

Severe Hypo- α -Lipoproteinemia During Treatment With Rosiglitazone

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Thiazolidinedione drugs are in widespread use for the treatment of type 2 diabetes. In addition to improving insulin sensitivity, they generally result in a modest elevation of plasma HDL cholesterol. We report three patients, all of whom had preexisting diabetic dyslipidemia, who showed a profound reduction in plasma HDL cholesterol and apolipoprotein AI levels soon after the initiation of rosiglitazone therapy. In all three patients, HDL cholesterol levels returned to normal following drug withdrawal. The fact that this phenomenon was not seen in >1,400 patients studied in clinical trials indicates that it is likely to be rare and idiosyncratic. Until the frequency of this adverse reaction is clearer, it would seem advisable to ensure that plasma HDL cholesterol is documented before and rechecked after commencement of thiazolidinedione therapy.

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Rosiglitazone and pioglitazone are thiazolidinediones, which are in widespread use for the treatment of hyperglycemia in type 2 diabetes. As patients with type 2 diabetes have increased cardiovascular risk, the effects of these drugs on plasma lipid levels have also been of considerable interest. In general, both drugs have been found to increase plasma HDL cholesterol modestly, although pioglitazone is associated with a greater fall in plasma triglycerides (1). Thiazolidinediones act on the nuclear receptor peroxisome proliferator-activated receptor (PPAR) γ , whereas fibrates act on the closely related PPAR α (2). Fibrates have beneficial effects on plasma HDL cholesterol and triglycerides and thus are often used to treat the “diabetic” pattern of dyslipidemia (2). Occasional reports have, however, described a profound fall

in plasma HDL cholesterol and apolipoprotein (apo)AI during fibrate therapy (3). We now report three subjects showing a similar response to rosiglitazone.

CASE HISTORIES AND INVESTIGATION

Patient 1

A 64-year-old Caucasian man was diagnosed with type 2 diabetes and mixed hyperlipidemia and treated with metformin, a sulfonylurea, a statin, and bezafibrate over the next 3 years. He was shown to have peripheral sensory neuropathy and stable myocardial ischemia during this time. His glycemic control deteriorated such that his HbA_{1c} was 9% in December 2001. Rosiglitazone was introduced. His HDL cholesterol fell from 0.9 mmol/l before rosiglitazone to 0.31 mmol/l 4

months later, whereas HbA_{1c} fell concomitantly to 6.5%. The lipid abnormalities persisted, leading to the withdrawal of rosiglitazone in December 2002. Three months later, HDL cholesterol had risen to 0.95 mmol/l. ApoAI, but not apoAII, levels paralleled the changes in HDL cholesterol, with a nadir apoAI level of 0.57 g/l (normal range 1.1–2.05), while fasting triglycerides changed reciprocally (pretreatment, 4.0 mmol/l; peak during treatment, 8.0 mmol/l). Although there was a history of consumption of ~20 pints of beer per week (320 g alcohol), this remained steady throughout the period described.

Patient 2

A 64-year-old Caucasian woman was diagnosed with type 2 diabetes and treated with metformin alone for 3 years. Her HbA_{1c} level gradually deteriorated to 10.1%, whereupon rosiglitazone was introduced. HDL cholesterol, at 1.21 mmol/l before rosiglitazone treatment, dropped to 0.26 mmol/l over the next 3 months, while HbA_{1c} fell to 7.9%. Fenofibrate was added, but there was a further reduction in HDL cholesterol to a nadir of 0.11 mmol/l. At this point, the apoAI level was profoundly suppressed at 0.14 g/l, while the apoAII was only slightly depressed at 0.24 g/l. Once again, a modest reciprocal change in triglycerides was seen (pretreatment, 2.7 mmol/l; peak during treatment, 4.7 mmol/l). Both rosiglitazone and fenofibrate were withdrawn, and 3 months later, her HDL cholesterol had risen to 0.95 mmol/l. Alcohol consumption was consistently <40 g per week.

