Improvement of myocardial ischaemia by lipid lowering drugs

D. Tzivoni and J. Klein

Department of Cardiology, Jesselson Heart Center, Shaare Zedek Medical Center, Jerusalem, Israel

Introduction

Coronary artery disease is characterized by the presence of atherosclerotic plaques that may limit or obstruct coronary flow, and by abnormal endothelial function, which may reduce luminal diameter either at rest or during stress conditions. The role of endothelial dysfunction in the clinical expression and progression of coronary artery disease is not very well defined. As regression of atherosclerotic plaques cannot be achieved in most coronary artery disease patients, research has focused on the potential role of risk factor modification to improve endothelial function, retard progression of coronary artery disease and alleviate myocardial ischaemia and anginal symptoms.

Soft coronary atherosclerotic plaques with a high concentration of cholesterol-esters are highly likely to undergo disruption[1,2]. These cholesterol rich 'active plaques' are also characterized by a high concentration of monocytes and macrophages. Atherectomy specimens obtained from patients with acute coronary syndromes (mainly unstable angina) revealed a higher concentration of macrophages compared to specimens obtained from patients with stable angina[3]. Similar findings were reported from autopsy studies[4,5]. The macrophage releases metalloproteins such as interstitial collagenase, gelatinase and stromalyisin[1], which can accelerate the breakdown of extracellular matrix and promote plaque disruption. Reduction of cholesterol may not only reduce the lipid content of the plaque, but can also reduce the accumulation of monocytes and macrophages[1,3,6], thereby contributing to transformation of the 'active plaque' into a less active or quiescent plaque. In addition, lowering of LDL levels increases nitric oxide formation, which reduces platelet adhesion and thrombus formation[7-10]. In coronary segments with atherosclerotic plaque, local secretion of endothelium-derived relaxing factor is reduced and release of endothelin-1 is increased[11] leading to an exaggerated vasoconstrictive response in the areas of atherosclerotic plaque. This excessive vasoconstriction probably plays a significant role not only during unstable angina[12], but also in the many daily occurrences of ischaemic episodes in which increased coronary tone plays an important role[13,14]. It appears that the reduced risk of acute ischaemic events is the result of a reduced tendency to exaggerate local vasoconstriction, secondary to lipid lowering. Improved vasomotor tone may improve daily occurrences of ischaemia and its main clinical expression, angina pectoris.

Cholesterol level and endothelial function

In normal coronary arteries, acetylcholine induces endothelial-dependent vasodilation while in pathological conditions such as atherosclerosis[15,16], hypercholesterolaemia[17-19] or hypertension[20], infusion of acetylcholine causes vasoconstriction, indicative of abnormal endothelial function. Hypercholesterolaemia, and more specifically oxidized LDL, impairs endothelial-dependent dilatation. Oxidized LDL causes inactivation of nitric oxide by excess production of oxygen free radicals[21], activation of protein C kinase and activation of inflammatory processes with accumulation of monocytes/macrophages and T lymphocytes[22]. The decrease in nitric oxide production is associated with reduced vasodilatory reserve, increased platelet adhesion and induction of a procoagulant state[22], which may initiate thrombus formation[23]. In a study of 34 patients with coronary artery disease, the response of normal coronary segments during infusion of acetylcholine[24] ranged from minimal coronary dilatation (+3·7%) to severe constriction (−53%). Cholesterol level and the total number of risk factors were independently associated with coronary constriction in response to acetylcholine. The authors suggested that endothelial dysfunction is an early marker of atherosclerosis, which is exaggerated by external risk factors such as high cholesterol levels. Seiler et al.[25] found that hypercholesterolaemia...
was associated with impaired exercise-induced coronary dilatation in angiographically normal coronary arteries. Patients with a mean cholesterol level of 173 mg. dl⁻¹ had an 18% increase in coronary diameter during exercise, while in patients with a mean cholesterol level of 288 mg. dl⁻¹, no vasodilation was observed. Tsurumi et al. [36] found that in patients with coronary artery disease, the level of plasma lipoprotein(a) was more closely associated with an abnormal coronary response to acetylcholine than the levels of total cholesterol or LDL. It is known that cholesterol enters the plaque in the form of LDL and lipoprotein(a) [27,28]. Lipoprotein(a) has been shown to be an independent risk factor for coronary artery disease [29].

