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Correlation between immunological-inflammatory markers and endothelial disfunction in the early stage of coronary heart disease

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ABSTRACT

Classical risk factors for endothelial dysfunction (ED), such as age, gender, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and smoking history are utilised for the Framingham score and Systemic Coronary Risk Estimation (SCORE) for evaluation of the 10-year cardiovascular risk in routine practice. Nonetheless, pro-inflammatory mediators are deeply involved in the initiation and the progression of ED and coronary artery disease (CAD), and act additionally or independently of metabolic factors before clinical manifestations of the disease appear. C-reactive protein, a marker of intimal thickening of the myeloid-related protein 8/14 heterodimer, monocyte chemotactic protein 1, interleukin-15, the cytotoxic mediator, granulysin, and the matrix metalloproteinase 9 could be valuable, single, fast, and non-invasive laboratory tools for ED deterioration degree assessment. We propose to investigate the impact of pro-inflammatory biomarkers on ED, measured by previously established clinical methods in patients with yet undiagnosed CAD and at medium risk for an acute coronary event. It could be useful to measure and correlate the concentration of particular inflammatory markers in peripheral blood samples and the results of the Framingham and SCORE charts, multislice computed tomography coronary angiography, echocardiography, brachial artery flow-mediated dilatation, carotid-femoral pulse wave velocity, ankle-brachial index, carotid wall thickening, myocardial perfusion scintigraphy, and particularly, cardiac magnetic resonance imaging. The goal would be that the degree of correlation between particular inflammatory markers and the results of some methods for the assessment of ED or cardiac ischaemic imaging could be emphasised and pro-inflammatory markers positioned in the pathogenetic algorithm of CAD.

Introduction

Coronary artery disease (CAD) is a multifactorial disease, characterised by a chronic inflammatory process occurring primarily at the atherosclerotic plaque [1]. The plaque development starts early in life [2] with endothelial dysfunction (ED) and progresses silently without any symptoms at different rates [3]. It depends on various metabolic and inflammatory factors, as well as the genetic background of the patient [3]. Deterioration of endothelial function increases with aging, particularly due to the enhancement of pro-inflammatory cytokines [4]. Women are protected during the reproductive years when, compared to men, there are anti-inflammatory actions of progesterone and oestrogen, particularly during pregnancy, when progesterone primes the helper T cell 2 (Th2) and the tolerogenic response [3]. Postmenopausal hormone deprivation leads to the enhancement of cell-mediated immunity processes in women [5], as well as impairment of the vasodilating endothelial function [5]. Thus, postmenopausal women's cardiovascular risk is equated with the risk in men of the same age [3]. Cumulative cigarette smoking was strongly associated with blood levels of interleukin-6 (IL-6), C-reactive protein (CRP), and fibrinogen inflammatory markers [6]. Serum IL-6 is significantly associated with all-cause and cardiovascular mortality in hospitalised patients with CAD

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[7]. IL-6 decreases the concentration of high-density lipoprotein (HDL) cholesterol causing lipid imbalance [8]. Hypercholesterolemia and low-density lipoprotein (LDL) oxidation are leading causes of ED and atherogenesis [1], which are especially expressed in patients who are obese and those who have diabetes [9]. Elevated levels of CRP and IL-6 predict the development of type 2 diabetes mellitus and support a possible role for inflammation in diabetogenesis [9]. Increased blood pressure starts with ED and further supports damage to the endothelial glycocalyx leading to underlying cell activation [10]. It involves a disproportion in endothelial secretion of endothelin, angiotensin II, thromboxane A2, and prostaglandin H2 as vasoconstricting agents, and nitrous oxide and prostacyclin, as vasodilating substances [10]. These changes lead to oxidative stress, thrombocyte adhesion, and aggregation on the arterial wall and chronic endogenous inflammation [10].

