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Case report. LDL increased after withdrawal of lovastatin therapy: Does it make sense to resume treatment given that, according to the latest important retrospective cohort study, LDL is not a true risk factor for cardiovascular disease?

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Abstract
Low density lipoprotein (LDL) cholesterol for decades has been considered the primary risk factor for cardiovascular diseases. The pharmaceutical research has developed effective drugs that lower blood LDL levels. The most effective drugs belong to the class of statins, which act as reversible enzyme inhibitors of the mevalonate pathway, which is involved in the biosynthesis of cholesterol and other steroid metabolites. Statins, in a significant percentage of users, cause side effects, especially muscle-related ones, which prevent continuation of therapy. Once therapy is stopped, blood LDL levels inevitably rise to their pre-treatment levels, which are therefore above the "optimal" threshold defined by scientific literature (<100 mg/dL).
Here we describe my personal case, where I started statin therapy due to an increased LDL level and, after two years of good result therapy, I was forced to interrupt it due to side effects affecting mainly leg muscles.
I) After a three-month follow-up without statins, the LDL level is high (139 mg/dL) but within the acceptable range (<159 mg/dL). Considering this fact, does it make sense to resume treatment, also supported with supplements/drugs which would reduce its effect?
II) A large retrospective cohort study recently published (2024) demonstrating that, contrary to what has always been established by mainstream scientific literature, LDL is not a risk factor for mortality between 79 and 190 mg/dL. Considering this fact, does it make sense to resume treatment, given that in this case the levels of LDL without therapy, are not harmful to health?

Keywords: Hypercholesterolemia, lovastatin, adverse effects, myopathy, withdrawal of statin therapy

Introduction

Cholesterol plays several important structural and metabolic roles fundamental for animal biology, including Homo sapiens, as a component of plasma membranes and precursors for the biosynthesis of steroid hormones (such as testosterone), vitamin D and bile acids [1]. Mainly derived from *de novo* biosynthesis and the intestinal absorption from the diet, cholesterol is also present in blood plasma at well-calibrated concentrations, as High Density Lipoproteins (HDL), Low Density Lipoprotein (LDL) and, to a lesser extent, Very Low Density Lipoprotein (VLDL). Alteration of these concentrations can lead to pathological consequences in humans, such as atherosclerotic cardiovascular diseases. In 2025, according to many scientific publications and to the most important worldwide clinics, including Cleveland Clinic [2], Harvard Medical School [3], Mayo Clinic [4], and Johns Hopkins Medicine [5], the value of LDL must be <100 mg/dL, otherwise it unequivocally will be the cause of the increase in mortality, especially by myocardial infarction [6]. While high LDL level is still considered among the main risk factors to coronary heart disease, a new retrospective cohort study published by British Medical Journal [7] and not yet fully taken into consideration from public health agencies worldwide, showed the lack or the inverse association between hypercholesterolemia and mortality. In fact, the lowest risk for long-term mortality exists in the wide range of 100-189 mg/dL LDL, while the greater danger is found below 79 mg/dL and above 190 mg/dL. Therefore, LDL appears to be not or be limited risk factor.

Exist a variety of dietary strategies designed to reduce LDL levels, including the American Heart Association diet, the Ornish diet, the Mediterranean diet, exercise, phytosterols, fiber, soy products and fish oil, but their actual functionality is doubtful. Pharmacological and research industry acted promptly to design and put on the market specific drugs to bring LDL level. In the early 1960s drugs that inhibited cholesterol synthesis became available on the market. Nevertheless, the milestone of hypercholesterolemia therapy is a variety of natural or synthetic drugs developed from 80s called statins [8] that are today among the most prescribed drugs in the World. Statins lower cholesterol levels from blood and act prevalently in hepatocytes and in skeletal muscles as competitive and reversible inhibitors of β-Hydroxy-β-Methyl-Glutaryl-Coenzyme A reductase, the enzyme key of the mevalonate pathway, involving in the synthesis of cholesterol and other metabolic steroid compounds, including coenzyme Q10, involved in electron transport-linked phosphorylation (Figure 1).

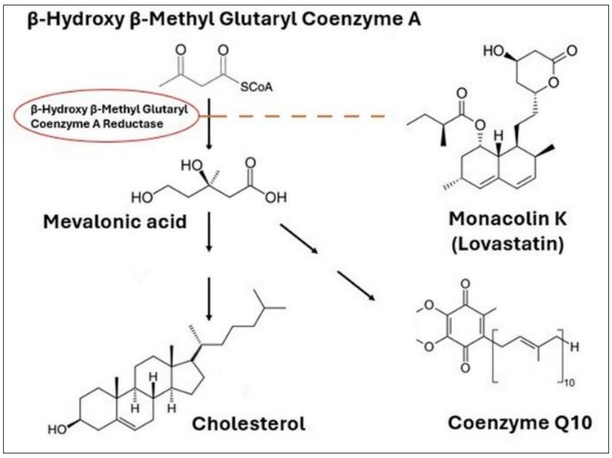

Fig 1: First step of cholesterol and coenzyme Q10 biosynthesis: involvement of lovastatin in β-Hydroxy-β-Methyl-Glutaryl-Coenzyme A reductase inhibition

