New Insights into the Statin-Cholesterol Controversy

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Introduction

Known biochemically as HMG-CoA reductase inhibitors, "statins" are the most prescribed pharmaceuticals in history and have become one of the most controversial classes of drugs in use today.

Beginning in the 1980s with lovastatin, they have been touted as the modern-day cure for the prevention and treatment of cardiovascular disease (CVD). From decreasing LDL-cholesterol to their supposed anti-inflammatory effects, it seemed there was much to applaud.

Powerful drugs often have unwanted and sometimes dangerous side-effects. This is an inescapable feature of isolated, purified, and concentrated chemicals and has become the defining aspect of pharmaceutical medicine. Statins are no exception.

Although denied for years, a number of health-compromising side-effects accompany the apparent benefits of statins. Adverse events include hepatotoxicity, diabetes, myopathies, insomnia, memory loss, confusion, peripheral neuropathy, impaired myocardial contractility, autoimmune diseases, rhabdomyolysis, erectile dysfunction, and mitochondrial dysfunction.[1-6] Nearly 900 studies have been published on the adverse effects of these medications.[7]

In a 2013 review in the *Journal of Endocrine and Metabolic Disease*, the authors found that for every 10,000 people taking a statin, there were 307 extra patients with cataracts, 23 additional patients with acute kidney failure, and 74 extra patients with liver dysfunction.[8-10] The review also revealed that statin therapy increased coronary artery and aortic calcification, muscle fatigability,[11,12] diabetes, and cancer. Additionally, erectile dysfunction was 10 times more common in young men taking the lowest dose of statin. This recent pivotal review revealed "a categorical lack of clinical evidence to support the use of statin therapy in primary prevention." Authors also found that statins actually increase rather than decrease CVD risk in women, the young, and people with diabetes.[13]

The Truth about Cholesterol

Most of the attention in CVD in the past 60 years has focused on cholesterol and saturated fats and their seemingly positive relationship to disease and prevention. Massive corporate-funded campaigns have further promoted the idea that cholesterol—a vital and essential nutrient required for neurological integrity and a multiplicity of biological functions—is an enemy to be avoided, or at the very least, minimized at all costs. Although medical textbooks made it clear years ago, it's now apparent from a growing body of evidence that cholesterol and saturated fats possess fundamental roles in disease prevention, and promote a myriad of beneficial effects from reducing inflammation to promoting healing processes in the body and nervous system.

Several recent studies have shown that lower serum cholesterol levels are associated with a lower survival rate (increased mortality) irrespective of concomitant diseases or health status.[14-16] With respect to cholesterol's protective effects on the body's genetic machinery and potential role in cancer prevention, a 2013 study by Kikuchi et al. found that low cholesterol levels were associated with higher oxidative DNA damage.[17] Once this relationship becomes better established, this could have significant implications for cancer prevention and treatment. It's reported that vitamin D, a steroid derived from cholesterol, has anti-cancer, immune modulatory activity—with higher serum levels of 1,25-(OH)2-D3 recommended for those with genetic susceptibility to cancer or undergoing cancer treatment.[18-21] In vitro and in vivo animal model studies have demonstrated the anti-tumor effects of vitamin D. And since the body needs adequate cholesterol levels to synthesize vitamin D, higher cholesterol levels may assist vitamin D in its full therapeutic potential. Furthermore, cholesterol has positive therapeutic and protective effects of its own.[22-25]

Statins and Increased Cancer Risk

The statin-cancer connection has been a topic of interest since the first studies in the 1980s, in which researchers found that statins such as compactin and lovastatin suppress human lymphocyte functions in vitro. Shockingly, in a 1996 study published in the journal *Immunopharmacology*, the authors found that the inhibitory activity of simvastatin, a lipophilic inhibitor, on sterol synthesis (HMG-CoA reductase activity) in lymphocytes was as much as 430 times more potent than that of pravastatin, and at low clinical doses, simvastatin was able to significantly increase cyclosporin-A induced lymphocyte suppression of T-cell response.[26,27]

That same year, a review published in the prestigious *Journal of the American Medical Association* stated:

