th>Genetic markers</th>
<th>OR (95 % CI)</th>
</tr>
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<tbody>
<tr>
<td>Allele G</td>
<td>1.58 (1.12–2.24)</td>
</tr>
<tr>
<td>χ² = 6.9; p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Genotype G/G</td>
<td>1.98 (1.25–3.16)</td>
</tr>
<tr>
<td>χ² = 8.4; p &lt; 0.05</td>
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</tbody>
</table>

**Table 2.** Frequency of alleles and genotypes of IL-6 gene polymorphic locus C-174G detection depending on BMI in patients with CAD and obesity

<table>
<thead>
<tr>
<th>Genetic markers</th>
<th>1 group Obesity I st. (n = 70)</th>
<th>2 group Obesity II st. (n = 71)</th>
<th>3 group Obesity III st. (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele C</td>
<td>24 (30 %)</td>
<td>19 (26.76 %)</td>
<td>20 (28.17 %)</td>
</tr>
<tr>
<td>Allele G</td>
<td>56 (70 %)</td>
<td>52 (73.24 %)</td>
<td>51 (71.83 %)</td>
</tr>
<tr>
<td>Genotype C/C</td>
<td>10 (12.5 %)</td>
<td>8 (11.27 %)</td>
<td>6 (8.45 %)</td>
</tr>
<tr>
<td>Genotype C/G</td>
<td>27 (33.75 %)</td>
<td>20 (28.17 %)</td>
<td>16 (22.54 %)*</td>
</tr>
<tr>
<td>Genotype G/G</td>
<td>43 (53.75 %)</td>
<td>43 (60.56 %)*</td>
<td>49 (69.01 %)#</td>
</tr>
</tbody>
</table>

*: reliability of differences with the 1 group (p < 0.05); #: reliability of differences with the 2 group (p < 0.05).


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