Severe HDL-c reduction during rosiglitazone therapy in an obese woman with type 2 diabetes

Redução severa de HDL-colesterol durante terapia com rosiglitazona em uma mulher obesa com diabetes tipo 2

Ricardo Luiz de Almeida[1], Paulo Fedrizzi[2], Daniela Fedrizzi[3], Tobias Skrebsky de Almeida[4]

SUMMARY

Treatment with rosiglitazone has been associated with severe paradoxical HDL-c reductions. To our knowledge, there are very few reports of this reaction occurring when patients are treated without the combination of a fibrate. A case of severe HDL-c lowering in a patient treated with rosiglitazone without a fibrate is presented. The patient has been treated at a private practice clinic in southern Brazil. A 64-year-old woman with a 2-year history of type 2 *diabetes mellitus* was referred to her endocrinologist in June 2008. Rosiglitazone 4 mg q.d. was prescribed. Nine months later, the patient experienced a 90.90% decrease of her HDL-c levels. Rosiglitazone was withdrawn and the HDL-c returned to baseline. This paradoxical HDL-c reduction is a potentially severe adverse event. Patients prescribed rosiglitazone should have their HDL-c levels measured before and during therapy. Arq Bras Endocrinol Metab. 2010;54(7):663-7

SUMÁRIO

O tratamento com rosiglitazona tem sido associado a reduções paradoxais e severas no HDL-c. Há muito poucos relatos dessa reação ocorrendo em pacientes tratados com rosiglitazona sem a combinação com um fibrato. Apresentou-se um caso de diminuição severa no HDL-c em uma paciente tratada com rosiglitazona sem fibrato associado. A paciente foi tratada em uma clínica privada no Sul do Brasil. Uma mulher de 64 anos com história de diabetes melito tipo 2 há 2 anos foi encaminhada ao seu endocrinologista em junho de 2008. Prescreveu-se rosiglitazona 4 mg uma vez ao dia. Nove meses depois, a paciente teve redução de 90,90% em seus níveis de HDL-c. A rosiglitazona foi retirada e o HDL-c retornou aos níveis prévios. Essa redução paradoxal do HDL-c é um evento adverso potencialmente severo. Pacientes aos quais se prescreve rosiglitazona devem ter seus níveis de HDL-c medidos antes e durante o tratamento. Arq Bras Endocrinol Metab. 2010;54(7):663-7

[1] Instituto do Coração da Serra Gaúcha, Caxias do Sul, RS, Brazil
[2] MD, Endocrinologist
[3] MD, MSc, Endocrinologist
[4] Universidade de Caxias do Sul (UCS), Caxias do Sul, RS, Brazil

Correspondence to:
Tobias Skrebsky de Almeida
Rua Dom José Baréa, 2444/702
95084-100 – Caxias do Sul, RS, Brazil
vladdark@gmail.com

Received on Dec/18/2009
Accepted on Aug/3/2010

INTRODUCTION

Thiazolidinediones (TZDs) are an interesting class of oral antidiabetic agents that act through the activation of the peroxisome-proliferator-activated receptors of the gamma subtype (PPARγ), which are nuclear receptors that regulate gene transcription, thus reducing insulin resistance. PPARγ agonism with rosiglitazone, one of the currently marketed TZDs, has shown to improve glycemic control in patients with type 2 *diabetes mellitus* (1). There have been numerous case reports showing a severe depression of high-density lipoprotein cholesterol (HDL-c) when patients were given a combined therapy of a TZD, mainly rosiglitazone, and a fibrate (2-7). There are, however, a very small number of reports describing this effect in patients treated with a TZD alone (3,8). Hence, we report a paradoxical and marked decrease in HDL-c levels of a patient prescribed rosiglitazone without a fibrate. The patient has provided us with permission to publish these features of her case, and the identity of the patient has been protected.

CASE REPORT

A 64-year-old Caucasian obese (Body Mass Index: 33 kg/m^2) woman with type 2 *diabetes mellitus*, dyslipidemia, depression and hypertension had been taking

