CASE REPORT

# HYPOCHOLESTEROLEMIA SECONDARY TO ATROVASTATIN THERAPY

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After the advent of Statins in 1960's, they are being extensively used as Antiathrogenic drug for Primary Hyperlipidemia, Angina, Ischemic Heart Disease (Medical or Post Surgical), Atherosclerosis, Diabetes mellitus and Hypertension. Rarely, these drugs have been observed to cause hypocholesterolemia. We present a case of forty years old male who was started on Atorvastatin after his angioplasty following anterior myocardial infarction. Six weeks after the start of antilipid drug patient developed symptoms of phobias, nightmares, insomnia, forgetfulness, body aches, muscle cramps, cognitive, sexual and psychomotor disturbances. On investigation he was found to have hypocholesterolemia. Atorvastatin was stopped and dietary restrictrictions were lifted. Over five month patients symptoms resolved as the serum cholesterol levels became normal. Because of similarities of symptoms of hypocholesterolemia secondary to antilipid therapy and the disease itself, hypocholesterolemia was overlooked initially by physicians. Patients on antilipids must be evaluated for any fall in serum cholerterol if they develop unusual symptoms and patients on long term antilipids must have regularly lipid profile checked.

**Keywords:** Hypocholesterolemia, Statins, Fiberates, HMG-CoA reductase, VLDL, HDL, Triglycerides, LPL

## INTRODUCTION

More than a hundred years ago a German Pathologist, Virchow discovered that cholesterol was raised in the arteries was of people with occlusive vascular disease. The cholesterol was found to be responsible for arterial wall thickenings and thus decreasing the radius in the arteries which in most of cases leads to hypertension and increase risk of occlusive vascular diseases.[1] In 1950's the Framingham heart study revealed the correlation between high blood cholesterol levels and coronary heart diseases. In order to lower the higher cholesterol levels HMG-CoA reductase became the natural target.[2] 1970's the Japanese microbiologist Akira Ando discovered the 1st natural product with powerful inhibitory affects on HMG-CoA reductase in a fermentation broth of Pencillium citrinum named as Compactin (ML 236B or Mevastatin). In 1978, Alfred Albert and colleagues at Merck Research Laboratories discovered a new natural product in fermentation broth of Aspergillus terreus, showed good inhibition of HMGR was named Mevinolin, which later became known as lovastatin.[3] Since then various derivatives have been widely used to treat athrogenic dyslipoprotenemias.[4] They principally decrease triglycerides, cholesterol and increase high-density lipoproteins (HDL). Leading to significant reduction in coronary heart disease.[5] Statins acts by HMG-CoA reductase enzymes, hence inhibiting the HMRG which blocks the cholesterol synthesis in liver and produces water soluble hydroxy-methyl glutrate which is broken down into non toxic products by other enzymes and are excreted from the body. Short acting statins must be taken at night for their maximum actions (simastatins) while long acting Atrovastatin showed no difference of timings for its maximum affects.[14] Decreasing the liver cholesterol by blocking it synthesis they increases LDL and VLDL receptors on liver cell membranes which increases LDL and VLDL (bad cholesterol) transport into liver for degradation and VLDL. Antilipids including statins were extensively used over the past five decades along with other medicines as protective to venous grafts after CABG.[9]

Since cholesterol is essential for all animal life in the world. Body can synthesise 1 gm of cholesterol in liver daily. Its total body contents about 35 gm in young adults. Daily requirements of cholesterol in young adults is 300 mg. Daily fat requirement in young adults is 60–65 g.[10]

Cholesterol is required to build and maintain cell membranes. It regulates the membrane fluidity via its hydroxyl group for permeability for many substances. Phospholipids and sphingolipids which are integral part of cell membranes decreases the positive ions absorption (Protons and Sodium).[11] It is essential for caveolac and clathrin coated pits for endocytosis. Myelin sheath is also rich of cholesterol.[12] Cholesterol if basic raw molecule for steroid hormones including cortisol, aldesterone in adrenal glands as well as sex hormones, progesterone, estrogens and testosterone in ovaries of females and testes of males respectively. Some research indicates that cholesterol may act as an antioxidant.[13]

Hypocholesterolemia may be primary or secondary. Primary hypocholesterilemia and hypotriglycemia is caused by hyperthyroidism, liver diseases, malabsorption, inadequate absorption if

nutrients from intestines malnutrition, totally vegetarians.[14] Secondary hypocholesterolemia and hypotriglycemia can occur after the use of antilipids drugs, like statins and fiberates. Major affects on human body are depression, night mares, loneliness, insomnia, phobias, suicidal tendency, Cancer (mainly prostatic), cerebral haemorrhage, deterioration of cognitive function, and ataxia.[15–18]

