

REVIEW

Statins: The Drugs for the 21st Century?

Ginter E¹, Simko V²

Institute of Preventive and Clinical Medicine, Bratislava, Slovakia. ginter.emil@mail.t-com.sk

Abstract: This review summarizes the current evidence on beneficial effect of statins on the atherogenesis and the preventive potential of coenzyme Q 10 to avoid statin-induced myopathy.

Statins, originally discovered in molds are the most effective medication to decrease the low-density cholesterol (LDL-C) which is the key participant in atherogenesis. Statins accomplish this by inhibiting the hydroxymethyl glutaryl coenzyme A reductase, an enzyme that is rate limiting for cholesterol biosynthesis. Inhibition of HMG CoA reductase stimulates in the liver the LDL receptors. The result is an increased clearance of LDL particles from the bloodstream and by this mechanism statins have proved to be highly effective in reducing the cardiovascular risk, as amply documented in clinical studies confirming inhibition of atherosclerosis. Additional beneficial effect of statins occurs by modulation of endothelial functions and by diminishing vessel wall inflammation. Statins reduce the level of the C-reactive protein, a strong predictor of adverse cardiovascular events. Beneficial effects of statins on endothelial dysfunction and synthesis of nitric oxide NO were described. Different statin preparation might differ in their antioxidant effects (Fig. 2, Ref. 46). Full Text (Free, PDF) www.bmj.sk. Key words: heart disease, statins, side effects, myopathy, coenzyme Q10, low density lipoproteins.

Japanese investigators hypothesized that some microorganisms may produce inhibitors of hydroxymethyl glutaryl coenzyme A reductase (HMG CoA) as a defense against other microbial agents. Mevalonate is a precursor of many substances required by microorganisms for integrity of their cell wall (cytoskeleton). When they searched thousands of species of microorganisms, the biochemists isolated mevastatin, a molecule produced by *Penicillium citrinum*. Unexpectedly, this molecule inhibited not only mevalonate but also the synthesis of cholesterol (Fig. 1).

This discovery initiated an enormous interest in the United States that had been under the spell of excessive cardiovascular (CV) mortality. The first commercially available statin, lovastatin was introduced by Merck pharmacological industry. Statins were confirmed to effectively reduce the low-density cholesterol (LDL-C). The Japanese biochemist Akira Endo was awarded thirty years later the prestigious Lasker Prize for the discovery of an agent that blocks the synthesis of cholesterol.

Pharmacological industry continuously modifies statin molecules (1). After lovastatin, fluvastatin, pravastatin and simvastatin it has been atorvastatin, cerivastatin, pitavastatin and, recently the allegedly most effective rosuvastatin. Imaging studies (intravascular ultrasound) reported regression of atheromatous plaques in secondary clinical trials with Rosuvastatin (2). Statins belong now to the world's second most commonly prescribed medicine (after cancer drugs). They were used by 24 million North Americans in 2003–2004.

¹Institute of Preventive and Clinical Medicine, Bratislava, Slovakia, and ²State University of New York, Downstate Medical Center at Brooklyn, USA

Address for correspondence: E. Ginter, RND, DSc, Racianska 17, SK-831 02 Bratislava, Slovakia.

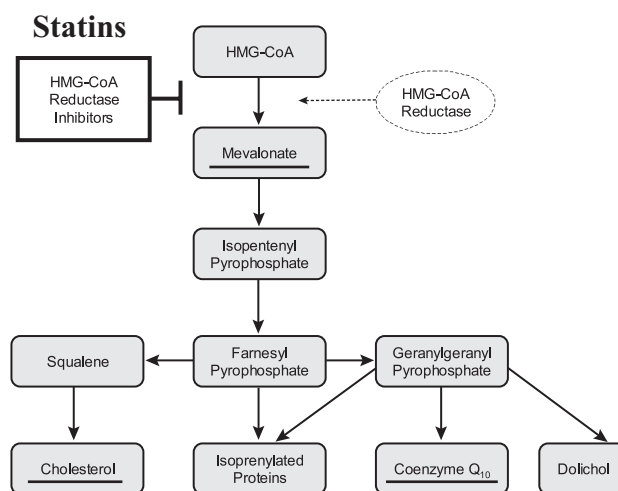


Fig. 1. Metabolic interventions of statins. Statins by inhibition of HMG-CoA reductase lower the formation of mevalonate, cholesterol and coenzyme Q10.

