The influence of antibiotics and statins on inflammation in coronary disease

Radan Stojanović*, Zorana Vasiljević†, Milica Prostran*, Mina Radovanović†, Branislav Stefanović†, Nebojša Radovanović†, Jelena Janković†, Mirko Lakićević†, Predrag Mitrović†, Ratko Lasica†, Zorica Nešić*, Zoran Todorović*, Marina Stojanov‡

School of Medicine, *Department of Pharmacology, Clinical Pharmacology and Toxicology, Belgrade; Clinical Center of Serbia, †Cardiology Clinic, Emergency Center, Institute of Cardiovascular Diseases, Belgrade; School of Pharmacy, ‡Institute of Medical Biochemistry, Belgrade

Key words: cardiovascular diseases; arteriosclerosis; inflammation mediators; anti-bacterial agents; hydroxymethylglutaryl – CoA reductase inhibitors.

Kljune reči: kardiovaskularne bolesti; arterioskleroza; zapaljenje, medijatori; antibiotici; hidroksimetilglutaril – CoA reduktaza, inhibitori.

Introduction

Cardiovascular system diseases are the leading cause of death in developed countries. According to the World Health Organization data, coronary artery disease is responsible for death of over seven million people per year, while only in the United States about two million patients are hospitalized with the diagnosis of acute coronary syndrome (acute myocardial infarction or unstable angina). The main cause of these diseases is arteriosclerosis. The arteriosclerotic process in the big arterial blood vessels begins very early, already in childhood. Risk factors for arteriosclerosis are: hypercholesterolemia, hypertension, diabetes mellitus, obesity, smoking and physical inactivity. The main mechanism is a modest, chronic inflammatory reaction as a response to the blood vessel damage.

Inflammation, infection and cardiovascular disease

Recently published data have shown that inflammation has a significant role in the appearance, the development, as well as in the consequent complications of arteriosclerotic process, like unstable angina pectoris and acute myocardial infarction. Endothelial injury represents the first step in atherogenesis. Early arteriosclerotic lesions are characterized by leukocyte infiltration. Endothelial expression of soluble intracellular adhesion molecule-1 (sICAM-1) facilitates the migration of leukocytes into the vascular wall. Also, an endothelial injury induces the synthesis of vasoactive molecules, cytokines and growth factors. Oxidized LDL cholesterol activates the endothelial cells to increase the expression of chemotactic molecules leading to the stimulated monocyte migration and formation of foam cells.

The idea of concomitance of coronary artery disease and infection has been known for over a century, and is based on a certain pathological, microbiological and epidemiological facts.

The role of the following bacterial and viral infective agencies were most frequently investigated: Chlamydia pneumoniae, Cytomegalovirus, Herpes simplex virus, Helicobacter pylori (1) and different bacterial causes of gum inflammation (2).

Based on the results of previous investigations, several mechanisms by which different infective agents can induce and accelerate the arteriosclerotic process have been suggested. These are:
years of age, 80% of the patients had antibodies against age, in the third decade of life, 50% of the investigated pa-
showed that the infection was rare before the fifth year of
arteriosclerotic process (3).
creased LDL-C and lowered HDL-C level, which favors the
sclerotic plaque are a good evidence of the relationship
complete understanding, yet.