metformin (500 mg b.i.d.), rosuvastatin (10 mg q.d.), paroxetine (15 mg q.d.) and atenolol/chlortalidone in a fixed-dose combination (25 mg/12.5 mg q.d.). The patient was fully adherent to the treatment, visiting her cardiologist and her endocrinologist at 3-6 month intervals. As of February 2008 her glycemic control gradually deteriorated and her HbA1C increased from 6.8% to 7.6% in June 2008. Rosiglitazone 4 mg q.d. was added. A month later, because of climacteric complaints, tibolone, at the dose of 2.5 mg q.d., was started. Her mean HDL-c level for the last 5 years was 53.2 mg/dL, being 55 mg/dL the last measurement before rosiglitazone introduction. At that time, her total cholesterol (TC) levels were 182 mg/dL, triglyceride (TG) levels were 156 mg/dL and low-density lipoprotein cholesterol (LDL-C) levels were 84 mg/dL. Nine months later, the patient presented with an HDL-c of 12 mg/dL and an HbA1C of 6.7%. Results were rechecked and confirmed before release. The test was performed again 13 days later and HDL-c was then found depressed to an impressive value of 5 mg/dL, a 90.9% decrease from pre-treatment levels. The other lipid parameters remained unremarkable and the patient reported no change in alcohol intake, dietary habits, body weight, health status and medication use. Both tibolone and rosiglitazone were withdrawn and, 6 weeks later, her HDL-c level had risen from 5 to 52 mg/dL. As her HbA1c levels remained between 6.5%-6.7% after discontinuation of rosiglitazone, she is now being treated with metformin and lifestyle modification only, with no change in hypertension and depression therapies.

DISCUSSION

We describe a patient with type 2 *diabetes mellitus* and dyslipidemia in whom HDL-c levels showed a profound decrease during treatment with rosiglitazone. To our knowledge, there are currently no reports showing such a severe depression in HDL-c levels (90.90% from pre-treatment levels) with rosiglitazone therapy when not combined with fibrates. Despite its detrimental effect on lipid parameters, rosiglitazone was responsible for a reduction of 11.84% in HbA1C levels. The HDL-c levels returned to pretreatment levels after rosiglitazone discontinuation.

The first report of a severe decrease in HDL-c concentrations with TZD therapy was published in 2003 (2), when Ebcioglu and cols. reported two cases of a paradoxical lowering of the HDL-c levels when patients were treated with a combination of a TZD and a fibrate. Both patients were receiving fenofibrate; one patient was prescribed troglitazone, whereas the other was prescribed rosiglitazone. Since then, several reports have been published, involving either rosiglitazone (3,5,6,8) or pioglitazone (4,8) in combination with several fibrates, including bezafibrate (3-5), fenofibrate (3,5,6) and ciprofibrate, but not gemfibrozil.

Of the published reports concerning paradoxical HDL-c lowering while on TZD alone, one reported a patient prescribed rosiglitazone in whom the HDL-c decreased by 78.51% from pre-treatment levels, reducing further when fenofibrate was added (3). The other reports ten patients from different databases in which rosiglitazone, pioglitazone and troglitazone were the prescribed medications (8).

The pattern of prescription responsible for HDL-c reduction as well as the pattern of medication withdrawal responsible for HDL-c recovery has differed among the published reports. There were some patients (5,8) who had already experienced HDL-c reductions while on fibrate alone. Of these, one patient had his HDL-c reduced further when rosiglitazone was added, while the other was already off fibrate when he started taking the TZD responsible for the paradoxical HDL-c drop. Interestingly, our patient was treated with fenofibrate in the past maintaining a stable lipid profile during treatment period.

Another group of patients (3,8) experienced severe HDL-c falls when prescribed a TZD alone one of which had his HDL-c further reduced after a fibrate was introduced. There were also patients (3,5) in whom plasma HDL-c, initially stable when on fibrate treatment, fell when a TZD was added. Similarly, a subset of patients (2,6) was stable when on TZD treatment but had a paradoxical HDL-c lowering when fibrate was started.

The HDL-c recovery was also achieved by different strategies. Some patients had their HDL-c return to baseline values after withdrawing fibrates (2,6,8) while others after withdrawing TZDs (3,5,8), and also there were patients in which switching to pioglitazone (5-6) raised their HDL-c.

The myriad of prescription patterns described above suggests that more than one different mechanism may be involved in this paradoxical HDL-c reduction. Low HDL-c has been established as a cardiovascular risk factor at least since the Framingham study. A recent review by Chirovsky and cols. (9) found that 48 studies sho-

wed some evidence of a statistically significant inverse relationship between HDL-c levels and coronary heart disease (CHD)/cardiovascular disease (CVD) risk. Studies in humans showed that an increase in plasma HDL levels correlated with slower progression of atherosclerotic lesions and possible stabilization of unstable atherosclerotic plaques (10). Also, HDL is capable of stimulating glucose uptake, thus opposing insulin resistance, which may be beneficial in diabetic patients.

Despite this significant amount of evidence, however, higher HDL-c levels may not necessarily be associated with lower cardiovascular risk (11). HDL particles may lose their antiatherogenic capacity and become dysfunctional. Very high plasma HDL-c and very large HDL particles may represent increased CHD risk when levels of apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) remain unaffected (11). In contrast, there are well-identified genetic disorders that present with low HDL-c and increased protection against heart disease. One such example is the variant form of apoA-I known as apoA-I Milano. Carriers of this mutation, characterized by an arginine-173 to cysteine-173 substitution, share a common lipid profile consisting in very low HDL-c and apoA-I levels, elevated triglycerides (TG) and surprisingly low cardiovascular event risk (12). It appears that this protective effect comes from the highly efficient efflux of cholesterol by mutant apoA-I.

