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Wykretowicz A, Deskur-Smielecka E, Furmaniuk J, Smielecki J
Wysocki H

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The Influence of Lipid Lowering on Soluble Tumor Necrosis Factor Receptor I in Patients with Angina Pectoris

A. Wykretowicz, J. Śmielecki, J. Furmaniuk, E. Deskur-Śmielecka, H. Wysocki

Inflammation plays an important role in the pathogenesis of atherosclerosis. It has been suggested that the beneficial effects of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on survival of patients with ischaemic heart disease may partly derive from their anti-inflammatory properties.

Aim of the study was to determine levels of soluble tumor necrosis factor receptor I (sTNF-RI) in patients with hypercholesterolaemia and angina pectoris, in a group of asymptomatic subjects (n = 20) with elevated serum cholesterol levels and in a control group (n = 20). Furthermore, we wanted to investigate the possible influence of 3-month treatment with simvastatin on plasma concentrations of sTNF-RI.

Results: Baseline concentrations of sTNF-RI in plasma were significantly higher in patients with hypercholesterolaemia and angina pectoris compared to the control group (1259 ± 90 pg/ml vs. 913 ± 98 pg/ml, p = 0.0366). Baseline sTNF-RI levels in hypercholesterolaemic subjects (1004 ± 92 pg/ml) were not significantly different from those in patients with angina pectoris or controls. In both study groups simvastatin had no effect on plasma sTNF-RI concentrations (patients with angina pectoris: 1259 ± 90 pg/ml vs. 1206 ± 117 pg/ml, hypercholesterolaemic subjects: 1004 ± 92 pg/ml vs. 929 ± 66 pg/ml).

Conclusions: (1) Patients with hypercholesterolaemia and angina pectoris have increased soluble tumor necrosis factor receptor I plasma levels in comparison with healthy subjects. (2) 3-month therapy with simvastatin has no effect on sTNF-RI concentrations in hypercholesterolaemic patients with, or without, ischaemic heart disease. ***J Clin Basic Cardiol 2005; 8: 65–8.***

Key words: *simvastatin, soluble tumor necrosis factor receptor I, sTNF-RI, hypercholesterolaemia*

A large body of evidence derived from laboratory research indicates that inflammation is involved in the initiation and progression of vascular atherosclerotic lesions [1, 2]. Inflammatory processes seems to play a particularly important role in events following coronary artery occlusion and subsequent reperfusion [3, 4]. On the other hand, it has been recently shown that elevated markers of inflammation are associated with increased risk of myocardial infarction and other atherosclerotic events [5–7].

Recent studies have reported beneficial effects of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on the survival of patients with ischaemic heart disease and the prevention of coronary artery disease in hypercholesterolaemic subjects [8–11]. It has been postulated that statins may exert effects separate from their lipid-lowering action, including anti-inflammatory properties [12–14], which may account for the clinical benefits.

Among inflammatory cells, the involvement of peripheral blood monocytes in the development of atherosclerosis has been best recognised. Adhesion and transendothelial migration of circulating monocytes are early events in atherosclerotic plaque formation [15]. Activated monocytes and macrophages release arrays of cytokines that affect other cells and modify the inflammatory reactions in response to injury or infection. The direct assessment of circulating cytokines levels may be of limited value because of their short half-life. Moreover, cytokines may exert autocrine, paracrine, and intracrine actions and may therefore be not released into the peripheral circulation. Therefore circulating cytokine receptors, which are cleaved from the target cell surface after contact with the corresponding cytokine, may be better markers of macrophage activation.

The initial purpose of the present study was to determine whether patients with angina pectoris and hypercholesterolaemia have increased levels of soluble tumor necrosis factor receptor I (sTNF-RI) in comparison with hypercholesterolaemic subjects and controls. Secondly, we wanted to assess the possible influence on plasma sTNF-RI concentrations of lipid-lowering therapy with the use of simvastatin, a hydroxy-methylglutaryl coenzyme A reductase inhibitor.

Material and Methods

The study population consisted of 20 patients with stable angina pectoris and serum cholesterol levels above 200 mg/dl (AP group) and 20 asymptomatic subjects, with total serum cholesterol concentrations exceeding 250 mg/dl (HC group). 9 healthy subjects with serum cholesterol levels below 250 mg/dl served as the control group (C group). Patients were only enrolled in the study if they had been on a low-fat, low-cholesterol diet (American Heart Association step I diet) and had not been taking any cholesterol-lowering drugs for at least 6 months. The exclusion criteria were a recent history of myocardial infarction (< 6 months), unstable angina pectoris, diabetes mellitus, active inflammatory disease, congestive heart failure, renal or hepatic impairment or pregnancy. The characteristics of each study group are summarised in Table 1.