teriosclerotic process starts with the activation of procoagu-
flammation, such as: leukocyte count, eryth-
cretins). Besides, there are the standard markers of the cell
zymes (IL-1, TNF-alpha) and adhesion molecules (se-
protein (hsCRP), serum amyloid A (SAA), proinflammatory
prise: oxidized LDL cholesterol, high sensitivity C-reactive
lowing up the inflammation process. These markers com-
apply to situations of unstable angina, the hsCRP values can predict the possi-
stable and unstable angina. Also, in the patients
has been proved (18). Berk et al. (19) have shown that the
 arteriosclerotic plaque, which can cause the  instability of the
 inflammatory effects, like the capability of monocyte activation,
 increment of their adhesion and complement activation in ar-
teriosclerotic plaque, which can cause the  instability of the
 microorganisms can directly settle in the intima of ar-
teriovascular disease, and also for the prognosis in patients with acute coro-
ary syndrome. Ridker et al. (10) have shown that the ba-
level of hsCRP can be a predictor of myocardial infarc-
ion in the apparently healthy subjects. Some earlier pro-
spective epidemiological studies have shown the connection
between leukocyte count, plasma fibrinogen concentration
and coronary vascular disease (11). The main role of in-
flammation markers assay is not only in pointing out the se-
verity of arteriosclerosis, but also in the prediction of the
degree of arteriosclerotic plaque destabilization and occur-
rence of the subsequent ulceration and thrombosis (12). In
new case-control studies, attention has been paid to the im-
portance of hsCRP and SAA assay. New, highly sensitive
 assays for CRP (hsCRP) can measure levels within the
„normal“ range (0,05 mg/l, depending on the assay), thus
enabling careful evaluation of underlying system inflam-
mation in the apparently healthy patients, as well as in those
with established coronary artery disease.
An increased level of hsCRP is considered as the
more powerful risk factor than TNF-alpha, IL-6 or SAA.
Thus, due to the existence of hsCRP in arteriosclerotic
plaque, but not in the normal blood vessel wall (13), it is
considered that it could be involved in the inflammatory
process.
The results of newer studies point out its direct proin-
flammatory effects, like the capability of monocyte activation,
increment of their adhesion and complement activation in ar-
teriosclerotic plaque, which can cause the instability of the
plaque (14,15). It was also shown that hsCRP can induce the
expression of adhered molecules (VCAM-1 and ICAM-1) on
human coronary endothelial cells (16). Those proinflamma-
tory effects of hsCRP are important in the occurrence, pro-
gression and complications of arteriosclerotic process (17).

In many studies, the connection between hsCRP value
and the risk of coronary artery disease and sudden death,
has been proved (18). Berk et al. (19) have shown that the
average values of hsCRP significantly differ between pa-
tients with unstable and stable angina. Also, in the patients
with chronic stable angina, the level of hsCRP is increased,
and in the correlation with the disease term (20). Few years
later, Liuzzo et al. (21) found out that the increased level of
hsCRP and SAA on admission to the hospital could predict
a bad prognosis for the patients with unstable angina. In
the patients with acute myocardial infarction as a consequence
of unstable angina, the hsCRP values can predict the possi-
bility of reinfarction (22–24). The increment of hsCRP in
patients with AMI and its correlation to CK-MB was proved
by de Beer et al. (25).
Considering all of the above, it is obvious that further investigation of hsCRP and other potential markers of arteriosclerosis and inflammation in the apparently healthy individuals and those with confirmed cardiovascular disease are necessary.

**Antibiotics therapy in coronary disease**

The established association between *Ch. pneumoniae* infection and coronary artery disease (CAD) determined by seroepidemiological and histopathological studies has led to the hypothesis that this organisms, as well as other bacterial and viral organism, causes or contributes to the inflammation in arteriosclerosis. Current research of the hypothesis suggesting infection influence on coronary disease has focused on *Chlamydia pneumoniae* and *Helicobacter pylori*. The role of *Ch. pneumoniae* was investigated in animal models as well as in clinical trials.

Meier et al. (26) examined whether the antibiotic therapy 3-year prior to AIM could decrease the risk of the first-time acute myocardial infarction. They found that the administration of tetracycline and quinolone antibiotics was associated with the reduction of the first myocardial infarction. However, no association between the past use of macrolides (primarily erythromycin), sulfonamides, penicillins or cephalosporins and the occurrence of AMI was found. The limitation of this study was in the fact that the used sample was not truly representative. Patients with major cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus) were not included. Therefore, the positive findings of this study do not represent the conclusive proof that the physicians should prescribe antibiotics for this purpose. Jackson et al. (27) found that the use of erythromycin, tetracycline or doxycycline five years prior to AMI was not associated to the risk of the first myocardial infarction.

