

View Point

Statin Drug Therapy May Increase COVID-19 Infection

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ABSTRACT

Enveloped viruses like Corona virus acquire their envelope from the host cell membrane which is a bilayer of phospholipid interspersed with cholesterol molecules and proteins. Viruses enter their host cell by coming in contact with their specific receptors. Experiments have shown that when cell membranes are depleted of cholesterol in vitro by Methyl beta cyclodextrin these Corona viruses are not able to enter the host cell membrane by the process of receptor mediated endocytosis. Statin inhibits HMG Co-A reductase, a key enzyme in the Mevalonate pathway resulting into either very low or no production of endogenous cholesterol by the human cells. This results into upregulation of LDL-R in the cell membrane which may lead to more cholesterol getting incorporated into the cell membrane through LDL-C from the plasma creating greater number of lipid rafts suitable for entry of enveloped viruses by receptor-mediated endocytosis.

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INTRODUCTION

Enveloped viruses like the Coronavirus acquire their envelope from the host cell membrane which is a bilayer of phospholipid interspersed with cholesterol molecules and proteins. Viruses enter their host cell by coming in contact with their specific receptors. These specific receptors then undergo conformational changes and induce fusion of the viral envelope with the host cell membrane leading to receptor-mediated endocytosis of the virus. For Coronaviruses, their specific receptors are Carcinoembryonic antigen cell adhesion molecule-1 (CEACAM-1).¹ Recent studies have shown that the receptors for the COVID-19 may be Angiotensin- Converting Enzyme (ACE) on the respiratory cells. Experiments have shown that when cell membranes are depleted of cholesterol in vitro by Methyl beta-cyclodextrin (M β CD) these Coronaviruses are not able to enter the host cell membrane by the process of receptor-mediated endocytosis.^{1,2} It is a well-known fact that cholesterol is vital for the stability and integrity of bilayer phospholipid membrane structure of eukaryotic cells and it may be equally vital for the stabilization of the Corona envelope.

Receptor-mediated endocytosis of enveloped viruses requires a fusion of the envelope (which is also a bilayer of phospholipid) with the host cell membrane, and studies have shown that this process occurs in areas of lipid rafts.¹⁻³ There are multiple areas in the eukaryotic cell membrane with a very high concentration of cholesterol and sphingolipids. These microdomains are known

as lipid rafts (because they float like rafts on the water surface). There is strong evidence that enveloped animal viruses select lipid rafts for their assembly and budding.⁴ What statin does is, it inhibits the Mevalonate pathway that produces cholesterol along with many other very important substances in the body. The mechanism of the Mevalonate pathway exists in almost all the cells of our body because cholesterol is vital for the stability and integrity of the cell membrane as well as intracellular organelles. The cell membranes and the intracellular organelles derive their cholesterol either from the endogenous source through the Mevalonate pathway or the exogenous source.⁵ The exogenous source are either the cholesterol synthesized by hepatic cells and released in the bloodstream or the cholesterol that comes from the foodstuffs that we ingest. Because the exogenous cholesterol is insoluble in the water of blood plasma it has to be transported in combination with protein which is soluble in water, so low-density lipoprotein (LDL) transports this vital cholesterol to all the cell membranes of our body. Statin inhibits 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG Co-A reductase), a key enzyme in the Mevalonate pathway resulting in either very low or no production of endogenous cholesterol by the human cells. Homeostasis of cholesterol inside and outside of a cell is tightly regulated by a complex network of intracellular organelles, proteins, and enzymes that involve in synthesis, import, export, esterification, and metabolism of cholesterol. In the membrane of Endoplasmic Reticulum (ER), sterol regulatory element-binding

proteins (SREBP), function as critical regulators of the genes involved in cholesterol uptake and biosynthesis, such as LDL receptors (LDL-R). Cholesterol level in ER acts as a sensor of intracellular cholesterol. Statins, often prescribed lifelong, creates a chronic deficiency of endogenous cholesterol. The decrease in ER cholesterol induces the translocation of SRE-BP from the ER to the Golgi and then to the nucleus for the transcriptional activation of the target genes, including those involved in cholesterol uptake and biosynthesis⁶, resulting into upregulation of LDL-R in the cell membrane. This constant upregulation of LDL-R in the cell membrane may lead to more cholesterol getting incorporated into the cell membrane through LDL-C from the plasma creating a greater number of lipid rafts suitable for entry of enveloped viruses by receptor-mediated endocytosis. Experiments have shown that increasing cholesterol concentration in the cell membrane enhances Coronavirus fusion with the cell membrane leading to enhanced infection and depletion of cholesterol from the cell membrane decreases the entry of these viruses into their host cells. It is a paradox that statins increase cholesterol in the cell membranes which may enhance Coronavirus infection.

Lipid rafts also appear to be involved in the uptake of the malaria parasite *Plasmodium falciparum* by erythrocytes, a cell type that is normally incapable of endocytosis or phagocytosis.⁷ There may be a common mechanism by which the anti-malarial drug, chloroquine, which has been proposed for COVID-19 infection

works. Recent epidemiological data show that hypertensives, diabetics, coronary artery disease, and cerebrovascular disease patients are the ones that are developing fulminant COVID-19 disease⁸ and these are the patients who are most frequently prescribed statins for either primary or secondary prevention of cardiovascular diseases. According to an article published in the British Medical Journal in 2004 France, Germany, Italy, Spain and the UK of the European continent are the countries with the highest rate of statin intake.⁹ The USA is another country where statins are extensively prescribed. These are the parts of the globe with the highest number of Corona infections. Whereas a study published in 2016 in BMJ Open Diabetes Research and Care¹⁰ analyzed prescription data in India and found only 50% of patients with diabetes were prescribed with statins much lower compared to western countries. This could partly explain the relatively lower frequency of Corona infection in the Indian subcontinent. I would thus like to conclude by putting forward my hypothesis that statins create a constant deficiency of endogenous cholesterol content of cells leading to constant upregulation of LDL-R, in turn leading to excessive incorporation of exogenous cholesterol into the cells and their cell membrane. This process leads to multiple lipid rafts on the cell membrane and enhances accessibility for Coronaviruses. This will need to be tested in Virology labs by looking for whether there is a significant difference in Coronavirus infectivity of cells of patients taking statin and cells of individuals not taking a statin.

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