

## Case Study

# Severe decrease in high-density lipoprotein cholesterol with the combination of fibrates and ezetimibe: A case series

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**Abstract:** A sudden and severe drug-induced decrease in plasma high-density lipoprotein cholesterol (HDL-C) is a rare condition. We report 2 patients with familial hypercholesterolemia treated with statins and fibrates and 2 others with mixed dyslipidemia treated with fibrates, who presented with a sudden and severe decrease in HDL-C (from -44% to -95%, compared with baseline). Three of the patients were treated with fibrates and had a sudden decrease in HDL-C after the adjunction of ezetimibe. HDL-C returned to normal levels after discontinuation of the offending therapies. In 2 of these patients, the reintroduction of ezetimibe with no fibrates did not affect HDL-C. In conclusion, we report a new profile of patients who are at risk for a sudden drop of HDL-C related to treatment with a combination of fibrates and ezetimibe. Although a sudden drop of HDL-C is a rare event, we recommend to carefully monitor plasma HDL-C in patients submitted to both drugs.

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## Background

Low levels of high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of cardiovascular disease.<sup>1</sup> A mild-to-moderate reduction in HDL-C is a frequent situation mostly associated with metabolic syndrome, hypertriglyceridemia, insulin resistance, lifestyle<sup>2</sup> and less likely to renal or hepatic diseases as well as autoimmune and inflammatory disorders.<sup>3</sup>

It is not frequent to have patients with very-low HDL-C levels (<0.40 mmol/L). This is observed in some inherited disorders as deficiency in adenosine triphosphate-binding cassette transporter A1 (ABCA1), apolipoprotein A-I (Apo A-I), or lecithin-cholesterol acyltransferase.<sup>4</sup> However, this condition can also be acquired and was depicted by Goldberg and Mendez as “Disappearing HDL syndrome.”<sup>2</sup> In some cases, the origin is easily diagnosed in case of major hypertriglyceridemia, high dose of androgen treatments, sepsis, or severe hepatic insufficiency. The origin is less obvious when it is related to a malignancy or a paradoxical response to peroxisome proliferator-activated receptor agonist treatments, for example, fibrates and/or glitazones.<sup>3,5-7</sup> It is therefore critical to identify these situations as discontinuation of

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the offending agents often ensues with normalization of the plasma HDL-C levels.

Herein, we report 4 patients who presented with a severe decrease in plasma HDL-C concentrations. The first one was consistent with previous cases reported in the literature, for example, fibrate treatment. For the other 3 patients, we report a severe decrease of HDL-C observed with the introduction of ezetimibe treatment on the top of fibrate treatments.

## Case presentations

### Patient 1

A 55-year-old Caucasian man with no history of major disease and no other cardiovascular risk factors was treated with fenofibrate (200 mg), which replaced rosuvastatin (10 mg) because of muscle intolerance in 2009. In 2012, with this treatment, the HDL-C level was decreased to

0.69 mmol/L (Table 1); and in 2013, he was referred to our lipid clinic because the HDL-C level dropped further down to 0.33 mmol/L. Fenofibrate was withdrawn and the following month, the HDL-C level was back to 1.33 mmol/L. HDL-C was measured as in all the following cases, using enzymatic kits (Boehringer Mannheim GmbH, Germany) after chemical precipitation of Apo B containing particles (sodium phosphotungstate-MgCl<sub>2</sub>).

### Patient 2

A 52-year-old Caucasian man with familial hypercholesterolemia (heterozygous for low-density lipoprotein receptor mutation) and a severe cardiovascular disease was treated with fenofibrate (200 mg/day), atorvastatin 10 mg/day (intolerant to higher doses), acebutolol (200 mg/day), nicorandil (10 mg/day), aspirin (100 mg/day), and LDL apheresis (started in 2001) twice a month. The combination of statin and fibrates was well tolerated. The coronary heart disease was stable, but ezetimibe (10 mg/day) was added in January 2005 due to high LDL-C