Several published clinical trials are available on the antibiotic treatment for secondary prevention of arteriosclerotic cardiovascular disease. STAMINA study (28) (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina) was a double-blind, randomized, placebo-controlled trial designed to investigate whether antibiotics used against *Ch. pneumoniae* and *H. pylori* reduced the levels of inflammatory markers (i.e. CRP, fibrinogen, white blood cell count) and adverse cardiac events. Patients were randomized to receive 1 of 3 different treatment regimens within one week: (1) placebo, (2) amoxicillin, omeprazole and metronidazole or (3) azithromycin, omeprazole and metronidazole. The study included 325 patients with unstable angina pectoris or acute myocardial infarction, and the follow-up period was 1 year. The primary end points were cardiac death and readmission due to the acute coronary syndrome. It was found that antibiotics produced a reduction of recurrent episodes of unstable angina requiring hospital admission. However, no significant difference in total mortality. Still, the number of recurrent myocardial infarctions or cardiac deaths over the course of the year was not sufficient to produce meaningful results. The investigators did not find a significant association between the baseline infection status and the different treatments' effects. Also, it was noted that amoxicillin produced a reduction in CRP levels only in the patients with unstable angina. Fibrinogen level was reduced in both patient groups receiving antibiotics.

The ROXIS (Roxithromycin Ischemic Pilot Study) (29) was designed to examine the effect of 30-day roxithromycin therapy (300 mg/day) in the patients (n=202) with unstable angina pectoris or non-Q-wave myocardial infarction. The study was double-blind, randomized, multicenter, placebo-controlled, and designed as a pilot study since approximately 4,000 patients were needed to generate an 80% statistical power to truly detect significant clinical differences. The end points were recurrent angina, acute myocardial infarction and death. The results of the study showed that there were no significant differences between the investigated groups for these individual endpoints (2 recurrent angina in the roxithromycin group vs 5 in the placebo group, no myocardial infarction vs 2, without death vs 2) at 6 months. A statistically significant difference was found only when all endpoints were combined as the triple endpoint (2 vs 9). The study has a lot of limitations (i.e. small number of patients, short follow-up period) and, although the results of this study suggested some benefits from the antibiotic therapy, it should be interpreted with a grain of salt.

The next small study (n=302) that tried to examine the effect of antibiotics in secondary prevention of coronary disease events was ACADEMIC (30). The study was designed to give an answer to whether azithromycin therapy can reduce cardiovascular events in comparison to placebo in the patients with stable coronary disease, seropositive to *Ch. pneumoniae*. Final outcomes were defined as cardiovascular death, resuscitated cardiac arrest, nonfatal myocardial infarction, stroke, unstable angina requiring hospitalization, and the unplanned coronary interventions after two years. Patients were randomized to receive placebo or azithromycin (500 mg/day for three days and then 500 mg/week for 3 moths). It was found that a 3-month course of azithromycin was not associated with the reduction in cardiovascular events in comparison to placebo. Like ROXIS, the ACADEMIC study was not adequately powered to prove that antibiotic therapy did reduce cardiovascular events. The lack of benefits from antibiotic therapy was supported by the ANTIBIO study (Antibiotic Therapy After an Acute Myocardial Infarction) (31). The purpose of the study was to examine whether roxithromycin (300 mg/day for 6 weeks; n= 433) could reduce morbidity or mortality in the patients with acute myocardial infarction in comparison to placebo (n=439). Therapy was started at a median of 4 days after the admission to the hospital. Total mortality during 12-month follow-up was the primary end point. Total mortality between groups was 6.5% in roxithromycin vs 6% in the placebo group.
Additional information on the effect of antibiotic treatment in the stable patients after an acute myocardial infarction was available from the adequately powered WIZARD study (n>7000) (Weekly Intervention with Azithromycin for Atherosclerosis and its Related Disorders) (32). It was found that a 3-month therapy with azithromycin produced a significant reduction in death and myocardial infarction during the first six months. However, a loss of azithromycin effect in time was noticed, which led to the conclusion that a longer antibiotic therapy might be even much more effective (33, 34).

