Case Report

Unexpected and Abnormally Low HDL Cholesterol Levels on Combination Hypolipidemic Therapy

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Abstract

In general, Indians have low HDL cholesterol levels. Fenofibrate, a drug widely used in the treatment of hypertriglyceridemia, usually also increases HDL cholesterol. There have been a few reports in the literature of a paradoxical decrease in serum HDL-cholesterol in patients treated with fenofibrate, either alone or in combination with a statin. We report three cases of paradoxical decrease in serum HDL- cholesterol in type 2 diabetic patients treated with a statin-fenofibrate combination. ©

Introduction

The fibrate group of drugs, widely used to treat hypertriglyceridemia usually also increase the cardio protective HDL- cholesterol levels. However, there have been a few reports describing a paradoxical decrease in the serum HDL- cholesterol in patients treated with fibrates alone[1-7] or in combination with statins.[8] This phenomenon has been reported with bezafibrate,[4,6] ciprofibrate[3,5] and more recently, with fenofibrate.[7] There are also reports of a decrease in HDL cholesterol with a fibratestatin combination.[8] We document here three cases of paradoxical decrease in serum HDL-cholesterol in diabetic patients on a statin / fibrate combination. We believe this is the first report from India on this topic.

Case Reports

Case No. 1

A 51 year old male presented to our centre with type 2 diabetes of 11 years' duration. His diabetes had been stabilized with two divided doses of insulin along with oral hypoglycaemic agents. He was a non- smoker and was on treatment for hypertension.

Physical examination revealed no abnormality. His body mass index was 26.36 kg/m^2, blood pressure was 110/72 mm Hg and his renal function was normal. He had been on treatment for hypercholesterolemia and was on Atorvastatin (10 mg daily). On this dose, his serum lipid values were: serum cholesterol: 164 mg/dl; serum triglycerides: 327 mg/dL; HDL cholesterol: 36 mg/dl; LDL cholesterol: 63 mg/dl; VLDL cholesterol: 65 mg/dL. In view of the raised triglycerides, he was started on a combination of Atorvastatin (10 mg daily) and fenofibrate (200 mg daily). When he returned for follow-up after 6 months, his lipid profile was as follows: serum cholesterol: 89 mg/dL; serum triglycerides: 123 mg/dl; LDL cholesterol: 62 mg/dL; VLDL cholesterol: 25 mg/dL and the HDL cholesterol had dropped to dangerously low level of 2 mg/dL. Fenofibrate was stopped and substituted with micronised Niacin 375 mg daily. However the patient could not continue therapy with niacin since he developed severe flushing. Hence niacin therapy was stopped and therapy was continued with atorvastatin alone. After therapy with atorvastatin alone, his HDL cholesterol level rose again to 34 mg/dl.

Case No. 2

A 46 year old male presented to our centre with type 2 DM associated with systemic hypertension and dyslipidaemia. He was overweight and had a blood pressure of 140/90 mm of Hg. He is a non-smoker and his diabetes was under good control with oral hypoglycemic agents. His renal function was normal. He had been on treatment for dyslipidaemia with fenofibrate (200 mg). On this dose, his serum lipid values were: serum cholesterol: 180 mg/dl; serum triglycerides: 237 mg/dl; serum HDL: 21mg/dl; and serum LDL: 131 mg/dl respectively. In view of the raised triglycerides and LDL, he was started on a combination of atorvastatin and fenofibrate. At the next visit 6 months later, his serum HDL cholesterol was found to have dropped to 8 mg/dl. The fenofibrate was stopped and after this, his HDL cholesterol increased to 23 mg/dl with atorvastatin alone.

Case No. 3

A 49 year old male, a non-smoker and teetotaller presented to our centre with type 2 diabetes of 10 years' duration, associated with diabetic retinopathy and neuropathy and hyperlipidaemia. His diabetes was under good control with two divided doses of insulin and oral hypoglycaemic agents. His renal function was normal.

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For hyperlipidaemia, he had been on treatment with atorvastatin 10 mg daily. With this dose, his serum lipid values were: serum cholesterol: 202 mg/dl; triglycerides 453 mg/dl; and HDL cholesterol: 38 mg/dl. In view of raised triglycerides, he was started on a combination of atorvastatin and fenofibrate. When he came for follow up after a month, his HDL cholesterol had dropped to 12 mg/dl and triglycerides to 305 mg/dl. At this time, fenofibrate was substituted with gemfibrozil. After 3 months, his HDL cholesterol rose to 33 mg/dl but triglycerides remained high at 405 mg/dl. Atorvastatin and fenofibrate combination was reintroduced at this time. At the next follow up after 5 months, the serum HDL cholesterol had again dropped to 6 mg/dl. After stopping the combination, serum HDL cholesterol again picked up to 21 mg/dl with gemfibrozil alone.

Discussion

Fibrates, generally prescribed for control of hypertriglyceridemia, usually produce a concomitant increase in HDL cholesterol. A paradoxical decrease in serum HDL cholesterol concentration has been reported with several fibrate compounds.[1-7] However, the mechanism of this phenomenon largely remains unclear.

A review of the literature reveals several interesting aspects to this phenomenon, namely (i) it occurs with fibrate monotherapy and / or statin + fibrate combination therapy (ii) it appears to be a class effect of the fibric acid derivatives (iii) there may sometimes be a fibrate dose dependency (iv) it may not be consistently reproducible, if such patients are re-challenged with fibrate (v) there is an increased catabolism and decreased synthesis of apolipoprotein A containing lipoprotein (vi) it may become evident as early as two weeks after initiation of fibrate therapy and full recovery may be observed within two weeks after cessation of the fibrate.[2]

There is only one report in the literature of a paradoxical decline in serum HDL cholesterol induced by a statin / fibrate combination[8] but in that case it was associated with abnormal renal function which could have contributed to this phenomenon. To our knowledge, our cases are unique in being the first report of a paradoxical and profound decrease in HDL cholesterol levels with a statin / fibrate combination in diabetic patients without renal impairment. In all three cases reported here, the statin was atorvastatin and the fibrate was fenofibrate. This suggests that this particular combination may be more prone to produce unusually low HDL cholesterol levels. However we cannot rule out the possibility that other statin / fibrate combinations may also make patients more prone to this phenomenon. The message to practising physicians is that whenever a statin/fibrate combination is used, in addition to looking for risk of myopathies, one should also look out for precipitous fall in HDL cholesterol levels. This is particularly relevant in the context of Asian Indians who are already known to have low HDL cholesterol levels.[9]

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