Reducing cholesterol levels, both in normal individuals and in patients with coronary artery disease, improves endothelial function. Seiler et al. [30] found that the vasodilatory response of the coronary arteries to exercise was improved in hypercholesterolaemic patients after 7 months treatment with bezafibrate 400 mg. day⁻¹ and reduction of serum cholesterol from 7·8 to 5·8 mmol. l⁻¹. Leung et al. [31] injected intracorony acetylcholine into 25 patients with cholesterol >6·2 mmol. l⁻¹ and normal coronary arteries and found a 14% reduction in vessel diameter. After 6 months of cholesterol-lowering diet and cholesteryramine, repeat injection of acetylcholine revealed coronary dilatation of 13·3%. The improvement in vasodilatory response was proportionate to the degree of cholesterol lowering.

Treasure et al. [32] assessed endothelial function in 23 coronary patients after 12 days and 5·5 months of treatment with lovastatin 40 mg twice daily or lipid lowering diet. After 12 days there was no difference in the vasoconstrictive response to acetylcholine, even though the cholesterol level was significantly reduced. After 5·5 months of therapy in the lovastatin group, the vasoconstrictive response disappeared, while in the diet group, there was no change in the vasoconstrictive response (-18%). Thus, recovery of endothelial function is not immediate, it takes more than 12 days of lipid lowering. Anderson et al. [33] found that after one year of treatment the improvement in endothelial function was more pronounced in patients assigned to lovastatin and an antioxidant (propocul) than in patients assigned to lovastatin and cholesteryramine. It is possible that by preventing the activity of oxygen-derived free radicals, antioxidants may have prevented endothelial damage. Tamai et al. [34] demonstrated that even after a single LDL apheresis in hypercholesterolaemic patients, with significant reduction in LDL level, the vasodilatory response to acetylcholine improved, with an increase in nitric oxide production.

**Cholesterol lowering and ischaemia**

During exercise testing, ischaemia is determined mainly by the severity of the coronary lesions and therefore is very reproducible [35]. Ischaemia during daily life, as detected by ambulatory ECG monitoring, develops during exertion, mental stress, cigarette smoking or without any apparent provocation [36-38]. Daily ischaemic episodes develop at a lower heart rate (lower ischaemic threshold) than during exercise [12,39]. Even in the same individual, some episodes develop at high heart rates while others at low heart rates. The development of ischaemic episodes during daily life at heart rates which are significantly lower than during exercise testing probably indicates that coronary vasoconstriction is responsible for the reduced ischaemic threshold [13,14]. It is therefore logical to assume that impaired endothelial function contributes to changes in coronary tone in patients with advanced coronary artery disease, and that lipid lowering may reduce the frequency of daily ischaemic episodes. Raby et al. [40] performed 48 h ambulatory ECG monitoring in 185 patients with stable coronary artery disease and positive exercise tests. In patients with cholesterol levels below 240 mg. dl⁻¹, 43-47% had ischaemic episodes during daily life, compared to 75% of patients with cholesterol >241 mg. dl⁻¹. Also, the frequency of ischaemia was higher in patients with high cholesterol.