It can be concluded that the role of infection remains controversial and still unresolved. As shown, data from the performed trials did not bring about any unified attitude in regard to the value of an antibiotic therapy in the patients with acute or stable coronary disease. It is unknown whether some beneficial effects of antibiotics might be caused by a specific antibacterial action or their general anti-inflammatory effect. The optimal dose of an antibiotic, the therapy duration and the appropriate dose regimen (35, 36) are still unknown. Also, the possible interactions between antibiotics and other prescribed drugs for cardiovascular diseases (37–39) should be taken into consideration. Therefore, nowadays, antibiotics have not been still indicated for the prevention and the therapy for the acute coronary syndrome. The results from new trials might provide a more definitive conclusion.

**Statins and coronary disease**

Statins are selective inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the liver and other tissues. They produce relatively large reductions in plasma total and LDL cholesterol levels and are a well-established class of drug for the treatment of hypercholesterolemia (40). Statins are generally well tolerated. The most important adverse effects, although rare, are myopathy and the asymptomatic increase in hepatic enzyme levels. Between 1–3% of the patients have experienced an increase in the levels of hepatic transaminases that requires monitoring. The frequency of myopathy is dose-dependent, and increased during the multiple-drug therapy. The most important interactions occur at the pharmacokinetic level. Simvastatin, lovastatin, atorvastatin and cerivastatin are biotransformed in the liver by cytochrome P450 3A4 isoform (41). Because of that, it is important to know the interactions between statins and other drugs that can inhibit this enzyme (macrolide antibiotics, antifungal imidazoles, warfarin, verapamil).

Five large randomized clinical trials showed the benefits of statins therapy in primary and secondary prevention. The two of them were primary prevention studies (AFCAPS/TexCAPS and WOSCOPS – West of Scotland Coronary Prevention Study). The other three were secondary prevention trials (4S-the Scandinavian Simvastatin Survival Study; CARE-Cholesterol and Recurrent Events and LIPID-Long Term Intervention with Pravastatin in Ischemic Disease).

AFCAPS/TexCAPS (42) was a trial designed to examine the effects of lovastatin on an average-risk healthy population with normal total cholesterol levels (mean 5.71 mmol/l). The primary end point was the first major coronary event (sudden death, myocardial infarction and unstable angina pectoris) after the average follow-up period of 5 years. The primary end point was significantly reduced in the lovastatin group in comparison to the placebo. However, there was no difference in the total mortality between these groups. The results from AFCAPS/TexCAPS primary prevention study emphasized that in those patients who were not at a high risk of coronary death, the therapy goal was to lower cholesterol, but it was not enough for a significant decrease in mortality rate. It was obvious that in primary prevention, the cholesterol lowering therapy in patients at high risk would provide a bigger benefit.

The 4S study (43) included 4444 patients with angina or previous myocardial infarction and serum cholesterol between 5.5 and 8.0 mmol/l. Patients were randomized to receive simvastatin or placebo, and followed up for a median of 5.4 years. Simvastatin treatment reduced total cholesterol level by 25% and LDL by 35%. Also, simvastatin reduced major coronary events (coronary death, myocardial infarction or resuscitated cardiac arrest) and total mortality. Furthermore, it was noticed that simvastatin also reduced the need for coronary revascularization. However, there was no difference in noncardiovascular deaths between the simvastatin and placebo groups. The 4S study clearly established that simvastatin therapy reduced morbidity and mortality in hypercholesterolemic patients with coronary heart disease. It seems logical that the patients with the elevated cholesterol levels and cardiovascular heart disease should be treated with the lipid-lowering drugs to reduce future adverse events.

