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Case Study

Extremely Elevated High Density Lipoprotein Post Statin Usage: A Case Report

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ABSTRACT

Statins are first line of treatment for patients diagnosed with dyslipidemia for lowering LDL cholesterol. Statins cause modest increases in HDL-C probably mediated by reductions in CETP activity. It is established to contribute to cardiovascular benefits. High HDL-C is associated with cardiovascular benefits but no upper limit has yet been established. Studies have shown that paradoxically extremely high HDL cholesterol levels are associated with an increased risk of atherosclerosis and cardiovascular events. Here we present a case of high HDL in a patient who was on statin and was reported to have suffered from episodes of cardiovascular events as well as cerebrovascular accident .

INTRODUCTION

Coronary arterial disease and Cerebrovascular accidents or strokes have several common risk factors and pathophysiological events. Atherosclerosis is one of those common major factors. High density lipoprotein cholesterol (HDL-c) is a group of heterogenous lipoprotein which is considered to be anti-atherogenic good cholesterol because of its involvement in transport of sterols and lipids [1]. Dyslipidemia has been established to be a risk factor for Cardiovascular diseases as well as stroke both hemorrhagic and ischemic. Guidelines for management of atherosclerosis focus on decreasing Low density Lipoprotein (LDL) concentration levels for risk reduction yet there is an increasing interest in HDL as the second line of therapy [2]. Though studies have shown an inverse relationship between HDL- c and CHD, literatures have also shown that an high HDL cholesterol level much higher than reference interval herald significant risk factors for atherosclerosis related disorders like early cardiac events [3-5]. This inverse relationship of HDL and cardiovascular disease can hint towards similar relationship between HDL and cerebrovascular accidents as well. In the present case report, a case of extremely high-density lipoprotein is presented to underscore the fact that an overshooting value of serum HDL is in fact sometimes detrimental for the cardiovascular health and acts as a promoting factor for atherosclerosis.

Case report :

A 53 year old female patient with a past medical history of hypertension and Coronary heart disease (2021 ,September) came with complain of convulsion following Cerebrovascular accident (2023, January). On prescribing by her clinician , she came to our laboratory for her lipid profile assay as per her clinician's suggestion in September 2022 . She was on regular medication with Telmisartan 40mg and Amlodipine 5mg combination (Telpress AM 40), Chlorthalidone 12.5(CTD 12.5) , Atorvastatin 10mg (Lipikind 10) ,Clonazepam 0.5 mg (Lonazep 0.5) and was on close observation . On follow up after 5 months in February 2023 , she was suggested to repeat her serum lipid profile along with urea , creatinine , sodium and potassium levels .Certain parameters clearly showed changes .

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Table 1: Results of parameters done on September 2022 & February 2023

Parameters	Sept 2022	Feb 2023
FBS	96mg/dl	113mg/dl *
PPBS	97mg/dl	104mg/dl
Total Cholesterol	182mg/dl	179 mg/dl
Triglyceride	158 mg/dl	61 mg/dl
HDL	58 mg/dl	103* mg/dl
LDL	94 mg/dl	66 mg/dl
VLDL	33 mg/dl	13 mg/dl
SODIUM	134mEq/l	131 mEq/l
POTASSIUM	4.3 mEq/l	4.3 mEq/l
UREA	27 mg/dl	15 mg/dl
CREATININE	0.9 mg/dl	0.76 mg/dl

The table clearly reveals that statin usage have lowered total cholesterol , LDL ,VLDL .Triglyceride have also shown a decrease in value . However HDL have shown a notable rise in value .

A significantly elevated serum HDL cholesterol (>60 mg/dL [1.6 mmol/L]) may exhibit inheritance from parents. It has been observed also in patients having history of chronic alcoholism and thyroid diseases. Drugs like phenytoin and insulin can also cause an abnormal elevation in HDLc levels. Finally, regular moderate or heavy exercise have been also found to be associated with higher HDLc levels. However, our concerned patient did not reveal such associations.

Discussion :

Rising concentrations of HDL-C as "good cholesterol" has been established to be associated with low cardiovascular risk [6-7]. However, the exact mechanism revealing how high serum concentration of HDLc protects us against the cardiovascular risk factors has not been elucidated exactly till now. So, the interplay of HDLc and atherosclerosis is complex although several explanations have been forwarded till now in an effort to address this association.

One such explanation mentions the metabolic inter-relationship HDLc and the apo B-containing lipoproteins like LDLc and VLDLc that stresses on the fact that a low HDLc levels are associated with increased serum triglycerides (TG) and VLDL via the intermediary role of cholesteryl ester transfer protein (CETP) that may ultimately lead to a high risk of CHD [8]. Furthermore, a lowered HDLc values show significant association with metabolic syndrome related disorders like obesity and type 2 diabetes mellitus [9]. Certain lifestyle matters like smoking and exercise also exert influential effects on HDL levels. Above all several genetic factors including independent and interrelated genetic associations have been reported to be associated with HDLc levels [10].