While statins are the most effective agent in the management of atherogenesis, they are only one in a series of other medications that act by different mechanisms: Fibrates, bile acid binding resins and the most recent addition of ezetimibe, an inhibitor of intestinal absorption of cholesterol.

Statins and lipoprotein metabolism

Statins lower cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Inhibition of this

enzyme in the liver stimulates LDL receptors, resulting in an increased clearance of LDL from the bloodstream. Statin therapy continues to increase among US adults and this has led to substantial improvements in LDL-C control (1). LDL-C quality rather than quantity exerts an important effect on CV risk. LDL comprise multiple sub classes with discrete size, density and physico-chemical behavior that influence their atherogenicity. Small dense LDLs are predictors of CV mortality. Different effectiveness of various statins on atherogenesis may be related to their specific effect on LDL subclasses (3). In 2006 there were published seven trials of statins in nearly 43,000 patients (4). In patients without clinical diagnosis of coronary heart disease (CHD) statin therapy decreased future major coronary and cerebrovascular events but not the overall mortality. Another meta analysis in 2007 pooled six statin trials including 110,271 patient-years (5). Compared with moderate statin therapy, intensive statin administration reduced all-cause mortality in patients with recent acute coronary events but not in patients with stable CHD. Use of statins was significantly associated with a decreased risk of incidence or recurrence of atrial fibrillation in patients with a history of previous atrial fibrillation or after an acute coronary syndrome (6). Statin therapy provided effective protection for non-hemorrhagic stroke (7).

In 2008 the reports related to the effect of statins in CHD included about ten meta analyses and hundred thousands of clinical cases (7–15). These clinical studies confirmed statins to lower LDL-C and to reduce major adverse CV events in patients with systemic hypertension, in type two diabetes, in patients undergoing cardiac intervention and in chronic kidney disease.

Anti-inflammatory and antioxidant effects of statins

Recent clinical studies are suggesting that statins may affect the CV system beyond their influence on the LDL. Statins also act on the immune functions and on vascular inflammation. Many of the beneficial pleiotropic effects of statins are the result of modulated endothelial function and inhibition of inflammatory processes.

The established model of atherogenesis envisioned a normal CV system as smooth blood vessels with unobstructed blood flow. When LDL-C particles reached a critical limit they accumulated with the platelets on the endothelial surface, generating a plaque with cholesterol. This obstruction reduced oxygen delivery to target organs. When the heart muscle or brain became compromised, the result was a myocardial infarction or a stroke.

We now know that this popular model is incomplete. The vessel wall contains cells that actively communicate with their environment. These cells are under the influence of immune mechanisms and exposed to the adverse effect of oxygen free radicals. When the immediate environment is unfavorable it contributes to the deposition of oxidized LDL deposits in atheromatous plaques.

There are at least three components involved in atherogenesis: 1) A high level of circulating LDL particles, 2) Altered immunological mechanisms contributing to vessel wall inflammation, and, 3) Dysbalance in oxygenation/ reduction resulting in an oxidative stress and oxidation of LDL particles (16–17) (Fig. 2).

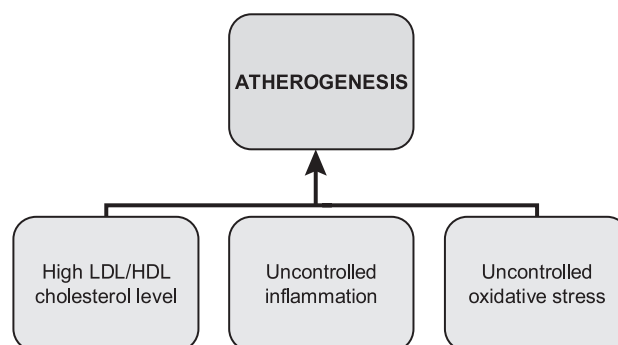


Fig. 2. Three decisive factors in atherogenesis: high LDL/HDL cholesterol concentration in blood plasma, uncontrolled inflammation of artery intima and uncontrolled activity of free radicals (oxidative stress).

