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To cite this article: Andrea Rosanoff & Mildred S. Seelig (2004) Comparison of Mechanism and Functional Effects of Magnesium and Statin Pharmaceuticals, Journal of the American College of Nutrition, 23:5, 501S-505S, DOI: [10.1080/07315724.2004.10719389](https://doi.org/10.1080/07315724.2004.10719389)

To link to this article: <https://doi.org/10.1080/07315724.2004.10719389>



Published online: 18 Jun 2013.



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## Review

# Comparison of Mechanism and Functional Effects of Magnesium and Statin Pharmaceuticals

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**Key words: enzymes: HMG-CoA Reductase, LCAT, desaturase; statins, magnesium, dyslipidemia: LDL-C, HDL-C, TG; heart, arteries**

Since  $Mg^{2+}$ -ATP is the controlling factor for the rate-limiting enzyme in the cholesterol biosynthesis sequence that is targeted by the statin pharmaceutical drugs, comparison of the effects of  $Mg^{2+}$  on lipoproteins with those of the statin drugs is warranted. Formation of cholesterol in blood, as well as of cholesterol required in hormone synthesis, and membrane maintenance, is achieved in a series of enzymatic reactions that convert HMG-CoA to cholesterol. The rate-limiting reaction of this pathway is the enzymatic conversion of HMG CoA to mevalonate via HMG CoA. The statins and Mg inhibit that enzyme. Large trials have consistently shown that statins, taken by subjects with high LDL-cholesterol (LDL-C) values, lower its blood levels 35 to 65%. They also reduce the incidence of heart attacks, angina and other nonfatal cardiac events, as well as cardiac, stroke, and total mortality. These effects of statins derive less from their lowering of LDL-C than from their reduction of mevalonate formation which improves endothelial function, inhibits proliferation and migration of vascular smooth muscle cells and macrophages, promotes plaque stabilization and regression, and reduces inflammation. Mg has effects that parallel those of statins. For example, the enzyme that deactivates HMG-CoA Reductase requires Mg, making Mg a Reductase controller rather than inhibitor. Mg is also necessary for the activity of lecithin cholesterol acyl transferase (LCAT), which lowers LDL-C and triglyceride levels and raises HDL-C levels. Desaturase is another Mg-dependent enzyme involved in lipid metabolism which statins do not directly affect. Desaturase catalyzes the first step in conversion of essential fatty acids (omega-3 linoleic acid and omega-6 linolenic acid) into prostaglandins, important in cardiovascular and overall health. Mg at optimal cellular concentration is well accepted as a natural calcium channel blocker. More recent work shows that Mg also acts as a statin.

### Key teaching points:

- The beneficial effects of the statin drugs are paralleled and complemented by those of Mg.
- Each inactivates the enzyme, HMG-CoA Reductase, which converts HMG-CoA to mevalonate—the initial step in formation of cholesterol.
- Mg, additionally, activates LCAT (lecithin-cholesterol-acyl-transferase) the enzyme that lowers LDL-C and TG levels, and raises HDL-C levels.
- Mg also activates a desaturase, that converts 3- and 6-omega fatty acids to prostaglandins.
- Statins, like Mg, have activities important in cardiovascular and overall health.

## INTRODUCTION

High plasma cholesterol has been acknowledged, since the mid-20th century, as a major heart disease risk factor. In the

last few decades, further knowledge about cholesterol has shown that the cardiovascular risk factor is associated with a high level of low density lipoprotein cholesterol (LDL-C) as well as a low level of high density lipoprotein cholesterol

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Journal of the American College of Nutrition, Vol. 23, No. 5, 501S–505S (2004)  
Published by the American College of Nutrition

(HDL-C), among other aspects of dyslipidemia, such as high triglycerides.

The Framingham Study found that low HDL-C is most predictive of heart disease, at least in middle aged men [1]. However, in the 1990s, three groups of experts (American and International) developed guidelines to prevent cardiovascular disease that recommended target goals to lower LDL-C levels with diet and, if necessary, statin pharmaceuticals [2,3]. The statin drugs, developed from the late 70s throughout the 80s [4–8], have provided patented products that facilitate an effective response to the medical objective of lowering LDL-C levels.

### Mechanisms by which Statins and Magnesium Control Cholesterol Biosynthesis

The cholesterol biosynthesis pathway converts acetyl coenzyme A, first to mevalonate, and after a series of intermediate steps, to cholesterol (Fig. 1) [9].