> All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal

exposure close to those prescribed to humans. In the meantime, the results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease.[28]

Angiogenesis is a necessary feature in healing and repair processes in the body, but like most processes, is under tight control. If overactivated, angiogenesis is a primary driver in cancer propagation. In addition to its immune-suppressing properties, simvastatin's ability to promote angiogenesis in vitro is well-documented. In a 2011 study published in *Neurosurgery*, researchers found that the drug also promotes angiogenesis following traumatic brain injury.[29] Like vascular endothelial growth factor (VEGFR, a primary anti-cancer target) and its associated receptors, simvastatin is of definite concern with respect to increased cancer risk through its angiogenesis-promoting activity, which is independent of the drug's cholesterol-lowering activity.

As previously mentioned, the cholesterol-derived hormone 1,25-(OH)2-D3 (calcitriol) has been shown to possess anti-cancer effects, but we also know that cholesterol too promotes a more robust immune system when serum levels are higher.[30,31] Mice with hypercholesterolemia due to LDL-receptor deficiency, challenged with bacterial endotoxin, had an eight-fold increased LD50, and a significantly lower and delayed mortality after injection with Gram-negative bacteria, compared with control mice.[32] Also, in rats, hypocholesterolemia induced with 4-aminopyrolo-(3,4-D) pyrimide or estradiol had markedly increased endotoxin-induced mortality compared to normal rats.[33] In a 1997 study by Muldoon and colleagues, 19 healthy adult men with a mean total cholesterol concentration of 151 mg/dl (low cholesterol group) were compared with 39 men of a similar age whose total cholesterol averaged 261 mg/dl. Relative to the high cholesterol group, men with lower serum cholesterol had significantly fewer circulating lymphocytes, fewer total T cells, and fewer CD8+ cells.[31]

These data make clear that higher levels of cholesterol may be needed for optimal immune function, and suggest a role for optimized cholesterol levels, as currently applied to vitamin D3, in cancer prevention. Based on these data, statin medications—with their cholesterol and coenzyme-Q10 (CoQ10) lowering effects, both key nutrients for the immune system, could increase cancer susceptibility, especially at higher doses.

Statins, Cholesterol, and Therapeutic Efficacy

The clinical observation that statins marginally lower both total and CVD mortality in high-risk individuals, as evidenced by their high number needed to treat (NNT), has been interpreted to show that cholesterol lowering is their primary effect in CVD prevention. The fact is, statins are just as effective whether cholesterol is lowered by a small amount or by more than 40 percent. Statin treatment has essentially the same effectiveness whether the initial LDL-cholesterol is high or low.[34,35] If high LDL-cholesterol were the driving force in CVD, one would expect the greatest effect in patients with the highest LDL-cholesterol, and in patients who experienced the greatest decrease in LDL-cholesterol, but this is not the case.

Peskin et al., in their excellent review of the statins-cholesterol controversy, found that, except for a very small and insignificant minority of patients, concurrently lowering LDL-C and raising HDL-C does not result in any benefit to the patient. The authors make reference to the anti-inflammatory activity of statins, which they attribute to probable cyclooxygenase (COX) suppression, but they conclude that this activity is marginal and far outweighed by the detrimental effects of statin therapy.[36]

Presuming that high cholesterol has a protective function, as previously suggested and observed, its lowering would oppose the "beneficial" effects of the statins and thus work against a dose-response relationship. The clinical data clearly support that this happens. For example, coronary mortality was reduced almost three times more (with simvastatin) in the 4S trial than in the HPS trial, despite the fact that LDL-cholesterol and total cholesterol decreased to a much lower level in the latter.[37,38] Thus, the primary mechanism for the observed beneficial effects of statin therapy appears to lie outside its cholesterol-lowering activity, and has been suggested to reside in its anti-inflammatory effects.

Mitochondrial and Neurotoxicity

With the understanding that both cholesterol and CoQ10 are neuroprotective[39-42] and essential for healthy neuronal function and repair processes, the natural question arises: Are statins neurotoxic?

The short answer is, yes.