Recent findings have suggested that the relationship between HDL and cardiovascular risk is more complex and extends beyond the plasma levels of HDL. Beyond quantity, other properties of HDL are very important for atheroprotection (13). The best documented property (9) is the ability of HDL to promote the unloading of excessive cholesterol from peripheral tissues and its transport to the liver for catabolism, a process which is known as reverse cholesterol transport (RCT) (13). RCT is believed to be one of the main explanations for the HDL-c atheroprotective effect. Through this pathway, HDL prevents the excessive accumulation of cholesterol in the arterial wall (13). Additionally, HDL has antioxidative, anti-inflammatory and antithrombotic effects (13).

The functional properties of circulating HDL-c levels, the kinetics of HDL-c metabolism, and the variable effects of HDL-c subfraction on atherogenesis are ignored by current laboratory measures of HDL-c. There is presently no reliable way to measure the functionality of the HDL particle, and, as a consequence, there is a lack of understanding of which aspect of functionality is most important and why. Further development is necessary to satisfy the urgent need for a reliable and easily applicable assay of HDL-c function (9).

Diabetes increases the risk of cardiovascular events by 2- to 4-fold, and cardiovascular disease accounts for almost two thirds of deaths among diabetic patients (14). Because of this, diabetes is actually considered a "cardiovascular disease equivalent". These considerations taken into account, one must be careful when prescribing antidiabetic drugs that may have any unfavorable effect on any risk factor for myocardial ischemia.

There has been a lot of controversy since the Food and Drug Administration (FDA) released a safety alert concerning a possible increased risk of ischemic heart events in patients prescribed rosiglitazone. This press release was prompted by the results of a meta-analysis by Nissen and Wolsky, in which the authors found a 43% increase in risk for myocardial infarction (MI) with that drug (15). These data caused great concern because the metabolic effects of TZDs were presumed (although not proven) to reduce the risk for ischemic heart disease (IHD). The increased susceptibility to fluid retention and heart failure with rosiglitazone was well known, but the link between rosiglitazone and ischemic heart events was received with great surprise. Until then, rosiglitazone was believed to carry a favorable risk profile. By reducing hepatic and peripheral insulin resistance, TZDs lower plasma glucose and insulin levels and may be associated with improvements in plasma lipoproteins and certain inflammatory cytokines (14). The FDA decided not to withdraw rosiglitazone from the market but included special warnings regarding the potential risk for myocardial ischemia especially in patients taking nitrates and in those for whom rosiglitazone was added to insulin therapy (14).

After Nissen's paper, several publications have tried to clarify this matter, although only one clinical trial has been released since then. Glaxo-Smith-Kline, the manufacturer of rosiglitazone, supported the RECORD Study (16), designed to evaluate cardiovascular outcomes with rosiglitazone compared with metformin or sulfonylurea. In this study, 4,447 patients with type 2 diabetes inadequately controlled with metformin or sulfonylurea were randomized to receive either open-label add-on rosiglitazone or add-on metformin or sulfonylurea. The objective was to assess the non-inferiority of rosiglitazone in reducing hospitalizations or cardiovascular death. The completed trial sho-

wed a hazard ratio (HR) of 1.14 for myocardial infarction and 0.84 for cardiovascular death, both ratios with confidence intervals crossing the neutral line. Overall, the results of the RECORD study were considered inconclusive, mainly because of a lower than expected rate of events and an inadequate evaluation of other disease-modifying therapies such as statins.

At the same time the PROActive Study (17) was released, a trial of cardiovascular endpoints with pioglitazone, the other TZD currently marketed. PROActive showed no statistically significant effect of pioglitazone on the primary composite outcome, although pioglitazone treatment reduced a secondary composite outcome (all-cause mortality, non-fatal MI and stroke).

In 2009, a retrospective cohort study was published using United Kingdom general practice research databases, where investigators evaluated the risk of incident myocardial infarction, congestive heart failure and all-cause mortality associated with oral antidiabetic drugs (18). The TZDs as a group were not associated with risk of myocardial infarct. Among the TZDs, however, rosiglitazone was associated with a higher risk of all-cause mortality compared to pioglitazone. The authors admit that residual confounding factors may have biased the analysis.

Recently the APPROACH Study (19) was released, a trial designed to assess the effect of rosiglitazone on coronary atherosclerosis progression compared to glipizide. The primary endpoint was change in percent atheroma volume in the longest and least angulated epicardial coronary artery that had not undergone intervention in patients with an established cardiovascular history. The results showed no significant difference between groups, and the authors concluded that rosiglitazone did not significantly decrease the primary endpoint, compared to the active comparative drug glipizide. It is interesting to notice that this is a surrogate endpoint study, and that an answer about mortality and other hard endpoints is still lacking.