In contrast to the 4S, the WOSCOPS study (44) was designed to evaluate pravastatin therapy in the middle-aged men (45–64 years) without documented coronary heart disease but with elevated cholesterol level (LDL between 4–6 mmol/l). After randomization, the patients were given pravastatin (40 mg daily) or placebo during the following 5 years. It was found out that pravastatin treatment produced a reduction in total cholesterol by 20% and LDL by 26%. WOSCOPS is a primary prevention study, but it should be kept in mind that the patients enrolled in the trial were at a high risk of coronary events (the patients with elevated cholesterol level, more than a third of them were current smokers). The results showed that pravastatin reduced coronary events by 31%, and coronary heart disease death by 32%. At the same time, the need for revascularization procedures was reduced by 37%. There were no differences in noncardiovascular mortality between the groups. Data from WOSCOPS and 4S studies show that lipid-lowering therapy with statins in patients with confirmed cardiovascular disease or at a high risk of coronary disease have greater bene-
fit in comparison to those without prior coronary heart disease.

The CARE (45) and LIPID (46) studies included subjects with the "average" cholesterol levels. The CARE study was double-blind, randomized, designed to examine the effect of pravastatin on primary end points: coronary heart disease death and nonfatal myocardial infarction in patients with prior myocardial infarction. They had the average cholesterol level (total cholesterol level $< 6.21$ mmol/l and LDL level between $2.97-4.50$ mmol/l). The study lasted 5 years. The applied therapy reduced total cholesterol by 20%, and LDL by 28%. Pravastatin significantly reduced the primary end point defined as coronary death or nonfatal myocardial infarction. This was an important finding because it showed the benefits of lipid-lowering therapy in patients with a prior myocardial infarction and the average cholesterol levels. However, there was no significant difference in non-cardiovascular and total mortality. Significant reduction in myocardial infarction accounted for the significant reduction in primary end point in the CARE study. When we compared these findings with the results from the 4S study, we come to a conclusion that the patients with elevated cholesterol levels (4S) obtained greater benefit from statin therapy.

The second randomized study that compared the effects of pravastatin and placebo in the patients with the average total cholesterol levels was the LIPID study. The study lasted 6 years and included over 9000 patients. This study was important because it included the patients with prior myocardial infarction and unstable angina pectoris and a very broad range of the initial total cholesterol levels (4.0–7.0 mmol/l). It was designed to examine the effect of pravastatin on coronary mortality. The results show that pravastatin therapy significantly reduced mortality in the patients with prior myocardial infarction as well as with unstable angina pectoris. There was also a significant reduction of major coronary events (coronary death and nonfatal myocardial infarction) by 24%, coronary revascularization by 20% and nonhemorrhagic strokes. The greatest benefit from pravastatin therapy was in the patients with the highest LDL cholesterol level. Pooled data from WOSCOPS, CARE and LIPID studies, were examined in the PPP study (Pravastatin Pooling Project) (47). In the PPP individual patient data from these trials were pooled into a single database. In that way it was possible to find a difference in outcomes among the subgroups (women, patients with diabetes mellitus, elderly and patients with a low baseline cholesterol level). It was found that pravastatin significantly reduced coronary heart disease mortality (24%). Also, pravastatin therapy was associated with a non-significant difference in non cardiovascular deaths – 12% and in other vascular deaths – 17%. At the same time, there were no differences in the relative risk reduction between men and women. However, the reduction in absolute risk was much larger in those with a history of coronary heart disease. In elderly (65–75 years) and other high risk patients (diabetics, smokers) there were also significant risk reductions in clinical end points. Pravastatin treatment also improved the anti-hypertensive effects of other drugs. Also, data analysis from CARE and LIPID studies demonstrated the reductions in nonfatal and total stroke. In summary, the PPP study clearly demonstrated the efficacy and safety of pravastatin treatment in both primary and secondary prevention.