The rate limiting step of this pathway is the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase to mevalonate by the enzyme, HMG-CoA Reductase, the enzyme inhibited by the statins. If this crucial step in the cholesterol biosynthesis pathway occurs, and mevalonate is produced, the rest of the pathway reactions proceed and cholesterol, as well as other important intermediary substances such as geranyl pyrophosphate and farnesyl pyrophosphate, are synthesized. Without mevalonate formation, neither cholesterol nor the intermediary compounds can be synthesized. Among these compounds are geranyl and farnesyl pyrophosphate, which are involved in prenylation of proteins. The prenylated proteins have several important functions which are involved in cell growth as well as intracellular signaling [10–13]. In addition, farnesyl pyrophosphate is converted to the ubiquinone, coenzyme Q10. And, cholesterol is the starting point for biosynthesis of the steroid hormones (including estrogen, testosterone and progesterone) as well as vitamin D and its hormonal derivatives, and the bile salts. Bile salts aid in the digestion of fats, including the fat soluble vitamins, and are the main excretion route for cholesterol from the body.

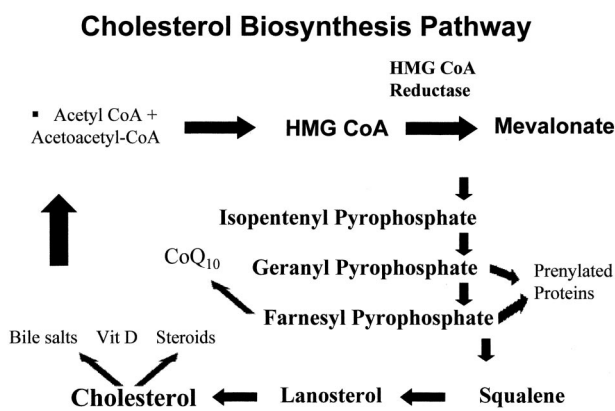


Fig. 1. Cholesterol biosynthesis.

Statins are mainly derivatives of mevalonolactones, called “inactive lactones,” which attach to the enzyme, HMG-CoA Reductase, and competitively inhibit it. In lowering the activity of this rate-limiting enzyme [14], statins inhibit the biosynthesis of mevalonate as well as cholesterol and the other intermediary substances in this pathway.

Natural control of HMG-CoA Reductase involves long and short term mechanisms [9]. Long term controls include feedback inhibition by both cholesterol and mevalonate as well as by repression of gene expression by these and other compounds. Short term control is by covalent modification and requires magnesium (Mg). This occurs by phosphorylation of HMG-CoA Reductase that requires the Mg-ATP complex. As long as both Mg and ATP are adequate, this phosphorylation can occur, and the enzyme can become inactive. In addition, the enzyme that activates the deactivation of HMG-CoA Reductase also requires Mg to be in the active form. Thus, at least two Mg-dependent reactions are required to deactivate HMG-CoA Reductase [9,15–17].

Inactive HMG-CoA Reductase can be reactivated by several enzymes, many of which can themselves be turned on or off by other enzymes and under a variety of conditions [9]. Some of these reactivating enzymes need Mg, others such as phosphatase, can use Mg or another divalent metal ions such as manganese (Mn) [18,19]. HMG-CoA Reductase control and, therefore, regulation of the cholesterol biosynthesis pathway is very complex, as well as sensitive to cellular conditions. But when there is a Mg deficiency, active HMG-CoA Reductase is less apt to be deactivated since the Mg-ATP complex is in short supply [20,21], while at the same time some reactivation enzymes, by using other ions such as Mn<sup>++</sup>, can continue the reactivating process, increasing the ratio of active to inactive HMG-CoA Reductase.

HMG-CoA Reductase exists in the cell in both its active and inactive forms. Usual ratios show relatively low active form (about 10% to 20%) with about 80% to 90% being inactive [22]. But this ratio can change with altered conditions. For example, both cholesterol [23] and farnesol (a pathway intermediate) [24], when relatively high, tend to deactivate more of the HMG-CoA Reductase enzyme’s active pool. When cellular Mg is low, this ratio tilts towards the active form, and when such a state occurs, more cholesterol, more mevalonate and more of the pathway’s other intermediates will be produced.

