

Reviewing the outlook on Cholesterol and Statins

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ABSTRACT:

The notion that cholesterol is bad for health and it causes cardiovascular/cerebrovascular disease is something we have harboured in our minds for decades. And statins have been rampantly prescribed and used to prevent hypercholesterolemia. A debate regarding how ethical this is has gone on for years. In this review article, an effort has been made to throw some light on this matter and to review its current status.

1. INTRODUCTION:

All of us have heard this saying, time and time again, that Cholesterol is very bad for health and consumption of cholesterol-containing fatty food increases chances of blockage of arteries leading to dire consequences like heart attack and cerebral stroke many fold. Nowadays, it is a trend among health-conscious individuals to opt for food devoid of saturated/trans fat because it apparently contains 'bad' cholesterol (LDL). Olive oil has replaced the ghee, butter and mustard oil of Indian households in last few decades because it is said to contain 'good' cholesterol (HDL). Lipid-lowering drugs called Statins are being rampantly prescribed by physicians since as early as 1980's to patients with high triglyceride/LDL levels with the belief that reducing blood cholesterol levels will lower chances of cardiovascular disease and death, ignoring the fact that overuse of statins can cause increased risk of Diabetes, cognitive impairment and memory loss and high risk of depression related suicide among other adverse effects. Before 2015 Dietary Guidelines Advisory Committee (DGAC) had limited cholesterol consumption to 300mg/day to prevent risks of heart disease. So, are we doing the right thing for our body since the last decade? What do the 2015 Dietary Guidelines given by DGAC say about cholesterol consumption? Are statins all that safe after all? What does the Food and Drug Administration (FDA) say about statins? Let's have a look.

2. SOME FACTS ABOUT CHOLESTEROL:

Before getting into the complexity of the whole situation let's have a brief idea about what Cholesterol is. In simple terms, Cholesterol is a lipid molecule which is synthesized by the Liver, Intestines, Adrenal glands, Reproductive organs, etc.

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It performs several important functions in the body like formation and maintenance of cell membranes, production of all steroid hormones, etc. Some researches (as have been mentioned below in the article) even show that it has antioxidant properties. The dietary Cholesterol that comes into the body is always in 'esterified' form which is poorly absorbed from the GI tract. A very important fact about Cholesterol is that any changes in intake are compensated by alternations in bodily production of cholesterol [i.e. if dietary intake is more, body production will be less and viceversa]. This is the reason why high animal food intake does not result in high cholesterol values. Cholesterol is a hydrophobic compound and cannot be transported in the body on its own. It is transported in the body with the help of lipoproteins that make it hydrophilic. These lipoproteins are divided into five classes on the basis of their particle size and density. They are as follows:-

- VLDL:** Very Low Density Lipoprotein
- LDL:** Low Density Lipoprotein
- HDL:** High Density Lipoprotein
- IDL:** Intermediate Density Lipoprotein
- U LDL:** Ultra Low Density Lipoprotein

When the lipid concentrations in blood increase, it is termed as hyperlipidemia. This condition can be diagnosed by screening a patient's lipid profile. Among the lipoproteins, the LDL, commonly referred to as "bad cholesterol", is held responsible for causing Cardio Vascular disease. Due to its low density, it gets deposited in arterial walls forming 'plaque', thereby robbing the arteries of their elasticity. With increasing age, this deposition causes narrowing of the lumen of arteries and finally blockage. When complete blockage takes place in the arteries supplying the heart, a person's heart muscle undergoes anoxia leading to ischemia and cell death. This damaged muscle is then inefficient to pump the blood inside the heart which leads to what we call a 'heart attack'. Similarly, when the arteries supplying the brain are completely clogged, there is loss of blood supply to the brain tissue and anoxia as a result of that. Hence a person has a stroke. Smoking, Obesity and Sedentary lifestyle are some of the major risk factors for this phenomenon. The lipid hypothesis is a medical idea regarding a link between blood cholesterol levels and occurrence of heart disease. An accumulation of evidence has led to the acceptance of the lipid hypothesis by most of the medical community; however, a minority contends that the evidence does not support it, and that mechanisms independent of blood cholesterol levels are responsible. This dispute is referred to as the "cholesterol controversy". [*Harrison's Principle Of Internal Medicine 18th edition (2012)*, *Davidson's Principle and Practice of Medicine 21st Edition (2010)*]

3. UPDATES ABOUT THE RECENT CHOLESTEROL STATUS :

Every five years, the US Department of Agriculture and Department of Health and Human Services release an update of the Dietary Guidelines for Americans (DGA). These recommendations are based on a review of the latest research compiled by the Dietary