All three atherogenic components synergistically contribute to CHD. Thus, in addition to LDL-C it is also the C-reactive protein (CRP) that is a strong predictor of CV events. CRP is one of the acute phase reactants. Its level rises dramatically during processes of inflammation.

Ridker (18) grouped patient populations according to total cholesterol/ HDL-C levels and CRP in blood into progressively rising quintiles. CV risk at the lowest CRP and highest total/ HDL-C was four times higher compared to individuals who have normal both values. Conversely, when the total/ HDL-C is at the lowest level and CRP is highly elevated, the CV risk increases two times. Remarkably, patients with the highest both total/ HDL-C and CRP have nine times higher CV risk compared to people with normal values.

In another impressive clinical study Ridker (19) documented the protective effect of statins in a selected group of 18,000 individuals who had normal LDL-C but elevated CRP. In this JUPITER trial of apparently healthy individuals without hyperlipidemia but with elevated CRP, rosuvastatin significantly reduced the incidence of future major CV events.

The production of endothelium-derived nitric oxide (NO) synthesized by nitric oxide synthase (NOS) plays a central role in the maintenance of endothelium homeostasis. NO is an important messenger molecule involved in many physiological and pathological processes. Reactive oxygen species directly inactivate NOS (20). Limitation of vascular reactive oxygen species can restore endothelial function in humans. After a series of animal studies it was demonstrated that after pravastatin treatment the NOS activity was significantly potentiated in humans also (21). Different statin preparation might differ in their antioxidant effects and effects on NO production.

It is interesting that the protective effect of statins appears to be independent of the level of HDL-C. Research in molecular biology of these processes (22–25) suggests that by inhibiting the HMG-CoA reductase statins also reduce the synthesis of isoprenoids. These are important lipid attachments for intracellular signaling molecules. Statins may exert cholesterol-indepen-

dent or pleiotropic effect by inhibiting these small guanosine triphosphate (GTP) binding proteins that are involved in cell proliferation.

Side effects of statins

In the United States the prevalence of obesity is continuously rising but CVD mortality is declining. This opposite trend suggests that medications like statins are having an important impact. Along with the positive reports and the tendency to prescribe statins to ever larger groups of population, it is essential to consider potential side effects of interference with cholesterol metabolism.

Using statins as potential first-line pharmacological agents to reduce cholesterol has been the subject of some controversy. Cholesterol is a lipid present in the cell membranes and subcellular organelles. It plays a key role in maintaining membrane fluidity, thereby influencing transmembrane signals. Cholesterol in the brain accounts for about 25 % of total body stores. It promotes myelin formation and synaptogenesis. Also, it serves as a building block for all steroid hormones. The primary site of action of statins is the liver but some statins inhibit cholesterol synthesis also in other tissues, including the brain.

Recently, statin uncontrolled use in childhood has been subject to an intensive discussion. Because of growing evidence that atherosclerosis begins at an early age and that obesity and hypercholesterolemia in children may increase the risk of life-time CVD, the American Academy of Pediatrics in July 2008 recommended statins among potential first line agents for childhood hypercholesterolemia. This induced a strong controversy (26). Concern was expressed that a child's brain at the age of eight years remains in development and that long-term pharmacotherapy in childhood may adversely affect immune functions, hormonal balance and the overall energy metabolism.

Regarding potential side effects of statins, in meta analyses the data of over 70,000 patients were analyzed (27). Serious events were infrequent. Statin therapy was associated with greater odds of adverse effects compared with placebo but with substantial clinical benefit. Treating one thousand patients with statins would prevent 37 clinical CV events but only five adverse effects would be observed.