At all doses studied, the ratio of cost in biological dysfunction to benefit for these drugs is a very poor one (i.e. high cost, little to no benefit), as revealed by the hundreds of studies documenting their negative effects. At moderate to high doses, they're undoubtedly problematic and associated with numerous side-effects, such as muscle pain, fatigue, increased risk for new-onset diabetes, insomnia, increased cancer risk, memory problems, and cognitive deficits. These are most likely a function of CoQ10 depletion coupled with dose-dependent lowering of the essential nutrient in both the body and the brain—cholesterol. Furthermore, cholesterol's critical esterified essential fatty acids (e.g. linoleic acid) are also lowered, leading to additional potential patient risk.[36] With more than 40 years of research documenting the adverse effects of statins on the immune system and mitochondrial energy system, which affects all body systems, especially those with the highest energy requirements (e.g. brain, heart, liver, kidneys, muscles)—if there was one drug to avoid, in the interest of greater energy

and total health, it would be the statins.

Functional medicine physician Mark Hyman, who has written extensively on statins, made the following statement on his popular blog (dr.hyman.com) regarding statins' effect on exercise capacity and mitochondrial function:

> We used to think that there were very few side effects associated with this drug, but the truth is, up to 20 percent of statin users have experienced serious side effects like muscle pain, damage, and aching or high muscle enzymes. Statins can also poison your mitochondria, which are your cells' energy-production factories and the single most important factor in healthy aging and wellness. Statins can hinder the mitochondria's ability to produce energy effectively and can even kill cells off completely…..
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> In one study, two groups of overweight, sedentary people were put on an exercise program for 12 weeks. One group was given a statin and the other group wasn't. After 12 weeks, the group that had been taking the statin saw no improvement in their fitness level. It was as if they hadn't exercised at all! In fact, when muscle biopsies were performed, doctors found the members of this group had four and a half percent less energy-production capacity in their cells. They were actually in worse condition than before they started the exercise program![43]

Other drugs also possess side-effects—e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and angiotensin-converting-enzyme (ACE) inhibitors, but what makes statins notably problematic is that they deplete two key nutrients required for the health and vitality of every cell in the body. From a purely "functional" standpoint, creating deficiencies in two primary brain nutrients simply does not make sense, from any perspective.

It is well known that the brain has a high, immutable requirement for cholesterol. With its high fat (membrane) density, it contains the highest cholesterol concentration (approximately 23 percent to 25 percent) of any tissue in the human body, which is a substantive clue to the functional importance of cholesterol and fat in brain function.[44] If the brain receives less than the needed amount of these nutrients, function suffers. This was clearly revealed in one of the largest cohorts ever studied. Participants from the original 1948 cohort of the Framingham Heart Study with lower, "desirable" cholesterol levels (<200 mg/dL) displayed poorer performance on cognitive measures, which place high demands on abstract reasoning, attention, concentration, word fluency, and executive functioning.[45] Furthermore, the body lacks a cholesterol sensor, meaning there is no required LDL-C regulation.

While not antioxidants in the true, chemical sense of the word, saturated fats and cholesterol, as structural components of the body's cells and organelles, function in this capacity as "structural antioxidants." They provide increased stability and resistance to oxidation, and thereby promote enhanced metabolic/system stability and integrity. They are the most stable of the spectrum of structural fats. Saturated fats such as those found in coconut oil and animal fats (e.g. grass-fed butter, eggs, cheese, meat) are incorporated into cell membranes, where they impart oxidation-resistant, anti-aging properties we are just beginning to recognize and appreciate.