Guidelines Advisory Committee (DGAC). In a recently released report offering recommendations for the 2015 DGA, the DGAC concluded, "Cholesterol is not a nutrient of concern for overconsumption." If the 2015 DGA, due out this fall, includes this advice, no longer will there be a recommended upper limit for dietary cholesterol intake. [<http://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf>]

Chris Kresser, a holistic medical practitioner based in the United States and rated one of the 100 most influential people in health and fitness worldwide, has written in his article **"The Diet-Heart Myth: Cholesterol and Saturated Fat Are Not the Enemy"** how little dietary cholesterol has to do with increased risk of cardiovascular diseases. Here is an excerpt from the aforementioned article: *"Most of us grew up being told that foods like red meat, eggs and bacon raise our cholesterol levels. This idea is so deeply ingrained in our cultural psyche that few people even question it. But is it really true? The diet-heart hypothesis-which holds that eating cholesterol and saturated fats raises cholesterol in our blood-originated with studies in both animals and humans more than half a century ago. However, more recent (and higher quality) evidence doesn't support it. On any given day, we have between 1,100 and 1,700 milligrams of cholesterol in our body. 25% of that comes from our diet, and 75% is produced inside of our bodies by the liver. Much of the cholesterol that's found in food can't be absorbed by our bodies, and most of the cholesterol in our gut was first synthesized in body cells and ended up in the gut via the liver and gall bladder. The body tightly regulates the amount of cholesterol in the blood by controlling internal production; when cholesterol intake in the diet goes down, the body makes more. When cholesterol intake in the diet goes up, the body makes less."* [<http://chriskresser.com/the-diet-heart-myth-cholesterol-and-saturated-fat-are-not-the-enemy/>]

Lots of fat lowering drugs are available in the market these days, namely Statins, Fibric acid derivatives, Bile acid sequestrants, Nicotinic acid, Ezetimibe, etc. Among these, the most widely used group is the Statins. Introduced in 1980s, this class of drugs act by inhibiting a rate limiting enzyme in cholesterol synthesis called *HMG-CoA REDUCTASE*. As a result of this, cholesterol synthesis reduces in the body. Alongside, they also cause catabolism of LDL by a mechanism called "receptor upregulation". Therapeutic doses of statins have the ability to reduce cholesterol by 20-50%. The other drugs lower body lipids by different mechanisms. Statins are the first line drugs used to treat hyperlipidemia since 1980s. [*Harrison's Principle Of Internal Medicine 18th edition (2012), Davidson's Principle and Practice of Medicine 21st Edition (2010)*]

4. SOME INFORMATION ABOUT STATINS :

Before proceeding any further, let's have a look at the history of statins.

[https://en.wikipedia.org/wiki/Discovery_and_development_of_statins]

More than a century ago, Rudolf Ludwig Carl Virchow, a German pathologist, discovered that cholesterol was to be found in the arterial walls of people who died from occlusive vascular diseases, like myocardial infarction. The cholesterol was found to be responsible for

the thickening of the arterial walls and thus decreasing the radius of the arteries which leads in most cases to hypertension and increased risk of occlusive vascular diseases. *Thrombose und Embolie (1846-1856)* is a book written by him which has his work and study regarding this. In 1913, a study by Nikolai Anitschkow showed that rabbits fed on cholesterol, developed lesions in their arteries similar to atherosclerosis, suggesting a role for cholesterol in atherogenesis. [https://en.wikipedia.org/wiki/Rudolf_Virchow]

In the 1948 the Framingham heart study, under the direction of the National Heart Institute (now known as the National Heart, Lung, and Blood Institute or NHLBI), led by Dr. Thomas Royle Dawber, revealed the correlation between high blood cholesterol levels and coronary heart diseases. Following up from that study, the researchers explored a novel way to lower blood cholesterol levels without modifying the diet and lifestyle of subjects suffering with elevated blood cholesterol levels. The primary goal of the technique was to inhibit the cholesterol biosynthesis in the body. Hence HMG-CoA reductase (HMGR) became a natural target. HMGR was found to be the rate-limiting enzyme in the cholesterol biosynthetic pathway. There is no build-up of potentially toxic precursors when HMGR is inhibited, because hydroxymethylglutarate is water-soluble and there are alternative metabolic pathways for its breakdown. [<https://www.framinghamheartstudy.org/>]

In the 1970s the Japanese microbiologist, Akira Endo, who was studying the relationship between fungi and cholesterol synthesis, first discovered natural products with a powerful inhibitory effect on HMGR in a fermentation broth of *Penicillium citrinum*, during his search for antimicrobial agents. The first product was named compactin (ML236B or mevastatin). Animal trials showed very good inhibitory effect as in clinical trials, however in a long term toxicity study in dogs it resulted in toxic effects at higher doses and as a result was believed to be too toxic to be given to humans. In 1978, Alfred Alberts and colleagues at Merck Research Laboratories discovered a new natural product in a fermentation broth of *Aspergillus terreus*, their product showed good HMGR inhibition and they named the product mevinolin, which later became known as lovastatin.