The impaired endothelium becomes a significant source of pro-inflammatory cytokines, chemokines, and growth factors. In humans, monocyte chemotactic protein 1 (MCP-1) is produced, expressed, and secreted mostly by inflammatory cells and dysfunctional endothelium [11], as a member of the CC chemokine family [11,12]. It increases the expression of adhesion molecules on monocytes and recruits them in the arterial wall [1,12]. MCP-1 maturates recruited monocytes into macrophages and helps them to secrete pro-inflammatory IL-1 and IL-6 cytokines, and releases lysosomal enzymes and tissue factors responsible for coagulation. It affects the functions of the surrounding immune cells, such as cluster of differentiation 4 (CD4) + and CD8 + T cells, natural killer (NK) cells, and dendritic cells, which are also chemoattracted by chemokines in the locally thickened intima [12] during the formation of early atherosclerotic lesions [1,3]. Macrophages are stopped locally by endocytosis of LDL-cholesterol [1], which supports them in production of tumour necrosis factor α (TNF-α) [13] and interleukin-15 (IL-15) [14]. Both cytokines, TNF-α and IL-15, activate immunity-mediated by T lymphocytes and NK cells, which are recruited to the artery wall after monocyte infiltration, especially in the area damaged by blood flow [3], and metabolic [3] and inflammatory factors [3]. These activated lymphocytes secrete matrix metalloproteinase 9 (MMP-9), responsible for extracellular matrix degradation [11,15] and myeloid-related protein-8 (MRP-8) and myeloid-related protein-14 (MRP-14), which promote recruitment of more leucocytes [16]. Activated leucocytes are highly cytotoxic to smooth muscle and endothelial cells [1]. Plaque rupture is considered to be induced by activated T cells and TNF-Related Apoptosis-Inducing Ligand (TRAIL)-mediated apoptosis [17]. In a previous study, we showed that the frequency of granulysin-expressing lymphocytes increased in the peripheral blood of patients with non-ST elevation myocardial infarction (NSTEMI) treated conservatively at day 7 [18]. However, on day 14, it significantly decreased in T, NK, and both CD56 (+dim) and CD56 (+bright) NK subsets, probably due to the infiltration of the central zone of myocardial infarction under the influence of IL-15 in *peri*-necrotic cardiomyocytes [18]. Patients with NSTEMI have a strong and prolonged perforin-mediated systemic inflammatory reaction, which may sustain auto-aggressive reactions towards myocardial tissue during the development of myocardial infarction [19]. The unwanted side effect of cytotoxic mediators can lead to harmful systemic immune reactions directed towards dysfunctional endothelia [20]. The plaque rupture and partial or complete artery stenosis cause insufficient myocardial oxygen supply and, consequently, acute coronary syndrome development. Only the removal of cardiovascular risk factors by systematic application of persistent disease prevention and promotion of healthy lifestyles has declined the trend in stroke mortality for all ages in the last 10–15 years [21], but the disease has not been eradicated. Therefore, it would be important to have non-invasive pro-inflammatory marker(s) for estimation of the degree of atherosclerotic disease and plaque vulnerability, as well as for the risk of major cardiac events, including myocardial infarction or sudden cardiac death.

Hypothesis

Cardiovascular risk assessment, either with the Framingham calculator or SCORE charts is based on the classical risk factors, including serum concentrations of cholesterol, blood pressure, age, sex, diabetes mellitus, and smoking status [22,23]. All these factors cause endothelial impairment, accompanied by cytokine, chemokine, and inflammatory marker production, causing atherosclerotic plaque formation, and occasionally rupture of the plaque [3]. However, there are no scores showing the direct influence of immunological pro-inflammatory mediators on cardiovascular risk, although pro-inflammatory mediators are deeply involved in the initiation and progression of ED.

We propose to investigate the impact of pro-inflammatory biomarkers on ED and on the atherosclerotic process, which is measured by previously established clinical methods in patients with suspected CAD, as 50% of cardiovascular events occur in patients with no symptoms, atypical cause of disease, and low or intermediate risk score. We hypothesise that the inflammatory mediators, CRP, TNF-α, MCP-1, IL-15, granulysin, MRP-8/14 heterodimer, and MMP-9 correlate with the severity of the atherosclerotic process estimated by the Agatston score and plaque formation visualised by multi-slice computed tomography (MSCT) coronary angiography in patients with intermediate cardiovascular risk better than the assessment by the SCORE chart and Framingham risk score. It could also be useful to assess the relationship of the particular pro-inflammatory factor with the results of the evaluation of the ED (brachial artery flow-mediated dilatation, carotid-femoral pulse wave velocity, ankle-brachial index, and carotid wall thickening) or the functional consequences of the early subclinical myocardial ischaemia mediated by ED as measured by echocardiography parameters, myocardial perfusion scintigraphy, positron-emission tomography CT, and cardiac magnetic resonance imaging (CMR). The degree of correlation between a particular inflammatory marker and some methods for the assessment of ED/atherosclerotic lesions could be demonstrated.

Our hypothesis is based on the data of earlier investigations: (I) CRP participates in the atherogenic process by attaching to LDL, activating complement, and aggravating inflammation, leading to the formation of vulnerable plaques [24]; (II) The plasma levels of IL-6 are related to plaque inflammation and vulnerability and IL-6 is shown to be a more sensitive and specific marker in vascular inflammation than CRP, correlating with increased risk for future myocardial infarction in healthy men [25]; (III) IL-15 is expressed in atherosclerotic plaques [14] and can be the mediator of the disease as an alternative factor of T cell activation along with oxidised LDL stimulation [1], the effective chemoattractant for resting and activated T and NK cells in vitro [26], and the enhancer of the cytotoxic molecules, perforin [27] and granulysin [28], expression at the gene and protein levels even in immunosuppressed decidual lymphocytes and purified NK cells; (IV) Cytotoxic molecules granulysin [18] and perforin [29] proteins are highly expressed after NSTEMI in patients without primary percutaneous coronary interventions; (V) MCP-1 causes early plaque formation [12] and vulnerability by the recruitment of monocytes and their differentiation into macrophages in the presence of LDL-cholesterol [11]; (VI) Macrophages in the atherosclerotic vessel wall secrete significant concentrations of MMP-9, which regulates collagen degradation leading to plaque destabilisation [11,15]; (VII) Plasma MRP-8/14 heterodimers predict the increased risk of first and recurrent cardiovascular events by promoting vascular leucocyte recruitment [30].

Evaluation of the hypothesis

To evaluate our hypotheses, the patients with atypical chest pain and intermediate cardiovascular risk can be enrolled after signing an informed consent. These patients should not have a history of a previous coronary event(s) and the only medications taken should be antihypertensives. Patients taking statins or any inflammatory drug