Research over the last decade has shown that high blood levels of cholesterol correlate with a lower mortality index and a better outcome following a first stroke.[46] A high-cholesterol diet was found to be protective of cognitive functions in rats subjected to anoxia,[47] and patients suffering from Alzheimer disease (AD) have been found to possess lower levels of cholesterol in cerebrospinal fluid in the lipid fraction of brain membranes, resulting in altered membrane function.[48,49] Higher neuronal cholesterol has not been shown to correlate with greater Aβ production, nor has it been shown that neurons in AD patients have more cholesterol than control neurons. Rather what has been revealed is that patients with AD show a specific down-regulation of seladin-1, a protein involved in cholesterol synthesis suggestive of a possible protective role of cholesterol in this neurodegenerative disorder.[50]

In the toxicological/chemical realm, applying the principle of "like dissolves like," we know that lipids such as cholesterol function as "organic buffers" in biological systems with their ability to sequester and thus neutralize organic toxins—e.g. polychlorinated biphenyls (PCBs) and methyl-mercury compounds, while also participating in a plethora of biological functions. As biological buffers, cholesterol and fats protect the body and brain from harmful toxins. Along with this toxin-buffering activity, these multi-purpose lipids function as building blocks in essential cellular structures (e.g. lipid bilayers, lipid rafts) and life-giving hormones. Thus, in this capacity cholesterol and the highly stable, anti-inflammatory, saturated fats confer powerful neuroprotective effects in the body.

As with all drugs, chemicals, and nutrients, statins' relative neurotoxicity depends on dose. We know that statins' effect on decreasing serum cholesterol level, along with the level of the cellular antioxidant, energy-producing molecule CoQ10, is dose-dependent. This is without question a major problem, and is responsible for many, if not all, of the side-effects associated with statins. At the same time, the minimal therapeutic effect of statins on CVD appears to reside primarily in their cholesterol-independent, anti-inflammatory effects.[51,52]

Knowing this information is the first step in making better-informed decisions about the use of this class of drugs, or any drugs, especially over the long term. If indeed this analysis is correct, then there are more effective and safer anti-inflammatory agents (e.g. curcuminoids,[53,54] astaxanthin,[55-57] tocotrienols,[58,59] and magnesium[60,61]), which do not deplete essential nutrients and have fewer-

to-no unwanted side-effects. These should be considered as beneficial, highly viable alternatives to statin medications.

Natural Alternatives

Of note in the deluge of statin and cholesterol research is a groundbreaking 2004 study by Rosanoff and Seelig in the Department of Physiology and Pharmacology at the State University of New York, comparing the mechanism and functional effects of magnesium with statin pharmaceuticals. The authors state that magnesium acts as a natural statin and modulator of HMG-CoA-reductase activity.[62]

The key point here is that unlike statins, which are potent inhibitors of HMG-CoA-reductase, causing numerous adverse effects, magnesium acts as a "modulator" or controller of this enzyme, allowing the enzyme to function as it was designed to, with wide-spectrum activity and the ability to adapt to changing physiological demands. Magnesium is also essential for the activity of lecithin cholesterol acyl transferase (LCAT), which regulates LDL-cholesterol, HDL-cholesterol, and triglyceride levels, as well as the enzyme desaturase, which statins do not directly affect. Desaturase catalyzes the first step in the conversion of essential fatty acids into prostaglandins—important in cardiovascular and total health. Magnesium has also been shown to have antioxidant activity, lowering markers of inflammation (e.g. C-reactive protein), and at optimal cellular concentrations is a well-accepted, natural calcium channel blocker, and through its varied biological activities modulates vascular tone and blood pressure.[61-65]

Unlike magnesium, which promotes normal, balanced physiological processes and serves as an absolute requirement in a multiplicity of metabolic functions in the body, statins disrupt normal cellular functions. They are undesirable at best, and have numerous, well-documented, health-compromising effects at their worst, through their normal mode of action.

Research by Rosanoff and Seelig, as well as others, has been applied successfully in naturopathic or functional medicine for many years. Magnesium and other "functional nutrients" offer a multitude of metabolic, neurologic, cardiovascular, and whole-body benefits, free of adverse effects, when taken in the form of bio-compatible, well-absorbed forms (e.g. glycinate, orotate, threonate) of the nutrient.[65-71]

Conclusion

As the statin-cholesterol controversy shows, it is time to recognize the benefits of natural medicine (i.e. functional medicine) for disease prevention and the maintenance of optimal health and wellness, instead of relying on pharmaceuticals that treat and suppress one problem, while often creating a dozen others, without ever fully addressing and resolving the original complaint.

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