Elderly patients (72–80 years) with the total cholesterol levels between 4 and 9 mmol/l were included in a double-blind, randomized, placebo-controlled PROSPER study (PROspective Study of Pravastatin in Elderly at Risk) (48). The study included 5804 high-risk elderly persons. The study was designed to examine the effect of pravastatin on the risk of coronary heart disease, cerebral vascular events and cognitive function. After randomization they received pravastatin (40 mg daily) or a placebo within 3 years. It was found that pravastatin treatment produced a reduction in LDL cholesterol (34%) and coronary mortality (24%). There was no difference in stroke reduction, but the incidence of transitory ischemic attack was reduced by 25%. This study clearly showed the benefit of pravastatin therapy in primary and secondary prevention in elderly population.

Clinical trials have shown that statins reduce the risk of coronary events and mortality in patients with a stable arteriosclerotic disease of the coronary arteries. It was of interest to evaluate the effects of statin therapy in an acute coronary syndrome (ACS) because statins can modulate mechanisms involved in the physiopathology of ACS.

The important question is when statins should be given to patients with myocardial infarction or unstable angina? Recent data from clinical studies suggest that lipid-lowering therapy initiated immediately after the admission due to ACS, can reduce recurrent events, and, possibly, all-causes of mortality. Four randomized controlled clinical trials have examined the use of statin therapy in an acute coronary syndrome: L-CAD (the Lipid-Coronary Artery Disease), MIRACL (the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering), FLORIDA (the Fluvasatin on Risk Diminishing After Acute Myocardial Infarction), and PTT study (the Pravastatin Turkish Trial).

The L-CAD study (45) was an open label, randomized study involving two groups of patients. Patients (n=70) in the first group started with pravastatin within 6 days after acute myocardial infarction and/or percutaneous angioplasty for unstable angina. All the included patients had total cholesterol between 5.18 and 10.36 mmol/l, and LDL cholesterol between 3.36 and 7.77 mmol/l. Pravastatin was combined, when necessary, with colestyramine and/or nicotinic acid, to achieve LDL cholesterol levels of 3.36 mmol/l or lower. In the control group, antilipidemic therapy was determined by the family physicians. The patients were monitored for 2 years. The end points were the total mortality, cardiovascular death, nonfatal myocardial infarction, need for coronary intervention, and the new onset of peripheral vascular disease. Angiographic changes after 6 and 24 months were also examined. In the pravastatin group,
total cholesterol was significantly reduced by an average of 20% and LDL cholesterol by 28% over the study period. In the control group ("standard care"), both values remained close to the baseline during the study. At the end of the study (after 2 years) the incidence of the combined end point in the pravastatin group was 23% in comparison to 52% in the control group. The results of L-CAD study suggested early statin treatment in these patients, but this study had limitations: small number of patients (11% in the pravastatin group received a second drug to achieve desirable LDL level and almost 25% in the control group received some antilipemic drugs) and should be interpreted with caution.

The MIRACL study (50) was designed to investigate the effects of atorvastatin (80 mg daily) initiated between 24 and 96 hours after admission to hospital in patients with the unstable angina and non-Q wave myocardial infarction. The follow-up period was 16 weeks. Primary end-points were defined as death, nonfatal AMI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization. Patients (n=3086) included in the study were at a high risk because the half of them had hypertension, 23% had diabetes mellitus type 2, and almost 30% currently smoked. Patients were excluded if the total cholesterol level at screening exceeded 7 mmol/l. The serum lipid levels at the time of randomization were almost identical in both groups (mean LDL 3.2 mmol/l, mean HDL 1.2 mmol/l, mean triglycerides level of 2.0 mmol/l). Atorvastatin produced reduction in LDL by 40% and triglyceride by 16%. Despite this, it was found that only the incidence of recurrent symptomatic myocardial ischemia was significantly reduced. There was no significant reduction in death, nonfatal myocardial infarction and cardiac arrest between the atorvastatin and the placebo group. However, there were fewer strokes in the atorvastatin group.