While statins are effective and safe for most people, some patients are in any case intolerant of these drugs and are unable to suffer the therapeutic dose, because of different adverse effects, particularly at the level of skeletal muscle. It is precisely the onset of these side effects that reduce the adherence to statin therapy. The studies indicate that until 25% of patients discontinue or reduce their statin treatment within a few years of starting treatment [9]. Since statins are reversible inhibitors of β-Hydroxy-β-Methyl-Glutaryl-Coenzyme A reductase, once therapy is stopped LDL level increases rapidly at levels considered worrying [10], but statins can be safely resumed with coenzyme Q10 supplementation, which is able to improve muscular symptoms [11].

Among the various true or presumed side effects attributed to the use of statins [12], the most common complaint is at the level of skeletal muscle, from mild to severe form, such as pain, cramp, swelling, soreness, tiredness, or weakness [13]. Because statins also block production of coenzyme Q10, implicated in mitochondrial energy production, its deficiency in muscle cells is involved in the pathogenesis of myopathy as side effect of statins themselves [14]. Very rarely, statins can cause rhabdomyolysis, which causes muscle destruction with the release of myoglobin into the blood. This disease is characterized by extreme muscle pain, an increase of inflammation liver enzymes, kidney failure induced by myoglobin, alteration of mental status and, in the most extreme case, fatal outcome. The risk of very serious side effects is extremely low, in fact, only a few cases of rhabdomyolysis occur per million people taking statins and can occur in presence of other diseases or when it is taken a high dose or in combination with other drugs [15].

Statins, in addition to their primary hypocholesterolemic function, can reverse endothelial tissues dysfunction induced by LDL transported across the endothelium via transcytosis. Statins are therefore able to lower LDL levels in endothelial cells, allowing the arterial vasodilation in the corpus cavernosum of penis. However, due to their inhibitory action on mevalonate pathway, statin therapy is associated with a reduced level of testosterone, that can induce or aggravate the symptoms of erectile dysfunction [16].

Furthermore, the use of statins is associated with an increased risk of acute pancreatitis [17] and a significant enhancement in the risk of type-2 diabetes [18], potentially due to statin-effects on the pancreatic β-cells, impairing their ability to produce and release insulin. The exact mechanism is unknown, but statin probably interferes with calcium and glucose signaling, and with transporter function of glucose in β-cells.

Case report

I am 45 years old and carry out physical activity by cycling and walking, no alcohol, one coffee-cup daily, and a predominantly vegetarian diet. Body mass: 50 kg (2025); blood pressure: 109/75 mmHg (2025, sitting, right arm); homocysteine: 13.50 µmol/L (2025, ECLIA Roche); ApoA1: 185 mg/dL (2025, immunoturbidimetry Roche); ApoB: 111 mg/dL (2025, immunoturbidimetry Roche). I have always been in good health, except for several episodes of renal colic (2008), with final expulsion of some calcium oxalate stones.

In the paternal side of my family, hypercholesterolemia is not reported; the paternal grandfather had idiopathic myocardial infarction at 60-years-old with a positive prognosis. My mother (at present 68-years-old) suffered of hypercholesterolemia, remitted through therapy with rosuvastatin plus ezetimibe; her parents both died of acute myocardial infarction: the mother at 45-years-old and the father at 52-years-old, nothing is known about their anamnesis.

In 2018, routine hematic analysis revealed to me quite high levels of total cholesterol (246 mg/dL) and LDL (166 mg/dL) compared to normality, while HDL was normal (78 mg/dL). The same things recurred with variability in the following years, but the family doctor did not consider any action because the values do not pose imminent risk. In autumn 2023, assessing the situation of LDL level, the new family doctor, prescribed a therapy based on fermented red rice equivalent to 5 mg daily of monacolin K (lovastatin) and then, given the notable response to the drug after two months (total cholesterol lowered by 35%), setting the dosage to 2.9 mg daily. The follow-up of the therapy was 2 years, from which the level of LDL was considered normal (101 mg/dL ± 11 mg/dL; number of observations: 7). The happening was reported in a previous case report [19].

After one year of lovastatin therapy, symptoms began to appear mainly in the leg muscles, specifically pain, cramps, swelling, soreness, tiredness, and weakness. General tiredness was also observed. The onset was not sudden, but rather very slow and sneaky, so much so that it was not fully felt until April 2025 when, nearly unsustainable, it was presumed that it might be an adverse effect of statin therapy, providing immediately for its suspension. Just before discontinuation, blood tests were performed to check specific muscle failure biomarkers, and dysfunction biomarkers of liver, pancreas and kidney (Table 1), organs typically affected during statin therapy, even without having encountered specific symptoms in this case.