Table 1. Characteristics of the study population

	AP group (n = 20)	HC group (n = 20)	C group (n = 9)
Age, years	57,5 ± 8,5	55,2 ± 2,1	42,0 ± 8,0
Sex m/f (n)	13/7	6/14	5/4
Smokers (past or current) (n)	7	10	2
History of myocardial infarction (n)	14	1	0
Hypertension (n)	14	10	0

AP group: patients with hypercholesterolaemia and angina pectoris; HC group: asymptomatic subjects with hypercholesterolaemia; C group: control group

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From the Department of Cardiology-Intensive Therapy, University School of Medical Sciences, Poznań, Poland

Correspondence to: Andrzej Wykretowicz, MD, PhD, Department of Cardiology-Intensive Therapy, University School of Medical Sciences in Poznań, ul. Przybyszewskiego 49, 60-355 Poznań, Poland, E-mail: awykreto@ptkardio.pl

This investigation was approved by the local Ethics Committee and all patients included gave their written informed consent to participate in the study.

Study Design
Peripheral blood samples were taken from each subject after an overnight fast for evaluation of serum lipid profiles and soluble tumor necrosis factor receptor I levels. Patients in the AP and HC groups received 20 mg simvastatin daily in addition to their habitual medication. No other changes in treatment were allowed during the study period. After 3 months treatment with simvastatin, blood samples were again taken for assessment of serum lipid profiles and sTNF-RI concentrations.

Lipid Profiles
Serum levels of total cholesterol, HDL cholesterol and triglycerides were determined by standard enzymatic methods. LDL cholesterol concentrations were calculated using the Friedewald formula.

Levels of Soluble Tumor Necrosis Factor Receptor I
The concentrations of sTNF-RI in serums samples were determined by the quantitative sandwich enzyme immunoassay technique (R&D Systems, Minneapolis, USA).

Statistical Analysis
Data analysis utilised standard descriptive techniques. The t-test for paired variables was used for within-group comparisons and the unpaired t-test was employed for between-group comparisons. A p-value < 0.05 was considered significant. All data are expressed as means ± SEM.

Results

Serum Lipid Profiles
The serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides are shown in Table 2. Total and LDL cholesterol concentrations decreased significantly after 3 months of therapy with simvastatin in both study groups. No changes were observed in the HDL cholesterol and triglycerides levels.

Serum Concentrations of Soluble Tumor Necrosis Factor Receptor I
The baseline concentrations of sTNF-RI were significantly higher in patients with angina pectoris than in healthy subjects (1259 ± 90 pg/ml vs. 913 ± 98 pg/ml) (Fig. 1). There were no significant differences between the hypercholesterolaemic subjects and the control group for baseline sTNF-RI levels (1004 ± 92 pg/ml vs. 913 ± 98 pg/ml). Baseline sTNF-RI concentrations tended to be lower in the HC group compared with the AP group ($p = 0.059$). Neither the AP nor the HC group demonstrated any change in sTNF-RI levels after 3-months therapy with simvastatin (AP group: 1259 ± 90 pg/ml vs. 1206 ± 117 pg/ml, HC group 1004 ± 92 pg/ml vs. 929 ± 66 pg/ml).

Discussion
Tumor necrosis factor plays a pivotal role in the inflammatory response. It exerts its effects by binding two distinct receptors designated TNF-RI and TNF-RII on the target cell surface [16, 17]. Both receptor types exist in a circulating soluble form, resulting from a proteolytic cleavage of their extracellular domains from the cell membrane [18, 19]. The biological role of the soluble tumor necrosis factor receptors is not clear. They may bind and inactivate circulating tumor necrosis factor and thus protect cells from the effect of this agent [20, 21]. It has been also suggested that soluble tumor necrosis factor receptors may serve as a biological reservoir for tumor necrosis factor, binding and stabilising it with subsequent controlled, slow release of this factor into the circulation [22, 23]. Soluble tumor necrosis factor receptors are present in human serum, but their levels increase markedly in acute infection or inflammation [24, 25]. Elevated soluble tumor necrosis factor receptor II levels have been recently reported both in patients with congestive heart failure [26] and angiographically proven coronary heart disease [27].