**Table 1** Lipids profile and lipid-lowering therapies of the 4 patients

Date	Total Cholesterol mmol/L (mg/dL)	HDL-C	LDL-C	TG	Lipid-lowering therapies
<b>Patient 1</b>					
19/12/2009	4.72 (171)	1.31 (51)	3.05 (119)	1.04 (92)	Rosuvastatin 10
06/06/2012	4.60 (179)	0.69 (27)	3.41 (133)	1.06 (94)	Feno 200
26/06/2013	4.50 (175)	0.33 (13)	3.44 (134)	1.53 (141)	Feno 200
28/01/2014	5.73 (223)	1.33 (52)	3.70 (144)	1.54 (136)	
16/01/2015	6.73 (262)	1.23 (48)	4.98 (194)	1.15 (102)	Atorvastatin 10 mg started
<b>Patient 2</b>					
12/01/05	9.00 (346)	0.81 (31)	6.84 (263)	2.91 (258)	Atorva 10 + Feno 400 + LDL apheresis
02/02/05	6.21 (239)	<b>0.13 (5)</b>	4.86 (187)	2.65 (235)	Atorva 10 + Feno 400 + LDL apheresis + ezetimibe10
16/03/05	6.92 (266)	<b>0.16 (6)</b>	4.84 (186)	2.23 (197)	Atorva 10 + Feno 400 + LDL apheresis + ezetimibe10
24/03/06	8.65 (330)	<b>0.23 (9)</b>	6.92 (266)	3.10 (275)	Atorva 10 + Feno 400 + LDL apheresis
05/04/06	10.64 (412)	0.96 (37)	8.26 (320)	3.13 (275)	Atorva 10 + nicotinic acid 500 + LDL apheresis
07/06/06	10.39 (403)	1.19 (46)	7.92 (307)	2.82 (247)	Atorva 10 + LDL apheresis
12/12/07	9.35 (364)	1.03 (40)	6.06 (236)	5.02 (444)	Atorva 10 + LDL apheresis + ezetimibe 10
1/04/15	10.30 (401)	0.90 (35)	7.58 (295)	5.02 (444)	Atorva 40 + LDL apheresis + ezetimibe 10
<b>Patient 3</b>					
14/03/05	5.16 (200)	0.98 (38)	3.74 (145)	0.97 (85)	Atorva 80 + Feno 160
11/06/05	5.01 (194)	<b>0.67 (26)</b>	3.77 (146)	1.25 (110)	Atorva 80 + Feno 160 + ezetimibe10
23/07/05	5.24 (203)	<b>0.62 (24)</b>	4.01 (156)	1.33 (117)	Atorva 80 + Feno 160 + ezetimibe 10
29/10/05	5.62 (218)	<b>0.77 (30)</b>	4.23 (164)	1.21 (138)	Atorva 80 + Feno 160
10/04/06	6.71 (260)	1.24 (48)	4.64 (180)	1.84 (161)	Atorva 80 + nicotinic acid 500
01/08/06	5.70 (222)	1.26 (49)	3.70 (144)	1.55 (137)	Atorva 80 + nicotinic acid 1500 + ezetimibe 10
01/10/11	5.19 (202)	0.85 (33)	3.39 (132)	2.07 (183)	Atorva 80 + ezetimibe 10
01/10/15	5.01 (195)	1.10 (43)	3.44 (134)	1.01 (89)	Rosuvastatin 20 + ezetimibe 10
<b>Patient 4</b>					
28/02/05	4.13 (159)	0.75 (29)	2.08 (80)	2.85 (252)	Feno 200
06/10/05	4.39 (169)	<b>0.36 (14)</b>	—	<b>6.28 (556)</b>	Feno 200 + ezetimibe 10
01/12/05	4.70 (183)	<b>0.57 (22)</b>	2.88 (112)	2.80 (246)	Feno 200
15/02/06	4.10 (159)	<b>0.52 (20)</b>	2.55 (99)	2.29 (201)	Feno 200
15/03/06	5.30 (204)	0.70 (27)	3.04 (118)	3.36 (295)	Feno 200
15/08/14	4.13 (159)	0.72 (28)	1.55 (60)	2.30 (202)	Rosuvastatin 10 mg

Atorva, atorvastatin; Feno, fenofibrate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride. The sudden decrease of HDL-C values are outlined in bold.

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