Table 1: blood marker tests investigated in this case report and typically investigated in the case of statin-induced side effects [20].

Blood test	Result
Liver	
C-reactive protein	0.40 mg/L
Aspartate aminotransferase	19 U/L
Alanine aminotransferase	16 U/L
Alkaline phosphatase	83 U/L
Pancreas	
Lipase	48 U/L
Pancreatic amylase	34 U/L
Kidney	
Urea	27 mg/dL
Inorganic phosphorus	3.2 mg/dL
Creatinine	1.06 mg/dL
Estimated glomerular filtration rate	85 mL/min
Skeletal muscle	
Creatine kinase	129 U/mL
Myoglobin	25 µg/L
Potassium	4.7 mmol/L
Total calcium	10.1 mg/dL
Glucose metabolism	
Glucose	87 mg/dL
Glycosylated hemoglobin	36 mmol/mol
Inflammation	
RBc sedimentation rate, 1h	5 mm/h

Blood tests revealed no abnormalities in the biochemical parameters of any of the tested organs, excluding any problem in them, and in muscles, excluding more serious diseases (e.g. rhabdomyolysis). Muscle symptoms completely remitted within two weeks following discontinued statin therapy, thus confirming the hypothesis that lovastatin was the cause of the muscle symptoms.
Following the suspension of therapy another side effect, that at first had gone unnoticed, was "observed" following its disappearance: the erectile dysfunction. It remained latent for several months, erroneously considered a normal event linked to incipient aging and to which should have gotten used to, but which evidently was induced by statin therapy.
Following the discontinuation of therapy, the LDL level increased by 24% in one week, remaining at this level for the entire three-month follow-up (139 ± 4.4 mg/dL, number of observations: 6) (Figure 2). The increase of LDL blood level is much lower than that reported in the literature: +30% after 4 days and +92% after 30 days of statin withdrawal [10]. Although the LDL level is higher than the value recommended by worldwide medical authorities (<100 mg/dL) it is lower than the upper limit recommended by the same panel (159 mg/dL). Since statins act reversibly on cholesterol biosynthesis (inhibitor of β-Hydroxy-β-Methyl-Glutaryl-Coenzyme A reductase), discontinuing therapy restores the LDL level to its pre-existing condition. Without any drug treatment, the natural restoration in the LDL metabolism can rarely occur sporadically. These fluctuations can be induced by psychosomatic disorders or be influenced by sleep disturbances; in fact, it was observed that the risk of a high LDL level is lower among males with canonical hours of sleep (≥8) [21]. However, in this case report both occurrences were not highlighted.

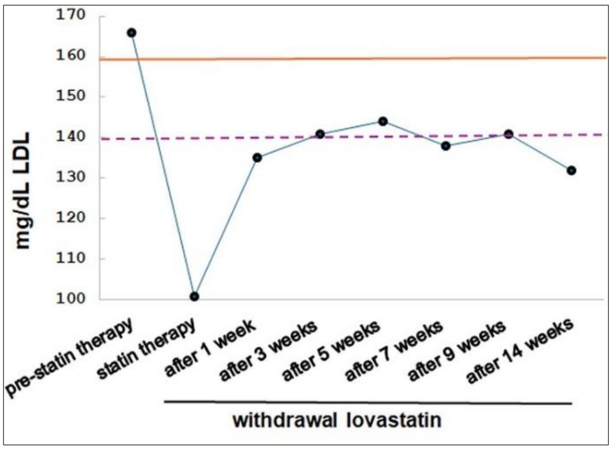

Fig 2: Diagram reassuming the case. LDL cholesterol analyses from serum were performed by the Roche enzymatic-colorimetric method. The results were reported in the line chart: LDL concentration (mg/dL) is in the y-axis, while follow-up period (weeks) is in the x-axis. Throughout the follow-up period the LDL value remains 139 ± 4.4 mg/dL (6 observations), also indicated by blue dotted line. Furthermore, the red line indicates the maximum LDL risk limit level allowed established by scientific research.

Regardless of the LDL levels found in this case report, it is not possible to ignore the recent retrospective cohort study edited by the British Medical Journal [7], where LDL (if it remains in the broad range 79-190 mg/dL) is not absolutely classified among the true risk factors for cardiovascular disease, unlike other established causes, very widespread in Western countries, such as high blood pressure, cigarette smoking and physical inactivity. For both reasons outlined in this report, the statin therapy will not be resumed.
So, does it make sense to monitor and obsessively adjust the blood LDL concentration by potentially dangerous drugs as is currently being done everywhere, despite the familiarity of cardiovascular diseases, even if the causes are unknown? The answer is probably no. Now, we can say it really, Godot has finally arrived [22].

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