### Comparison of Statins and Magnesium in Control of Cholesterol

All of the statin drugs significantly lower mean LDL-C, some raise mean HDL-C and some lower mean triglycerides, especially in patient groups with high initial levels [25,26]. In addition to these effects, the statins have consistently been found to:

- Reduce total mortality
- Reduce cardiac mortality

- Reduce the incidence of heart attacks, angina and other non-fatal cardiac events
- Reduce stroke mortality

These unexpected effects have been termed “pleiotropic effects” [27], (from the Greek prefix: pleio, meaning multiple or excessive and the suffix, tropic meaning influencing) and intuitively suspected that they were NOT due solely to lowered low density lipoprotein-cholesterol (LDL-C) levels. In investigating these pleiotropic effects, it was found that statins slow the progression of plaques and stabilize them. There is some evidence that statins can even reverse the plaque formation process, long thought to be a one-way process that is an inescapable part of aging. This seems to be accomplished, at the cellular level, by inhibiting migration and proliferation of vascular smooth cells (VSMCs) and macrophages, and increasing their rate of apoptosis:

- reduce the clot-forming process so important in plaque formation
- increase VSMC nitric oxide production by an upregulation of NO synthase (iNOS)
- improve endothelial function
- reduce inflammation in blood vessel tissue by lowering interleukin-6 and C-Reactive Protein [32,33]
- have anti-oxidant potential.

The above effects of statins are independent of plasma cholesterol levels, and are completely blocked by exogenous mevalonate and some isoprenoids [28–31].

These beneficial effects of statin medications has made them among the fastest growing prescribed medicines in the world, and as more clinical trials come in, their use is being seriously considered for more and more people, even some with normal cholesterol values, most lately those with diabetes. They are currently being seen more and more as ‘the answer’ to the epidemic of heart disease. But there are some adverse side effects [34–42].

In a small percentage of patients taking statin medications, liver enzymes and creatine phosphokinase (CPK) levels have risen [38]. A few patients have developed myalgia, some a severe rhabdomyolysis and even death. Most of these uncommon reactions occur when statins are co-prescribed with other drugs that are detoxified by the same hepatic system: the cytochrome P450 system, 3A4, that is also used by calcium channel blockers, grapefruit juice and some antibiotics, among others. In addition, patients on statins have had gastrointestinal complaints, and not much publicized are some psychological changes [42]. Like the positive effects of statins, these adverse effects, in experimental animals, can be reversed with mevalonate. Thus, the toxic effects of statins seem not to come from the statin itself, but to its effect, i.e. lowering of mevalonic acid and perhaps other intermediaries in its pathway towards cholesterol [34–42].

In comparing the effects of statins with that achieved by

normal magnesium levels or by magnesium supplements, we find that [43]:

- magnesium, as well as the statins, targets the enzyme, HMG CoA Reductase.
- magnesium is also necessary for the activity of lecithin cholesterol acyl transferase (LCAT), which lowers LDL and triglyceride levels and raises HDL-cholesterol levels [44–46].
- magnesium also activates desaturase and other important enzymes involved in lipid metabolism, which statins do not directly affect. Desaturase catalyzes the first step in the conversion of essential fatty acids (omega-3 linoleic acid and omega-6 linolenic acid) into prostaglandins [47–49], which, like the prenylated proteins, have a cascade of stimulating and inhibiting cellular effects important in cardiovascular and overall health.

HMG CoA Reductase is an important enzyme in lipid and cholesterol metabolism, but it is not the only one. The statins act by inhibiting, temporarily, the enzyme, in a dose response relationship whereas the magnesium ion ( $Mg^{2+}$ ) is an important part of a complex control and regulation of this important pathway. Both lower LDL-C, some statins can raise HDL-C and lower triglycerides, but Mg supplements do both quite reliably.

Both statins and normal Mg levels prevent clotting, reduce inflammation and prevent atherosclerotic plaques, but statins raise liver enzymes, can cause myopathy and have many other side effects, whereas Mg supplements tend to protect against myopathy and have temporary diarrhea or mild GI distress as the only side effect. An important comparison is also cost. Presumably, one should take statins life-long to maintain their pleiotropic benefits. Monthly cost of statin pharmaceuticals is at least \$100 US while magnesium supplements cost less than \$20 US per month.

## Conclusion

- Statin medications inhibit the same rate-controlling enzyme of the cholesterol biosynthesis pathway that requires adequate Mg for normal deactivation, regulation and control.
- Both the highly beneficial pleiotropic and adverse effects of statins appear to be caused by the decrease in mevalonate (and perhaps other intermediaries in the cholesterol biosynthesis pathway) rather than a lower LDL-C.
- Statin drugs lower LDL-C levels more sharply than do Mg supplements, but Mg more reliably acts to improve all aspects of dyslipidemia including raising HDL-C and lowering triglycerides, and has the same pleiotropic effects as statins without their adverse effects.

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*Received August 5, 2004.*