The FLORIDA trial (51) was a placebo-controlled, randomized multicenter study. The primary end point was a reduction in myocardial ischemia determined by 48-hour ambulatory ECG at 1 year and death and major adverse cardiac events (recurrent myocardial infarction, recurrent ischemia requiring hospitalization, or PTCA or CABG). Patients (n=540) with acute myocardial infarction were randomized to receive fluvastatin (80 mg/day) or placebo within the eight days of the admission. Patients had the baseline total cholesterol level <6.5 mmol/l. The LDL level was also lower than in both CARE and LIPID trials. It was found that fluvastatin produced a significant reduction in LDL, but beside this, there were no significant changes in ischemia. Also, there were no differences in death or major adverse cardiac events between the groups at the end of the study. No significant difference was noticed in the patients with severe baseline ischemia treated with fluvastatin.

In the PTT study (52) 150 patients with acute myocardial infarction were randomized to pravastatin or a placebo. The therapy was initiated 6 hours after the onset of chest pain. All patients were treated with intravenous fibrinolytic therapy. The results showed that a combination of pravastatin and thrombolytic therapy was better than thrombolytic alone. There were no differences in mortality between groups, but a reduction in recurrent angina was noted in the pravastatin group during the 6-month follow-up period. The investigators suggested that the benefit from the combination therapy might be attributed to the early plaque stabilization or regulation of endothelial and platelet function.