An interesting study was performed by Gould and co-workers [41] in 12 patients with stable angina pectoris, cholesterol >240 mg. dl⁻¹ and evidence of ischaemia by rest thallium-dipyridamole positron emission tomography imaging. After 90 days of an intensive cholesterol lowering regimen by diet or diet combined with lovastatin or cholesteryramine, the cholesterol level decreased from a mean of 297 to 224 mg. dl⁻¹ and LDL from 213 to 151 mg. dl⁻¹. Although there was no change in anti-anginal medication, the angina frequency in these patients was reduced by 51% and exercise duration increased from 10·7 to 13·3 min (P = 0.04). Perfusion defect decreased in size from 22% at baseline to 13% after 90 days (P = 0.009). Sixty days after cessation of the lipid lowering regime, cholesterol levels returned to baseline level and the tomographic filling defects returned to their previous size. The authors attribute the reduction in the extent of myocardial ischaemia to the improvement in flow capacity of the entire coronary arterial tree. As these changes occurred very early (90 days) before anatomical regression can take place they attribute the decrease in the extent of ischaemia to recovery of endothelial function. This assumption is supported by the return of ischaemia to its original extent after 60 days of withdrawal of lipid-lowering regimen. Schuler et al. [42,43] assessed the effect of physical exercise and low fat diet on myocardial ischaemia and progression of coronary artery disease in patients with stable angina pectoris and angiographic evidence of coronary artery disease. After 12 months, while the patients continued their anti-anginal therapy, the size of the thallium-201 perfusion defect only decreased significantly in the intervention group. Improvement in perfusion was observed both in patients with angiographic evidence of regression and in those without regression, indicating functional recovery of the endothelium.
A recent study by van Boven[441] assessed the effect of lipid lowering by pravastatin on daily ischaemic episodes. Seven hundred and sixty eight male patients with stable angina with serum cholesterol 4–8 mmol·l⁻¹ had 48 h ambulatory ECG monitoring before and 2 years after treatment with pravastatin 40 mg·d⁻¹ or placebo. During this period, patients continued their anti-ischaemic treatment. In the pravastatin group, total cholesterol was reduced from 6·02 to 4·9 mmol·l⁻¹. In this group, transient ischaemia was present in 28% of patients at baseline and 19% after 2 years of therapy (P = 0·02). There was no change in the cholesterol level or in the frequency of ischaemia in the placebo group. The number of ischaemic episodes decreased by 1·23 in the pravastatin group and by 0·5 in the placebo group (P = 0·04). Ischaemic duration decreased from 80 min at baseline to 42 min after treatment in the pravastatin group and from 60 to 51 min in the placebo group (P = 0·017). Clinical events occurred in 11% of patients receiving pravastatin and in 19% on placebo (P = 0·0042). Interestingly, Jukema et al.[45] found that the beneficial effect of pravastatin in the REGRESS trial was observed mainly in patients who received a combination of calcium antagonists and pravastatin. Another recent study by Andrews and co-workers[46] found that cholesterol lowering by lovastatin for 4–6 months markedly reduced the frequency of daily ischaemic episodes. In this study of 40 patients with stable coronary artery disease and evidence of ischaemia on ambulatory ECG monitoring, the median number of ischaemic episodes was reduced by four and the duration of ischaemia by 52 min, while there was no change in the placebo group. The authors stress that cholesterol lowering can improve clinical signs of disease activity and ischaemia after a period of less than 6 months. Improvement in myocardial ischaemia after only 3 months was noted by Eichstadt et al.[47]. In this study, cholesterol levels were significantly reduced in 17 patients with hypercholesterolaemia who received fluvastatin 40 mg·d⁻¹ for 12 weeks. Repeated SPECT thallium 201 stress testing revealed a 30% improvement in myocardial perfusion in the ischaemic segments. Improvement in myocardial perfusion was also observed by Aengevaeren et al.[48] after 2 years of cholesterol lowering by bi-weekly LDL apheresis combined with simvastatin in 42 patients with severe hypercholesterolaemia and extensive coronary artery disease.