Patient 3

A 64-year-old South Asian man was diagnosed with type 2 diabetes and managed in primary care for 10 years. He was then referred to our clinic with an HbA_{1c} of 11.4% despite treatment with metformin and glipizide and an HDL cholesterol level of 0.99 mmol/l. He had a history of ischemic heart disease and microalbuminuria. His other medication was felodipine and lisinopril. Because triglycerides were elevated to 3.8 mmol/l, beza-

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Abbreviations: apo, apolipoprotein; PPAR, peroxisome proliferator-activated receptor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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fibrate was introduced with dietary and lifestyle advice, and in August 2001, his HDL cholesterol was 0.98 mmol/l, triglycerides 1.9 mmol/l, and HbA_{1c} 8.7%. Rosiglitazone was commenced at 4 mg daily. Eight months later, after a severe intercurrent pneumonia, HDL cholesterol was 0.44 mmol/l and HbA_{1c} 9.9%. Increasing the dose of rosiglitazone to 8 mg daily led to the HDL cholesterol level declining further to 0.26 mmol/l and to HbA_{1c} dropping to 6.5%. The thiazolidinedione was withdrawn, and 4 months later, HDL cholesterol was 0.98 mmol/l. Corresponding apoAI levels were 0.27 g/l on rosiglitazone and 1.11 g/l after withdrawal (normal range 1.1–2.05). ApoAII was unchanged and within the normal range in both situations. Fasting triglycerides rose on treatment to a peak of 5.2 mmol/l. He consumed no alcohol.

Relevant serial lipid determinations and drug histories of all three patients are illustrated in Fig. 1, with apoAI and -AII levels in Table 1.

CONCLUSIONS—We describe three patients with type 2 diabetes and dyslipidemia in whom plasma HDL cholesterol and apoAI fell sharply during rosiglitazone treatment, with concomitant elevation of fasting triglycerides. This is unlikely to be a chance finding because in all case subjects, 1) the falls in HDL cholesterol and apoAI were profound and closely temporally related to the initiation of rosiglitazone therapy and 2) there was a rapid return of HDL cholesterol to pretreatment values on its withdrawal. Discordant with this exaggerated pattern of dyslipidemia, characteristic of insulin-resistant states, all three patients also showed a striking improvement in glycemic control in response to rosiglitazone (HbA_{1c} decrements 2.5, 2.2, and 2.2%, respectively), suggesting that PPAR γ signaling pathways relevant to glucose homeostasis are intact and robustly responsive to rosiglitazone.

As abundant evidence from prospective population studies shows that low levels of HDL cholesterol are strongly associated with an increased risk of atherosclerosis (4), this represents a potentially serious adverse event that requires detailed evaluation. The severe dyslipidemic response to rosiglitazone is clearly rare since it has not been observed in >1,400 type 2 diabetic patients studied in published clinical trials to date (5–7). Indeed, HDL cholesterol tended to increase on

