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Relationship between serum cytokines and growth factor level and coronary artery disease

Seyed Reza Mirhafez [a,b], Ahmadreza Zarifian [c], Mahmoud Ebrahimi [a], Ramin Fakhre Ale Ali [c], Amir Avan [d], Mohammad Tajfard [e], Mohsen Mohebati [a], Saeid Eslami [f,g], Amir Ali Rahsepar [a], Hamid Reza Rahimi [d], Hassan Mehrad-Majd [b], Gordon A. Ferns [h], Majid Ghayour-Mobarhan [a,i,*]

[a] Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran
[c] Student Research Committee, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Health Sciences Research Center, Department of Health and Management, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Pharmaceutical Recearch Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Department of Medical Informatics, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[h] Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK
[i] Biochemistry of Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Background: We have assessed the association between serum concentrations of 12 cytokines/growth factors and angiographically-defined coronary artery disease, comparing the concentrations in four groups (one control group and three case groups).

Methods: We studied a total of 426 subjects including; 98 control subjects and 3 case groups. The patient groups consisted of: coronary artery bypass graft (CABG) candidates ($n = 48$) and patients undergoing coronary angiography, with, or without obstructive coronary artery disease. Twelve cytokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, MCP-1, IFN-γ, EGF, and VEGF) were measured using a sandwich chemi-luminescence assays, on the Evidence Investigator® system.

Results: The four groups were well matched for demographic and clinical characteristics, except waist circumference, fasting blood glucose (FBG), total and LDL cholesterol and diastolic blood pressure that were significantly higher in case groups compared to the control group ($P < 0.05$ for all). There were significant differences between control group and the other three groups regarding the measured cytokines, such as IL-1α, IL-8, MCP-1, and VEGF ($P < 0.01$). Furthermore, IL-4, IL-6 and EGF were also significantly different between the control, obstructive coronary disease and CABG candidate groups ($P < 0.01$). Analysis of the ROC curve showed 92.1% sensitivity, 99.2% specificity and 100% positive predictive value (PPV) for VEGF in its ability to distinguish the CABG group at the cut-off point of 37.18 pg/ml.

Conclusion: The results of this study suggest that cytokines such as IL-1α, IL-4, IL-8, IL-10 and VEGF may play major roles in pathogenesis of CAD.

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Introduction

Coronary artery disease (CAD) continues to be the most common type of cardiovascular diseases and the major cause of death in both genders in the Western World [1]. The most prevalent clinical manifestations of CAD are myocardial infarction (MI), stable or unstable angina and sudden death. Atherosclerosis plays a prominent role in the pathogenic processes leading to CAD [2].

Cytokines are of cardinal importance in pathogenesis of atherogenesis, particularly CAD, by inducing inflammatory processes, immunological reactions, atherosclerosis, and resultant endothelial injury [3,4]. Cytokines are expressed by several tissues, but particularly leukocytes, that also contribute to atherosclerotic plaque instability and rupture; the latter leads to the exposure of thrombogenic collagen. Most cases of myocardial infarction (MI) occur due to thrombosis followed by plaque rupture [5–8]. These inflammatory processes within the atherosclerotic coronary artery, trigger an acute phase reaction, releasing inflammatory cytokines, especially interleukin (IL)-1, IL-2, IL-6, IL-10, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF) and monocyte chemotactic peptide (MCP)-1,

* Corresponding author at: Biochemistry and Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Fax: +98 5118002287.
E-mail address: ghayourm@mums.ac.ir (M. Ghayour-Mobarhan).

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that might cause endothelial dysfunction, leukocyte activation and vascular smooth muscle proliferation [9–11].

IL-2 leads to activation of immune cells, but its role in the process of atherosclerosis remains controversial [7]. IL-4 leads to the secretion of immunoglobulin (Ig)-E antibodies and inhibition of pro-inflammatory cytokines [7]. IL-6 and TNF-α have a potential direct role in atherogenesis but also induce the elaboration of C-reactive protein (CRP) by hepatocytes, which may also be involved in pathogenesis of atherosclerosis [12]. Being an independent risk factor of MI, IL-6 is also believed to be a valuable prognostic factor for unstable angina and MI, especially ST-segment-elevation MI [9,13,14]. IL-8 induces atherosclerosis through stimulation of monocyte migration and induction of vascular endothelium proliferation [15–17]. IL-10 is an inhibitory cytokine suppressing other inflammatory cytokines such as IL-1 and TNF-α [18]. TNF-α, which is an important pro-inflammatory cytokine, and IL-10 are expressed within the atherosclerotic plaque. Therefore, TNF-α/IL10 ratio is suggested to be a magnificent indicator of CAD progression [19]. IL-1β in concert with TNF-α induces the secretion of secondary cytokines such as IL-6 and IL-8. MCP-1 increases the vulnerability of atherosclerotic plaque by induction of monocyte activation and migration [20]. EGF, which induces monocyte activation and chemotaxis, is likely to play an important role in atherosclerosis [21]. The role of VEGF in the pathogenesis of CAD is controversial. On the one hand, it induces angiogenesis and reduces the adverse effects of CAD; On the other hand, it promotes the process of atherosclerosis [22].