Cholesterol lowering and clinical expression of coronary artery disease

Cholesterol lowering can reduce the lipid content of coronary plaques, making the plaques less active and less likely to rupture[31]. This transformation of an active to less active or inactive plaque is believed to be responsible for the reduction of cardiac events observed during treatment with lipid lowering drugs. Several large scale trials have proved that lipid lowering by various agents can reduce the frequency of myocardial infarction and sudden cardiac death by 30–35%.[49–52] Lipid lowering has been shown to improve other end-points which are not necessarily related to plaque rupture, such as the need for coronary angiography, coronary angioplasty or coronary bypass surgery. These interventions are driven by the patients’ symptoms and therefore one can assume that they were performed in patients who either developed or had worsening symptoms of angina pectoris. A coronary flow depends on both the anatomical and functional status of the coronary plaque and the overlying endothelium, it is possible that at least part of the clinical improvement observed during lipid lowering is related to restoration of endothelial function. In the CARE trial[49] after 5 years of treatment with pravastatin 40 mg·d⁻¹ in 2081 patients with previous myocardial infarction, the need for coronary bypass surgery was reduced by 26% and the need for coronary angioplasty by 23% (P = 0·01). The reduction in cardiac events was greater in patients with higher pre-treatment levels of LDL cholesterol. There was a borderline (−13%) reduction in frequency of unstable angina (P = 0·07).

In the Scandinavian Simvastatin Survival Study[50], among 4444 coronary artery disease patients, during 5·4 years of follow-up, there was a 30% reduction in mortality and a 39% reduction in definite myocardial infarction; however, there was also a 37% reduction in risk of undergoing coronary angiography or bypass surgery (P < 0·00001), which may be surrogate end-points for their worsening anginal status. In the West of Scotland trial[51] of 6595 men during a 4·9 year follow-up period, there was a 31% reduction in non-fatal myocardial infarction/coronary death (P = 0·0001). However, there was also a 31% reduction in the need for coronary arteriography (P = 0·007) and a 37% reduction in the need for coronary angioplasty or bypass surgery in the pravastatin group. In the REGRESS trial[52] of symptomatic men with coronary artery disease and normal to moderately elevated cholesterol, 2 years of treatment with pravastatin was associated with less progression of coronary artery disease and fewer new cardiac events. In the treated patients, there was a 57% reduction (P = 0·0004) in the need for coronary angioplasty. An aggressive approach to lipid lowering using partial ileal bypass in patients with coronary artery disease and hypercholesterolaemia was associated with a 40% reduction in mortality and non-fatal myocardial infarction[53]. There was also an impressive reduction of 63% in the need for coronary bypass surgery and 42% in angioplasty.
after long-term use\textsuperscript{55}. This effect is dose dependent\textsuperscript{56}. Hypercholesterolaemia and smoking synergistically impair endothelial function\textsuperscript{57} and increase risk of all cardiovascular events.

Menopause is associated with increased incidence of coronary artery disease, angina pectoris and vasomotor disturbances. Postmenopausal women receiving oestrogen replacement therapy have a considerably lower incidence of coronary artery disease and cardiac events\textsuperscript{58}. The beneficial effect of oestrogen on lipid profile\textsuperscript{59} is insufficient to explain the observed 50\% reduction in cardiac events. Williams et al.\textsuperscript{60,61} found that an abnormal coronary vasoconstrictive response to acetylcholine was converted into a vasodilatory response during acute and chronic oestrogen administration to ovariectomized atherosclerotic monkeys. Rosano et al.\textsuperscript{62} found that acute administration of 17\%estradiol had a beneficial effect on exercise-induced ischaemia in women with coronary artery disease.

Many coronary patients seek medical help for relief of their anginal symptoms. Suppression of myocardial ischaemia is therefore a very important goal that is associated with improvement in quality of life, fewer referrals for coronary angiography and subsequently fewer interventions. Therefore it is hoped that within a few months of lipid lowering therapy, many coronary patients will experience an improvement in their symptoms, and that within a year or two the frequency of myocardial infarction and mortality will also be reduced.

**Conclusion**

Lipid lowering therapy has been shown to be effective in the reduction of acute ischaemic events in patients with coronary artery disease, presumably due to stabilization of obstructive and non-obstructive coronary plaques. These medications, by improving endothelial function, seem to reduce symptomatic or asymptomatic ischaemic episodes. It seems, therefore, that by combining standard anti-anginal therapy with a rigorous programme to reduce dietary fat and cholesterol and the judicious use of lipid-lowering medications, severity and frequency of myocardial ischaemia and anginal symptoms would be alleviated.

**References**

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