The major function of HDLc is to maintain the reverse cholesterol transport optimally. Along with this HDLc also promotes the macrophage cholesterol efflux and an anti-inflammatory function. A significantly lowered LDLc oxidation due to the anti-oxidant activity of HDLc along with its lowering capacity of endothelial cell apoptosis have been also found to contribute to the anti-atherosclerotic effects of HDLc. HDLc also inhibits platelet aggregation along with a reduction in cellular adhesion molecule expression thus interfering with the thrombotic element of the atherosclerosis. Keeping in track with these explanations, it has been reported also that HDLc levels more than 75mg/dl in humans prolong their longevity as well as providing them a CAD free life [11].

As CETP mediate a reciprocal transport of cholesteryl esters and triglyceride between the HDLc and VLDLc, polymorphic variations in their cognate genes may affect its activity and result in abnormal HDLc activity. For example, substitution of isoleucine for valine at codon 405 (I405V) of the CETP gene has been reported to reduce the CETP protein activity that finally results in higher values of HDLc [12-15].

The universal guidelines issued by the Adult Treatment Panel III of the National Cholesterol Education Programme have specifically mentioned that the main contributing factors for increasing LDLc values in blood are cigarette smoking, blood pressure (≥140/90 mmHg), low HDLc (<40 mg/dL), family history of premature CHD and age (men ≥45 years; women ≥55 years) etc. Furthermore, an HDL-C ≥60 mg/dL level was considered as a "negative" risk factors due to the widely prevalent scientific assumption that it may remove one risk factor from the total battery of risk factors for CAD [16]. Recently, the revised adult treatment panel-III has suggested that the target is to achieve a decreased LDLc level at least 30 to 40 percent beyond TLC when a cholesterol lowering treatment is given [17]. Thus, the major aim of anti-atherogenic treatment still underscores strongly the importance of use of HMG CoA reductase inhibitors which along with decreasing the HMG CoA reductase activity, increases the LDL receptor activity simultaneously [18]. Other than these, statins also increase the HDLc levels, and apo A-I both. Based on the strong epidemiologic evidence, it is possible that this action may also provide an independent contributory beneficiary effect. There may be at least two reasons for the beneficial effects of statins on HDLc levels. Firstly, HMG-CoA reductase inhibitors like statins are supposed to elevate the peroxisome-proliferator receptor activator-alpha (PPARα) activity. The increased level of PPARα increases the synthesis of HDL precursor particles, Apo A1 [19]. Secondly, statins are also reported to alter the most important interplay between the metabolic

relationship of HDL and TG-rich atherogenic lipoproteins. Studies have reported that atorvastatin, a widely used statin drug, decrease the blood levels of CETP along with the rate of CETP-mediated cholesteryl ester transfer from HDL to VLDL. This relationship between the statins and CETP seems to be an indirect one as no direct evidence has been found that can indicate that statins have a direct inhibitory effect on CETP [20]. With statins, elevations in HDL-C range between 3% and 15%.

In spite of the predominant belief about the protective role of elevated HDLc, several studies at present have revealed that excessive high HDL cholesterol levels are sometimes linked to increased risks for atherosclerosis also in humans that ultimately increases the chances for an adverse cardiovascular events in them [20]. It has been found that in conditions having a very high HDLc in the blood, it has been found that HDL particles become aberrant in their antiatherogenic properties with decreased effectivity. In these conditions large HDL particles with decreased anti-inflammatory proteins and lipids were reported due to which they showed lesser antiatherogenic antioxidant properties [21-22].

Our patient had extremely high level of HDLc in the blood in spite of which she suffered from both coronary artery disease and cerebrovascular accident. We propose that this might be due to either of a CETP deficiency or genetic polymorphisms affecting the activity of CETP or both of them that might have resulted in such high levels of HDLc in this patient. Use of statins also might have increased her HDL levels although, we could not find the threshold dosage of this drug beyond which elevations in HDL levels in the blood can be linked to increase risk for atherosclerosis in humans. Finally, our patient was recommended to undergo further lipidology and genetic testing the results of which are waited at present.

Conclusion :

We share this extremely interesting case of very high HDLc to point out that high HDLc are not always protective against development of CHD as well as CVA . Increased risk is thought to be from dysfunctional HDLc particles that maybe more prevalent in individuals with very high serum HDLc levels. It also indicated that there is no gender specific bias in this case . Further studies will open the arena of more discussion on how much high HDL should be to be considered "good ".

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Conflict of interest

We have no conflict of interest.

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