Regarding cancerogenesis, authoritative trials documented at best only a neutral effect on cancer. In meta analyses including 6,662 cancers and 2,407 cancer deaths, statins did not increase or reduce the incidence of cancer (28). This has been confirmed in most recent meta analyses (29–31) that reported no effect of statins on cancer risk. It is of interest that adding ezetimibe to statin (combination therapy) for aortic stenosis resulted in excess of incidental cancers (32). This dictates a need for caution: Ezetimibe interferes with intestinal absorption not only of cholesterol but also of other molecules that could effect the growth of cancer cells.

Two of the most troubling statin side effects include muscle pain (myalgia), muscle disease (myopathy) and liver abnormalities, most prominently expressed in an elevation of the serum aminotransferase.

Statins block production of farnesyl pyrophosphate, an intermediate in the synthesis of coenzyme Q₁₀ (Fig. 1). This, along with the role of Co Q₁₀ in mitochondrial energy production has prompted the hypothesis that statin-induced Co Q₁₀ deficiency is instrumental in the pathogenesis of statin-induced myopathy (33–36).

Co Q₁₀ is an oil-soluble antioxidant. It forms a very effective redox system composed of ubiquinol (reduced form), semiquinone radical and ubiquinone (oxidized form).

Co Q₁₀ is a component of the electron transport chain in mitochondria and it participates in aerobic cellular respiration, generating energy in the form of ATP.

Its synthesis in the human body decreases with age. Meta-analysis of several clinical studies has shown that statin treatment reduces circulating levels of Co Q₁₀ (34). In some reports the decrease of plasma Co Q₁₀ level was very high, about 50 %. This could be related to statins lowering the plasma LDL. Co Q₁₀ is mainly transported by LDL but a decrease is also found in platelets and in lymphocytes of statin treated patients. This indicates a possible inhibition of Co Q₁₀ synthesis (37–40), in addition to its effect on transport functions.

In patients with chronic heart failure (not necessarily induced by CHD) a drop in Co Q₁₀, along with a decrease in total cholesterol was an independent predictor of mortality (41).

There are also some indications, considered contradictory that statin treatment affects muscle Co Q₁₀ levels. Statin-induced myopathy could then be attributed to a deficient supply of energy in the form of ATP to the muscle. Subsequently it is being postulated that Co Q₁₀ supplementation would reduce the degree of muscle pain associated with statin treatment. Initial attempts in administering Co Q₁₀ to statin-treated patients with myopathic symptoms had a positive outcome: pain severity significantly decreased after 30 days of statin therapy (42, 43). Co Q₁₀ is not only an essential co-factor in the mitochondrial electron transport pathway, but also a strong lipid-soluble antioxidant which has a well acknowledged antioxidant role by counteracting LDL and nitric oxide oxidation in the cardiovascular system (44, 45).

Recently there were three randomized trials with Co Q₁₀ supplementation in hypercholesterolemic patients treated with statins (46). The results of these trials have been contradictory: one seemed to support supplementation with Co Q₁₀ but the other two studies did not. Present evidence does not support Co Q₁₀ supplementation in statin-induced myopathy. Nevertheless, there are no known risks to Co Q₁₀ supplementation at pharmacological dosage.

Conclusion

Discovery of pharmacological value of statins was a complex trail that led from an agent produced by molds to protect themselves from other microorganisms, to a very effective medication. Statins reduce the LDL-C and they help to prevent CV disorders. Remarkably, statins while being of microbial origin, counter adverse effects of inflammation. There are internists and cardiologists who are convinced that many millions of apparently healthy people, even with normal cholesterol may benefit

from statins. This suggests a controversial dilemma: Is it time to place cholesterol-lowering statins in every medicine cabinet? Many other clinicians are more careful, pointing to the beneficial metabolic role cholesterol has in the animal organism. They warn of potential side effects of drastic universal cholesterol lowering in subjects with no evidence of heart disease. Sarcastically, they claim that “protective effect of statins does not warrant these should be used to fortify drinking water or to become another active ingredient added to commercially marketed cereals.”