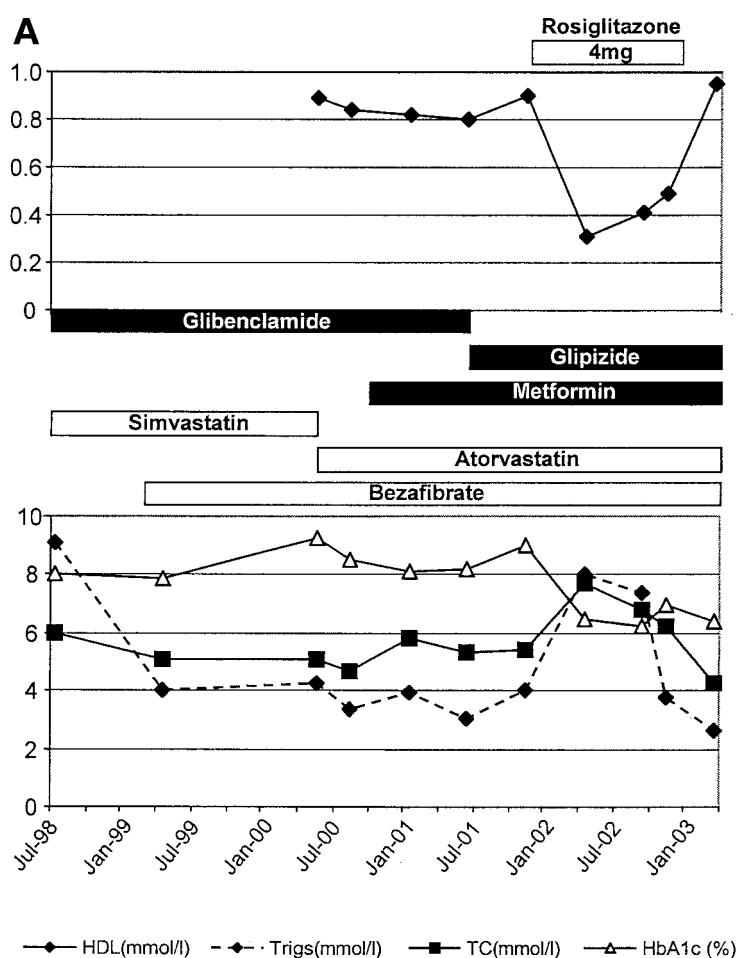
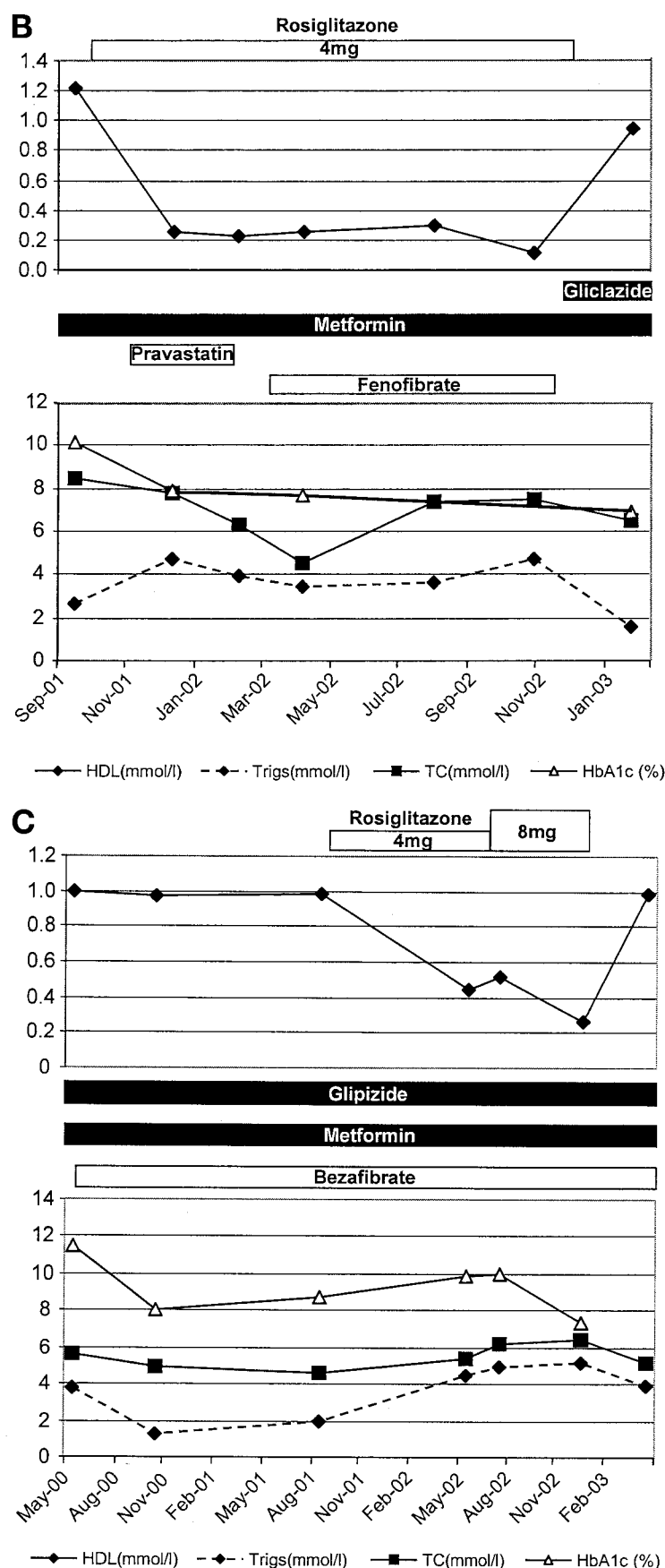


Figure 1—Serial measurements of lipid parameters and HbA_{1c} in relation to oral hypoglycemic and lipid-lowering therapy for patients 1 (A), 2 (B), and 3 (C). —◆—, HDL cholesterol (in millimoles per liter); —◆—, triglycerides (Trigs, in millimoles per liter); —■—, total cholesterol (TC, in millimoles per liter); —△—, HbA_{1c} (as percentage).

rosiglitazone therapy. There are no obvious distinguishing features of our patients who exhibited the aberrant response: all three were in late middle age and had baseline dyslipidemia, both common features of type 2 diabetes.