The analysis of large, randomized clinical trials suggested that the benefit from statin therapy in the reduction of adverse cardiovascular events could not be explained by the cholesterol reduction only. It was shown that statins could produce a rapid improvement of clinical outcome without angiographic evidence of a substantial regression of arteriosclerotic lesions. Besides well-known lipid-lowering effects, statins also produce the so-called "pleiotropic" effects. Statins inhibit the synthesis of isoprenoid intermediates such as farnesylpyrophosphate and geranylglycerolphosphat (53). In an acute coronary syndrome, statins improve the endothelial function, reduce the platelet thrombus deposition, and normalize hypercoagulability and fibrinolytic activity (54, 55). One of the earliest manifestations of arteriosclerosis is endothelial dysfunction with an impaired activity of nitric oxide (56–59). Statins increase the nitric oxide bioavailability by the stimulation of endothelial NO synthase (60) and by the reduction of oxidized LDL (56, 57). Inflammatory processes are involved in all the stages of arteriosclerosis. Statins reduce the number of inflammatory cells in the arteriosclerotic plaques by an inhibition of intercellular adhesion molecule-1 (ICAM-1). Levels of ICAM-1 are increased in the patients with dyslipidemia (63), hypertension (64) and diabetes (65). Also, it was found that the ICAM level is positively related to the intima-media thickness of carotid arteries (66). In hypercholesterolemic patients, fluvastatin decrease the ICAM plasma levels (67). ICAM-1 and VCAM-1 (vascular cells adhesion molecule) are very important because they mediate the adhesion of leukocytes to the endothelium of the blood vessels. It is known that the interaction between leukocytes and the vascular endothelium represent a crucial inflammatory step in the atherogenic process (68). It was shown that hypercholesterolemia enhances the adhesiveness of aortic endothelium for monocytes. Chronic administration of L-arginine inhibits atherogenesis in a hypercholesterolemic rabbit model due to the modulation of endothelial adhesiveness by nitric oxide (69). Nitric oxide has an important, protective role in regulating the leukocyte-endothelial cell adhesion. The production of vascular superoxide is increased in arteries in hypercholesterolemic animals and humans (70). It was shown that oxidized LDL in vitro activates endothelial cells to increase the expression of chemotactrant molecules leading to stimulate monocyte migration and formation of foam cells. Also, oxidized LDL impairs the production of nitric oxide. Fluvastatin can inhibit the LDL oxidation, reduce the vascular superoxide generation and the formation of arteriosclerotic plaque and,
in this manner, improve the endothelial dysfunction (71). In addition to lipid-lowering, antioxidant and antiinflammatory effects, statins may contribute to the arteriosclerotic plaque composition and stability. The stability of arteriosclerotic plaques is provided by extracellular matrix and thick fibrous cap. It is known that arteriosclerotic complications depend on the plaque composition and stability rather than on its volume (72). However, it is very difficult to characterize the composition of the plaque. Vulnerable plaques are composed of a lipid-rich core separated from the lumen by a thin fibrotic cap. The large lipid core is a consequence of monocytes transformation into tissue macrophages by the ingestion of oxidized LDL. The lipid core grows as a result of the accumulation of lipids in extracellular matrix and the death of lipid-laden macrophages. Reactive oxygen radicals from inflammatory cells oxidize LDL and cause the necrosis of the cells (73). The thin fibrous cap contains number of inflammatory cells (macrophages, mast cells, T-lymphocytes). Monocytes and macrophages can produce various enzymes (members of the matrix metalloproteinases) that degrade the extracellular matrix components (collagen, elastin) leading to arteriosclerotic plaques destabilization. Circumferential wall stress (cap "fatigue"), the characteristic of a lesion (location, consistency) and blood flow determine the fibrous cap vulnerability (74). It is believed that plaque is especially vulnerable when the lipid core accounts for more than 40% of the volume. Stabilizing the unstable arteriosclerotic plaques is a principal goal in reducing the risk of acute coronary syndrome. Statins can decrease the risk of plaque rupture via the inhibition of cholesterol accumulation in monocyte-derived macrophages and the reduction in inflammatory cell activity and the activity of matrix metalloproteinase. Also, decreased risk of plaque rupture is a consequence of statins effects on thrombogenicity they reduce the platelet aggregation (75) and coagulation (76). Statins may affect the platelet aggregation directly by the reduction of cholesterol content of platelet membranes, and indirectly by an increase in the nitric oxide activity. The time course of statins-induced changes varied: improving in endothelial function could be seen within one month therapy with statins; reduction in thrombosis risk at 3 and 6 months after the therapy initiation. Most trials showed a long latency (6 to 18 months) between the initiation of the statins therapy and the reduction in adverse cardiovascular events (myocardial infarction and cardiac death) (77).

Conclusion

The role of inflammation in the initiation, progression and complications of arteriosclerosis can be confirmed on the basis of the results published so far. Both the inflammation of arteriosclerotic plaque and systemic inflammation, can accelerate the evolution of atheroma and provoke an acute coronary syndrome (78). Clinical studies have confirmed the existence of a correlation between inflammatory markers and the prognosis after that event. It is obvious that markers of inflammation are not only the indicator of increased risk, but also the direct participants in the inflammatory process. Although it is known that elevated inflammatory markers denote the increased risk and that certain therapeutic protocols (statins, antibiotics) result in their lowering, there has not yet been any strong confirmation that the supression of inflammation and the consequent lowering of inflammatory markers reduce the adverse cardiovascular events. If it had, the inflammatory markers could be useful in monitoring the response to the cardiovascular therapy (statins, aspirin, antibiotics) that may modulate the inflammatory mechanisms.

The "inflammatory hypothesis" should be tested in a large clinical trial. More knowledge about the role of inflammation in the process of arteriosclerosis and its complications would bring the improvements in the area of its prevention and therapy.

REFERENCES

C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular disease: lack of a role of cytotoxin-associated protein A-positive strains and absence of a systemic inflammatory response. Circulation 1999; 100(23): 2326–31.


Li JJ, Fang CH. C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. Med Hypotheses 2004; 62(4): 499–506.


The paper was received on December 27, 2004.