[http://www.scienceheroes.com/index.php?option=com_content&view=article&id=126&Itemid=13]

The common names belonging to the Statin class of drugs are lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin etc. They were said to be remarkably well tolerated and safe. Notable side effects were: headache, nausea, bowel upset, rashes, sleep disturbances, Myopathy, etc. Other than this cognitive impairment was also seen, which maybe attributable to depression, a known complication of statins. [(K.D. Tripathi's book of *Pharmacology (2010)*, *Basic and clinical Pharmacology*, LANGE 11th Edition (2010), [http://www.amjmed.com/article/S0002-9343\(04\)00546-7/abstract](http://www.amjmed.com/article/S0002-9343(04)00546-7/abstract)]

5. RECENT ADVANCES ON STATIN INTAKE:

However, recent studies have shown a different story.

FDA (FOOD AND DRUG ADMINISTRATION, U.S.) has expanded its advice on Statin risks recently. The following has been taken from www.fda.gov, the official website of FDA - "If you're one of the millions of Americans who take statins to prevent heart disease, the Food and Drug Administration (FDA) has important new safety information on these cholesterol-lowering medications."

FDA is advising consumers and health care professionals that:

- Routine monitoring of liver enzymes in the blood, once considered standard procedure for statin users, is no longer needed. Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.
- Cognitive (brain-related) impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users.
- People being treated with statins may have an increased risk of raised blood sugar levels and the development of Type 2 diabetes.
- Some medications interact with lovastatin (brand names include Mevacor) and can increase the risk of muscle damage.

This new information should not scare people off statins, says Amy G. Egan, M.D., M.P.H., deputy director for safety in FDA's Division of Metabolism and Endocrinology Products (DMEP). "The value of statins in preventing heart disease has been clearly established," she says. "Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects." FDA will be changing the drug labels of popular statin products to reflect these new concerns. The statins affected include-

- Altoprev (lovastatin extended-release),
- Crestor (rosuvastatin),
- Lescol (fluvastatin),
- Lipitor (atorvastatin),
- Livalo (pitavastatin),
- Mevacor (lovastatin),
- Pravachol (pravastatin),
- Zocor (simvastatin).

Products containing statins in combination with other drugs include-

- Advicor (lovastatin/niacin extended-release),
- Simcor (simvastatin/niacin extended-release),
- Vytorin (simvastatin/ezetimibe)."

(<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm>)

Many online studies and articles have reported various undocumented side effects of statins. The following excerpt is taken from an online article written by Dr. Joseph Mercola, a US based physician- "A paper published in the American Journal of Cardiovascular Drugs

cites nearly 900 studies on the adverse effects of HMG-CoA reductase inhibitors, also called statins.

Muscle problems are the best known of statin drugs' adverse side effects, but cognitive problems and pain or numbness in the extremities are also widely reported. A spectrum of other problems, ranging from blood glucose elevations to tendon problems, can also occur as side effects.

The problem, however, is the fact that statin drugs oftentimes do not have any immediate side effects, and they are quite effective, capable of lowering cholesterol levels by 50 points or more. This makes it appear as though they're benefiting your health, and health problems that appear down the line are frequently not interpreted as a side effect of the drug, but rather as brand new, separate health problems.

For starters, some of the possible consequences of taking statins in strong doses, or for a lengthy period of time, include-

- Cognitive loss
- Neuropathy
- Anaemia
- Acidosis
- Frequent fevers
- Cataracts
- Sexual dysfunction

Other serious and potentially life threatening side effects include, but are not limited to:

- An increase in cancer risk
- Immune system suppression
- Serious degenerative muscle tissue condition (rhabdomyolysis)
- Pancreatic dysfunction
- Hepatic dysfunction. (Due to the potential increase in liver enzymes, patients must be monitored for normal liver function)

Further, adverse effects are dose dependent, and your health risks can be amplified by a number of factors, such as taking other drugs (which may increase statin potency), metabolic syndrome or thyroid disease."

<http://articles.mercola.com/sites/articles/archive/2010/06/12/unintended-statin-sideeffect-risks-uncovered.aspx>; https://www.statineffects.com/info/about_us.htm .

Dr. Beatrice Alexandra Golomb, a professor of medicine at the University of California, San Diego, School of Medicine, has made a study in the University of California regarding Statins and other lipid lowering drugs. In her article called "Do Statins Produce Neurological

Effects?” She has mentioned the following side effects of statins- “The most common adverse effects include muscle symptoms, fatigue and cognitive problems. A smaller proportion of patients report peripheral neuropathy—burning, numbness or tingling in their extremities—poor sleep, and greater irritability and aggression.