References

- Mann D.** Trends in statin use and low-density lipoprotein cholesterol levels among US adults: Impact of the 2001 National Cholesterol Education Program Guidelines. *Ann Pharmacother* 2008; 42: 1208—1215.
- Efthimiades A.** Rosuvastatin and cardiovascular disease: did the strongest statin hold the initial promises? *Angiology* 2008; 59: 62S—64S.
- Rizzo M, Rini GB, Berneis R.** Effects of statins, fibrates, rosuvastatin and ezetimibe beyond cholesterol: the modulation of LDL size and subclasses in high-risk patients. *Adv Ther* 2007; 24: 575—582.
- Thavendiranathan P, Bagai A, Brookhart A et al.** Primary prevention of cardiovascular diseases with statin therapy. A meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; 166: 2307—2313.
- Afilalo J, Majdan AA, Eisenberg MJ.** Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart* 2007; 93: 914—921.
- Fauchier L, Pierre B, de Labriolle A et al.** Antiarrhythmic effect of statin therapy and atrial fibrillation. A Meta-Analysis of randomized controlled trials. *J Amer Coll Cardiol* 2008; 51: 828—835.
- O'Regan C, Wu P, Arora P et al.** Statin therapy in stroke prevention: A meta-analysis Involving 121,000 patients. *Amer J Med* 2008; 121: 24—33.
- Josan K, Majumdar SR, McAlister FA.** The efficacy and safety of intensive statin therapy: A meta-analysis of randomized trials *CMAJ* 2008; 178: 576—584.
- Sillberg VA, Wells GA, Perry JJ.** Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: A meta-analysis. *Stroke* 2008; 39: 2622—2626.
- Ebrahimi R, Saleh J, Toggart E et al.** Effect of preprocedural myocardial infarction and major cardiac adverse events in percutaneous coronary intervention: A meta-analysis. *J Invasive Cardiol* 2008; 20: 292—295.
- Liakopoulos OJ, Choi YH, Haldenwang PL et al.** Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: A meta-analysis of over 30,000 patients. *Eur Heart J* 2008; 29: 1548—1559.
- Aronow WS.** Treatment of high-risk older persons with lipid-lowering drug therapy. *Amer J Ther* 2008; 15: 102—107.
- Strippoli GF, Navaneethan SD, Johnson DW et al.** Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *Brit Med J* 2008; 336: 645—651.
- Messerli FH, Pinto L, Tang SS et al.** Impact of systemic hypertension on the cardiovascular benefits of statin therapy — a meta-analysis. *Amer J Cardiol* 2008; 101: 319—325.
- Kearney PM, Blackwell L, Collins R et al.** Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. *Lancet* 2008; 371: 117—125.
- Libby P.** Atherosclerosis: the new view. *Sci Amer* 2002; 286: 47—55.
- Libby P.** The molecular mechanisms of the thrombotic complications of atherosclerosis. *J Intern Med* 2008; 263: 517—527.
- Ridker PM, Rifai N, Rose L et al.** Comparison of C-Reactive Protein and Low-Density Lipoprotein cholesterol levels in the prediction of first cardiovascular events. *New Engl J Med* 2002; 347: 1557—1565.
- Ridker PM, Danielson E, Fonseca FA, JUPITER Study Group.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med* 2008; 359: 2195—2207.
- Thomas SR, Witting PK, Drummond GR.** Redox control of endothelial function and dysfunction: molecular mechanisms and therapeutic opportunities. *Antioxid Redox Signal* 2008; 10: 1713—1765.
- Yemisci M, Ay H, Kocafe C et al.** Statin potentiates human platelet eNOS activity without enhancing eNOS mRNA and protein levels. *Cerebrovasc Dis* 2008; 26: 190—198.
- Wang CY, Liu PY, Liao JK.** Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med* 2008; 14: 37—44.
- Liao JK, Laufs U.** Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005; 45: 89—118.
- Lahera V, Goicoechea M, Soledad G et al.** Endothelial dysfunction, oxidative stress and inflammation in atherosclerosis: beneficial effects of statins. *Curr Med Chem* 2007; 14: 243—248.
- Selwyn AP.** Antiatherosclerotic effects of statins: LDL versus non-LDL effects. *Curr Atheroscler Rep* 2007; 9: 281—285.
- de Ferranti S, Ludwig DS.** Storm over Statins — The controversy surrounding pharmacologic treatment of children. *New Engl J Med* 2008; 359: 1309—1312.
- Lahera V, Goicoechea M et al.** Statin-related adverse events: a meta-analysis. *Clin Ther* 2006; 28: 26—35.
- Dale KM, Coleman CI, Henyan NN et al.** Statins and cancer risk. A meta-analysis. *J Amer Med Ass* 2006; 295: 74—80.
- Kuoppala J, Lamminpää A, Pukkala E.** Statins and cancer: A systematic review and meta-analysis. *Eur J Cancer* 2008; 44: 2122—2132.
- Alsheikh-Ali AA, Trikalinos TA, Kent DM et al.** Statins, low-density lipoprotein cholesterol, and risk of cancer. *J Amer Coll Cardiol* 2008; 52: 1141—1147.
- Hamilton RJ, Goldberg KC, Platz EA et al.** The influence of statin medications on prostate-specific antigen levels. *J Natl Cancer Inst* 2008; 100: 1487—1488.
- Drazen JM, D'Agostino RB, Ware JH et al.** Ezetimibe and Cancer: An uncertain association. *New Engl J Med* 2008; 359: 1398—1399.
- Elsayed RK, Evans JD.** Emerging lipid-lowering drugs: squalene synthase inhibitors. *Expert Opin Emerg Drugs* 2008; 13: 309—322.
- Marcoff L, Thompson PD.** The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Amer Coll Cardiol* 2007; 49: 2231—2237.
- Littarru GP, Langsjoen P.** Coenzyme Q10 and statins: biochemical and clinical implications. *Mitochondrion* 2007; 7 (Suppl): S168—174.
- Mabuchi H, Higashikata T, Kawashiri M et al.** Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. *J Atheroscler Thromb* 2005; 12: 111—119.