Coronary artery bypass grafting (CABG), one of the most common surgical procedures undertaken worldwide, is a widely used method to enhance the myocardial perfusion and improve the quality of life in patients with CAD [23,24]. In the present study, we measured the serum concentrations of 12 cytokines (IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, MCP-1, and epidermal growth factor (EGF)) and investigated their association with CAD.

Materials and methods

Study population

The study subjects ($n = 426$) including 209 males and 217 females were assessed. Routine angiography of coronary arteries was performed for 289 patients, at Ghaem Educational Hospital, Mashhad, Iran. Indications for coronary angiography were stable or unstable angina, recurrence of symptoms after revascularization, acute MI, patients undergoing non-cardiac surgery (preoperative), valvular heart disease, congenital heart disorders, congestive heart failure (CHF), aortic dissection, arteritis, hypertrophic cardiomyopathy, and chest trauma [25].

According to the results of angiography, the subjects were divided into two groups. Patients whose angiography results showed ≥50% obstruction in at least one coronary artery, who were assigned to the obstructive coronary disease group ($n = 196$). Patients who had less than 50% obstruction in their coronary arteries were assigned to the non-obstructive coronary disease group ($n = 93$). The third case group were CABG candidates ($n = 48$) who had severe symptoms of CAD and high risk of mortality.

Inclusion criteria for CABG candidates were: (1) Patients with asymptomatic ischemia, stable or unstable angina, non–ST-segment elevation MI (non-STEMI) or poor left ventricle (LV) function who have significant left main coronary artery stenosis or 70% or greater stenosis in the proximal LAD and proximal left circumflex artery; (2) Patients with asymptomatic ischemia or stable angina who have 3-vessel disease or have developed disabling angina despite maximal noninvasive therapy; (3) Patients with poor LV function who have proximal LAD stenosis with 2- or 3-vessel disease; (4) Patients with life-threatening ventricular arrhythmias caused by left main coronary artery stenosis or 3-vessel coronary disease; (5) Recurrent or incessant ischemia unresponsive to medical therapy in patients who have coronary anatomy suitable for surgery, or a remarkable area of myocardium at risk; (6) Patients younger than 75 years with STEMI or left bundle-branch block or posterior MI who have the potential to develop shock within 36 h of MI [26].

Exclusion criteria for the CABG candidates included hormone replacement therapy (HRT), pregnancy, prior history of coronary angioplasty or CABG, chronic obstructive pulmonary disease (COPD), overt clinical manifestations of infection or chronic inflammation, renal and hepatic diseases, and malignancies. All subjects were negative for viral markers of hepatitis and anti-HIV antibody.

Ninety-eight subjects were referred for their annual medical checkup or pre-employment examinations. They were used as the reference (control) group as they gave no history of cardiac symptoms and their electrocardiogram (ECG) had no abnormalities. The study was performed according to the declaration of Helsinki and approved by the ethical committee of research council, Mashhad University of Medical Sciences.

Clinic data collection

Data were obtained by using a general questionnaire including social and demographic characteristics; and anthropometric parameters were measured as described below. Blood pressure was measured using a mercury sphygmomanometer. Height and weight were measured in standing stature position with stadiometer and by electronic weight scales, respectively. Drug history was obtained from all subjects by simple questionnaires.

Blood samples

Blood samples (20 ml) were obtained in the early morning after an overnight fasting, were collected into plain Vacutainer™ tubes for cytokines and lipid profile. In order to measure fasting blood sugar, blood samples were taken into Vacutainer™ tubes, which contained fluoride-oxalate [27].

Blood samples were centrifuged to separate the serum and kept at −80 °C. We gauged total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glucose by Cobas auto-analyzer system (ABX Diagnostics, Montpellier, France) as the routine technique [27].

Subjects with a fasting blood glucose (FBG) less than 126 mg/dL were interpreted as being non-diabetic, using the American Diabetic Association criteria. Subjects with a FBG above 126 mg/dL were considered to have diabetes mellitus [27].

The laboratory measurement of cytokines

We used an Evidence Investigator® analyzer for the cytokine assays using sandwich chemiluminescence methodology. In this study, we measured 12 cytokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, MCP-1, IFN-γ, EGF, and VEGF) simultaneously.

Analysis of serum cytokines used an EV 3513 cytokine biochip array (Randox Laboratories, Crumlin, UK) for sandwich and competitive chemiluminescence immunoassay methods (previously explained by Randox Laboratories, Crumlin, UK) [28,29].

Statistical analysis

The Statistical Package for Social Sciences (SPSS version 16) was used for data analysis; Kolmogorov–Smirnov tests were used to assess normality. Statistical parameters (frequency, mean, and standard deviation (SD)) were determined for all variables. Normally distributed variables were reported as mean ± SD (median and IQR for variables without normal distribution). Clinical data and demographic information were compared among groups, using Student *t*-test and one-way ANOVA test for normally distributed variables, Mann–Whitney *U* and Kruskal–Wallis *H* test for non-normally distributed variables and chi-square test and Fisher exact test for categorical variables. A univariate

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