The mechanism of rosiglitazone-induced hypo- α -lipoproteinemia is, as yet, unclear. Either HDL cholesterol synthesis or degradation, or both, could be affected. The concurrent elevations in plasma triglycerides in our patients may be a cause or consequence of hypo- α -lipoproteinemia, but are reminiscent of the dyslipidemia of insulin resistance itself. In that situation, increased free fatty acid flux and increased apoB stability lead to hypersecretion of VLDL from the liver and thus to increased HDL triglyceride content through the action of cholesteryl ester transfer protein. This extra triglycer-

ide is hydrolyzed by hepatic lipase in particular, and the resulting smaller HDL particles and apoAI undergo increased catabolism (8). Several genes involved in this pathway are either subject to regulation by PPAR γ or are known to have polymorphisms in their promoter regions that may contribute to HDL cholesterol levels at baseline. It is reasonable to hypothesize that these or other subtle variations in genetic regulatory sequences underlie the idiosyncratic rosiglitazone response in humans. Comparative studies (9) suggest that such minor variation could also account for dramatic changes in the rate of apoAI synthesis, with PPAR agonists having opposite effects on apoAI transcription in humans and rats, determined by only a few nucleotides' difference in the apoAI gene promoter. Nongenetic factors may also play a role in the aberrant re-



sponse. Thus, PPAR γ is normally expressed only at very low levels in liver but is likely to be increased in the hepatic steatosis of obesity and insulin resistance (10), where it may act rather promiscuously on PPAR response elements or interfere with transcriptional activation by other PPAR isoforms. These possibilities remain to be studied in the case subjects described.

Whether this rosiglitazone-induced dyslipidemia is truly analogous to the paradoxical response previously described to various fibrates is unclear. Reports of severe fibrate-induced HDL cholesterol lowering have only occasionally documented apoAI and -AII levels and triglycerides. Where commented on, apoAI has indeed been profoundly suppressed, whereas in the single case documenting apoAII levels, these were commensurately low, unlike the present case (3). Triglycerides have generally, but not universally, been reported as mildly elevated.

Although two of the patients were taking a fibrate when rosiglitazone was commenced, patient 2 had received no fibrate before a profound reduction in HDL cholesterol. However, a further reduction in HDL cholesterol was seen when a fibrate was subsequently introduced to patient 2. We therefore cannot exclude the possibility that the coprescription of these two classes of PPAR agonists might exacerbate the HDL cholesterol fall in susceptible individuals. Of note is the recent report (11) of similarly profound declines in HDL cholesterol in two patients taking both thiazolidinediones and fibrates. However, in those subjects, the aberrant lipid responses were rectified by cessation of fenofibrate alone, with continued thiazolidinedione therapy, distinguishing them from the current report.

It is not possible to say yet whether this occasional hypo- α -lipoproteinemia is unique to rosiglitazone. Since pioglitazone has much lower usage in our region of the U.K., the denominators in any comparison are markedly different. However, the growing appreciation that many PPAR "agonists" are actually selective PPAR modulators with subtly different effects (2), in conjunction with clinical evidence of differential lipid responses to these agents, suggests that a rosiglitazone-specific effect is at least plausible. The finding of three cases of rosiglitazone-related hypo- α -lipoproteinemia in a rela-

Table 1—Concentrations of HDL cholesterol, apoAI, and apoAII on treatment with and after withdrawal of rosiglitazone

Patient	On rosiglitazone			Off rosiglitazone		
	HDL cholesterol (mmol/l)	ApoAI (1.1–2.05 g/l)	ApoAII (0.26–0.51 g/l)	HDL cholesterol (mmol/l)	ApoAI (1.1–2.05 g/l)	ApoAII (0.26–0.51 g/l)
1	0.49	0.57	0.28	0.95	1.06	0.37
2	0.11	0.14	0.24	0.95	ND	ND
3	0.26	0.27	0.36	0.98	1.11	0.33

ND, not done.

tively small clinical population is striking and contrasts with the data from clinical trials; our institutions serve a population of 780,000, and most patients with type 2 diabetes in this population are managed in primary care and are not recorded on our database. Nevertheless, we have recently identified a fourth patient locally with a similar response to rosiglitazone, whereas one further such response has been recorded by the U.K. Committee on Safety of Medicines (C.S.M., personal communication). Furthermore, rigorous postmarketing surveillance will be needed to gain a clearer idea of the frequency of this phenomenon and its generalizability to other drugs of the same class. In the interim, we suggest that it would be advisable to ensure that HDL cholesterol and triglycerides have been documented before commencement of thiazolidinedione therapy and that these are rechecked shortly after beginning these agents.

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