Interestingly, statins can produce very different outcomes in different patients, depending on an individual's medical history, the statin and the dose. Studies show, for instance, that statins generally reduce the risk of ischemic strokes—which arise when a blocked artery or blood clot cuts off oxygen to a brain region—but can also increase the risk of hemorrhagic strokes, or bleeding into the brain. Statins also appear to increase or decrease aggression. In 2015 my colleagues and I observed that women taking statins, on average, showed increased aggression; men typically showed less, possibly because of reduced testosterone levels. Some men in our study did experience a marked increase in aggression, which was correlated with worsening sleep.

Statins may also affect neurodegenerative disorders, such as dementia, Parkinson's disease or amyotrophic lateral sclerosis (ALS). For instance, some patients taking statins develop ALS or ALS-like conditions with progressive muscle wasting, which sometimes resolve when the patients stop taking the medication. The drugs may play a role in triggering symptoms, at least in those cases, but may also prevent the progression of such conditions in some settings. One possible explanation is that statins cause increases or decreases in tissue damage known as oxidative stress, involved in neurodegenerative diseases. The effects of statins are complex. We hope that further study will shed light on the neurological problems statins can cause and explain how to better protect those who experience these troubling complications.” In the study they conducted in the University of California, some light was shed on the newly talked-about side effects of statins that have become the topic of discussion nowadays.

6. LESSER-KNOWN SIDE EFFECTS :

6.1. Memory, Thinking and Concentration:

Some people report changes in memory, attention, or concentration on statins. They may have trouble finding the right word; may forget tasks they started to do; and may have trouble following conversations. Some people describe "holes in their memory." Some people worry that they are developing Alzheimer's. Of course, since people on statin drugs are often older, and may be experiencing age-related loss of memory, it makes it difficult to know whether the drugs are responsible. Many people report improvement in memory and thinking when they stop the drug; or improvement if they go on a lower dose. These findings suggest that the drug is responsible.

As of now there are two randomized controlled trials that have looked at thinking on these drugs. One was published in May 2000 in the journal called *American Journal of Medicine*. Dr. Matthew Muldoon, at the University of Pittsburgh, showed that statin drugs on average reduces “cognition,” that is to say, people who were on a statin drug did worse on tests of thinking and memory ability, even though they started out the same as those who were put on a placebo pill. These effects were “significant” statistically. On average the effects were considered to be small, but of course some people have no alteration, while others have bigger losses in memory and thinking. A second study by Dr. Muldoon shared similar findings. However, in another statin trial, no effect was seen on cognitive function. That study, in persons over 70, was not expressly designed to assess the effect of statins on thinking, but it did assess cognitive function.

6.2. Depression and Irritability:

Some people report changes in mood on statins. These include loss of interest in activities and loss of interest in social involvement. Some people report frank depression, but it is not known if these effects are more common in people on statins than in people who are not. However, some people reliably become down when on the drugs, and better when off, so that for these people there appears to be a relationship. It is possible that some people may also get a boost to their mood with low cholesterol, although this is less commonly reported. In some cases violence, psychosis, and suicide have been reported. We have published a small case series describing several instances of severe irritability arising on statins, resolving when statins were stopped, and returning when statin use was resumed.

6.3. Pain:

Although muscle pain is a well-recognized side effect of these drugs (and one that should be reported, so tests can be done), other pain effects have been reported by many people on statins, but have not been studied extensively include headaches, joint pains, and abdominal pain.

6.4. Peripheral Neuropathy:

Studies have confirmed that peripheral neuropathy (tingling and numbness or burning pain) may occur with statins.

6.5. Other Side Effects:

Sleep problems, sexual function problems, fatigue, dizziness and a sense of detachment are also reported with these drugs. Additionally, people have mentioned experiencing swelling, shortness of breath, vision changes, changes in temperature regulation, weight change, hunger, breast enlargement, blood sugar

changes, dry skin, rashes, blood pressure changes, nausea, upset stomach, bleeding, and ringing in ears or other noises.” [[http://www.scientificamerican.com/article/do-statins-produce-neurological-effects /](http://www.scientificamerican.com/article/do-statins-produce-neurological-effects/)]

7. INFERENCE:

Keeping all the above information in mind, it does bring us to the final question, are we doing the right thing for our body? Is the extensive use of lipid lowering drugs rational? Although called the safest Lipid Lowering drugs and best tolerated in patients, Statins do come with their share of grave side effects. Statins being available as over-the-counter medications worldwide is also something of great concern. Medicine is an evolving and ever-changing science. Things that are considered proven facts today, might not hold true tomorrow after all. Keeping that in mind, judicious use of medications on patients, measuring the pros and cons, is a physician's most important responsibility. Because after all, we are treating a patient, who is a human being, we are not just treating a disease.

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