- 37. Kawashiri MA, Nohara A, Tada H et al.** Comparison of effects of pitavastatin and atorvastatin on plasma coenzyme Q10 in heterozygous familial hypercholesterolemia: results from a crossover study. *Clin Pharmacol Ther* 2008; 83: 731–739.
- 38. Mabuchi H, Nohara A, Kobayashi J et al.** Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. *Atherosclerosis* 2007; 195: 182–189.
- 39. Chu CS, Kou HS, Lee CJ et al.** Effect of atorvastatin withdrawal on circulating coenzyme Q10 concentration in patients with hypercholesterolemia. *Biofactors* 2006; 28: 177–184.
- 40. Berthold HK, Naini A, Di Mauro S et al.** Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. *Drug Saf* 2006; 29: 703–712.
- 41. Molyneux SL, Florkowski SM, George PM et al.** Coenzyme Q 10: an independent predictor of mortality in chronic heart failure. *J Amer Coll Cardiol* 2008; 52: 1435–1441.
- 42. Chapidze G E, Kapanadze SD, Dolidze NK et al.** Combination treatment with coenzyme Q10 and simvastatin in patients with coronary atherosclerosis (Russian). *Kardiologiia* 2006; 46 (8): 11–13.
- 43. Caso G, Kelly P, McNurlan MA et al.** Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins. *Amer J Cardiol* 2007; 99: 1409–1412.
- 44. Molyneux SL, Young JM, Florkowski CM et al.** Coenzyme Q10: is there a clinical role and a case for measurement? *Clin Biochem Rev* 2008; 29: 71–82.
- 45. Senes M, Erbay AR, Yilmaz FM et al.** Coenzyme Q10 and high-sensitivity C-reactive protein in ischemic and idiopathic dilated cardiomyopathy. *Clin Chem Lab Med* 2008; 46: 382–386.
- 46. Schaars CF, Stalenkoef AF.** Effects of ubiquinone (coenzyme Q 10) on myopathy in statin users. *Curr Opin Lipidol* 2008; 19: 553–557.

Received January 4, 2009.

Accepted June 26, 2009.