## CASE REPORT

A forty years old male had anterior myocardial infarction. After stabilisation he underwent angiography, angioplasty and stenting. He had three stents, one in LAD, two in Right Coronary artery. Post stenting he became symptoms free and was put on Atrovastatin, Metaprolol, Asprin, Clopidogrel, and Lisinopril. His serum cholesterol was 4.3 mmol/dl and serum triglycerides were 1.2 mmol/dl before starting the anti lipid therapy. He was advised to restrain from fats and fatty food. He remained symptoms free for 4 weeks and used to walk 2–4 Km comfortably but after 4 weeks he started developing symptoms of nightmares, phobias, abnormal thinking, loneliness, insomnia, forgetfulness, un-usefulness for family and community, along with sexual weakness. By the end of 8 weeks of treatment he developed easy fatigability, inability to walk more than 1 Km, restlessness, muscles cramps, impotency, aggressiveness, and finally significant ataxia along with slowness in writing. He considered that these are features of the disease itself and was worried about his cardiac status. He came back to cardiologist in 6$^{th}$ week of treatment for review of his cardiac status. On investigations blood complete picture, coagulation profile, liver function tests, blood sugar, serum urea electrolytes, ETT, Echocardiography, serum calcium, serum proteins, X-Rays Chest-PA all were normal. ECG changes were reverted to normal except low amplitude R wave in anterior chest leads. Serum cholesterol was 32 mg/dl (1.7 mmol/dl) and triglycerides were 36 mg/dl (0.043 mmol/dl). This was cross-checked three times by pathologist and similar levels were found. Cardiac physician stopped the Atrovastatin, lifted the dietary restrictions and advised to take 1–2 eggs daily till recovery of blood cholesterol level to normal. Patient was reviewed weekly and his lipid profile was checked fortnightly. With stoppage of Atrovastatin and lifting of the dietary restrictions, recovery started within 2 weeks and he became symptoms free within 5 weeks. His lipid profile retuned to normal by 5 weeks. Now he is taking Clopidogrel, Asprin, and Lisinopril with dietry restrictions. He is symptoms free since then, can walk 3 Km daily comfortably. All investigations including serum lipid profile are within normal limits.

## DISCUSSION

Cholesterol was found athrogenic more than hundred years ago and associated with myocardial infarction by German Pathologist Virchow. Since then antilipid medicines research started to nullify the athrogenic effects of cholesterol. In early 1960's fibric acids derivatative and in 1970's Japanese Microbiologist Akira Endo discovered the 1$^{st}$ statin Mevastatin. These discoveries lead to synthesis of multiple fibric acids and statins to treat athrogenic dyslipidemias (hyperlipidemia). All scientists, pathologist, cardiac physicians are concentrating on hyperlipidemia since almost 50 years, hence producing more and more new antilipid drugs. They mainly are concentrating on hyperlipidemia (hypercholesterolemia, hypertriglycemias) because they are definitely associated with increasing morbidity and mortality due to ischemic myocardial diseases, stroke, hypertension and diabetes mellitus. Now hundreds and thousands of patients all over the world are using various types of fiberates and statins for Angina, ischemic heart disease, stroke, atherosclerosis, diabetes mellitus and hypertension. In spite of extensive use of antilipids in above multiple diseases, hypocholesterolemia as adverse affect of antilipid drugs is rarely investigated on large scale studies. Although it is a rare adverse affect of antilipid drugs but must be kept in mind for patients who are using these drugs from years. Hypocholesterolemia associated symptoms resembles with the toxic facts of statins and fiberate along with diseases themselves. Hence it is very difficult to think about primary or secondary (therapeutic) hypocholesterolemia in these patients but if patients on antilipid drugs develop unusual psychomotor, cognitive, skeletal symptoms, then patient must be investigated for hypocholesterolemia. Moreover patients on long term antilipid therapy must have fortnightly or at least monthly serum lipid profile levels. It will help the physicians to evaluate the response and ruling out the hypocholesterolemia which will be beneficial for the patients to adjust the dose and detection along with treatment of highly curable rare adverse affect of antilipids (hypocholesterolemia), and avoiding the permanent damage from this is the rare adverse affect.

## CONCLUSION

Hypocholesterolemia is a rare therapeutic adverse affect of antilipid drugs like statins and fiberates. But is totally curable by stoppage of concern medicine along with diet adjustment. However if not diagnosed in time, patient remains long period in hypocholesterolemic state, it can lead to permanent psychomotor, cognitive, motorsystem damage, hypoadrenalism, infertility in both males and females along with permanent affects of fat soluble vitamins deficiencies and fat itself. Hence patients on long term antilipid therapy must be monitored regularly for

response and rare potentially damaging but absolutely curable adverse affect the hypocholesterolemia with timely intervention.

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