Our study was designed to evaluate sTNF-RI levels in hypercholesterolaemic patients presenting with or without the symptoms of angina pectoris. We observed significantly higher sTNF-RI levels in patients with angina pectoris in comparison with the control group. This finding is in keeping with previous studies demonstrating activation of the tumor necrosis factor system in patients with ischaemic heart disease [27] and indicates that sTNF-RI, in addition to sTNF-RII, may be a potential immunologic marker of coronary heart disease. In contrast, there were no significant differ-

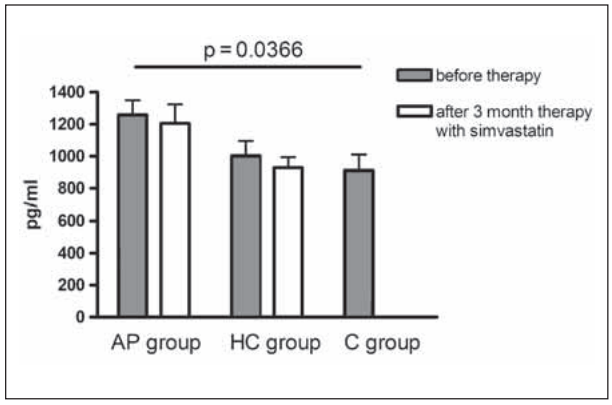

Figure 1. Concentrations of soluble tumor necrosis factor receptor I (sTNF-RI) in patients with angina pectoris and hypercholesterolaemia (AP group), in asymptomatic subjects with hypercholesterolaemia (HC group) and in the control group (C group)

Table 2. Serum lipid profiles in the study population before and after 3-months treatment with simvastatin

	AP group			HC group		
	Before therapy	After therapy	p	Before therapy	After therapy	p
Total cholesterol (mg/dl)	277 ± 8	207 ± 8	< 0.0001	298 ± 9	221 ± 4	< 0.0001
HDL cholesterol (mg/dl)	42 ± 2	44 ± 2	n.s.	55 ± 3	57 ± 2	n.s.
% HDL cholesterol	14 ± 1	21 ± 1	0.0002	18 ± 1	26 ± 1	< 0.01
LDL cholesterol	195 ± 8	126 ± 7	< 0.0001	214 ± 8	137 ± 4	< 0.0001
triglycerides	199 ± 11	186 ± 20	n.s.	160 ± 19	164 ± 24	n.s.

AP group: patients with hypercholesterolaemia and angina pectoris; HC group: asymptomatic subjects with hypercholesterolaemia

ences in sTNF-RI levels between the asymptomatic patients with hypercholesterolaemia and the control group. Interestingly, there was a tendency towards lower values of circulating sTNF-RI in hypercholesterolaemic subjects compared to patients with angina pectoris. These results suggest that myocardial ischaemia is the factor triggering activation of the tumor necrosis factor system in patients with atherosclerosis.

As hydroxy-methylglutaryl coenzyme A reductase inhibitors have been suggested as having direct anti-inflammatory properties [12–14], we investigated the influence of 3-months therapy with simvastatin on serum levels of sTNF-RI. Despite significant decreases in both total and LDL-cholesterol levels, sTNF-RI concentrations remained unchanged in both study groups, indicating that treatment with simvastatin has no effect on tumor necrosis factor system activation. Although there is a growing number of studies demonstrating the anti-inflammatory effects of statins, most of them investigated the properties of either pravastatin [12–14, 28], lovastatin [29], or cerivastatin [30]. Data concerning the influence of simvastatin on the inflammatory response are sparse and often contradictory. In some studies simvastatin was found to reduce cytokines concentrations in human plasma [31, 32], while other studies demonstrated that it had no effect on the production of cytokines by monocytes [33] or even enhanced it [34]. In our previous study [35] we found that simvastatin did not influence plasma interleukin 6 levels in hypercholesterolaemic subjects. It is possible that different hydroxy-methylglutaryl coenzyme A reductase inhibitors, despite their common lipid-lowering mechanism of action, may vary greatly in their influence on inflammatory processes. These differences may result from their distinct pharmacokinetic properties [36]. On the other hand, the immunologic response involves a number of cytokines, growth factors, and vasoregulatory molecules that interact in numerous positive and negative feedback mechanisms. Factors influencing one particular cytokine may therefore have no, or even contradictory effects, on other components of the system. The possibility cannot be ruled out that a 12-week course of treatment with simvastatin was not long enough to exert a significant influence on the tumor necrosis factor system, despite the reduction in serum cholesterol levels. It is noteworthy that although several of the non-lipid mechanisms of action of statin drugs are apparent within the first weeks of therapy [37], much longer treatment is necessary to yield an improvement in mortality and morbidity [8]. To the best of our knowledge, this is the first study to investigate the influence of simvastatin treatment on soluble tumor necrosis factor receptor I levels. For a better assessment of the anti-inflammatory properties of hydroxy-methylglutaryl coenzyme A reductase inhibitors, further detailed studies are required.

In conclusion, we found that soluble tumor necrosis factor receptor I levels are increased in patients with hypercholesterolaemia and angina pectoris. 3-months therapy with simvastatin was shown to have no effect on sTNF-RI concentrations in hypercholesterolaemic subjects with, or without, ischaemic heart disease.

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