An interesting study published first online in the British Medical Journal investigated a possible relationship between authors' conflicts of interest and their position on the "rosiglitazone controversy" (20). A systematic review was performed for articles citing and commenting two index publications on the matter (Nissen's meta-analysis and RECORD Study). Interestingly, the results showed a strong association between authors with favorable views on the safety of rosiglitazone and financial conflicts of interest these authors had with the manufacturers of rosiglitazone, pioglitazone and most of the manufacturers of antidiabetic drugs. Authors with unfavorable views on the issue were largely free of financial conflicts of interest.

To date, the issue remains unsolved. Pharmaceutical companies, the government and the medical community should join efforts to make new, specially designed clinical trials focused on TZD use and cardiovascular events. In the meanwhile, clinical judgment and a careful analysis of the currently published data must guide us on the appropriate prescription of rosiglitazone. In our view, considering the general risk profile of our patient (obese, hypertensive, post-menopausal) and the remarkable reduction of HDL-c that occurred, withdrawal of rosiglitazone was the most safe measure to be taken at that moment.

In conclusion, the paradoxical HDL-c reduction that may ensue while patients are treated with a TZD either alone or in combination with a fibrate is a potentially serious adverse effect. When prescribing rosiglitazone, one must consider possible implications on the lipid profile, since the drug's cardiovascular safety profile remains uncertain. Diabetic patients have multiple cardiovascular risk factors at the same time, and these factors must all be considered together. Clinicians should be aware that HDL-c is one of the single strongest predictors of CHD, and, therefore, it needs to be measured in all patients at risk, as in the case of our patient. This report strengthens the recommendation that HDL-c levels should be measured before TZD and/or fibrate therapy is introduced, and that it should be rechecked regularly thereafter.

Acknowledgements: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. Rosiglitazone short-term monotherapy lowers fasting and postprandial glucose in patients with type II diabetes. Diabetologia. 2000;43(3):278-84.
2. Ebcioglu Z, Morgan J, Carey C, Capuzzi D. Paradoxical lowering of high-density lipoprotein cholesterol level in 2 patients receiving fenofibrate and a thiazolidinedione. Ann Intern Med. 2003;139(9):W80.
3. Sarker A, Semple RK, Dinneen SF, O'Rahilly S, Martin SC. Severe hypo-alpha-lipoproteinemia during treatment with rosiglitazone. Diabetes Care. 2004;27(11):2577-80.

4. Senba H, Kawano M, Kawakami M. Severe decrease in serum HDL-cholesterol during combination therapy of bezafibrate and pioglitazone. J Atheroscler Thromb. 2006;13(5):263-4.
5. Shetty C, Balasubramani M, Capps N, Milles J, Ramachandran S. Paradoxical HDL-C reduction during rosiglitazone and fibrate treatment. Diabet Med. 2007;24(1):94-7.
6. Venero CV, Thompson PD, Fernandez AB. Reduced high-density lipoprotein cholesterol in patients receiving rosiglitazone and fenofibrate. Am J Med. 2008;121(10):e3-4.
7. Mymin D, Dembinski T, Friesen MH. Iatrogenic severe depression of high-density lipoprotein cholesterol. J Clin Pharmacol. 2009;49(7):865-71.
8. Savage RL, Kiuru A. Thiazolidinediones and lowered HDL cholesterol. Diabetes Care. 2005;28(9):2329-30.
9. Chirovsky DR, Fedirko V, Cui Y, Sazonov V, Barter P. Prospective studies on the relationship between high-density lipoprotein cholesterol and cardiovascular risk: a systematic review. Eur J Cardiovasc Prev Rehabil. 2009;16(4):404-23.
10. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79(1):8-15.
11. van der Steeg WA, Holme I, Boekholdt SM, Larsen ML, Lindahl C, Stroes ES, et al. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. J Am Coll Cardiol. 2008;51(6):634-42.
12. Franceschini G, Sirtori CR, Capurso A, 2nd, Weisgraber KH, Mahley RW. A-IMilano apoprotein. Decreased high density lipoprotein cholesterol levels with significant lipoprotein modifications and without clinical atherosclerosis in an Italian family. J Clin Invest. 1980;66(5):892-900.
13. Tsompanidi EM, Brinkmeier MS, Fotiadou EH, Giakoumi SM, Kypreos KE. HDL biogenesis and functions: role of HDL quality and quantity in atherosclerosis. Atherosclerosis. 2010;208(1):3-9.
14. Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione Drugs and Cardiovascular Risks. A Science Advisory from the American Heart Association and American College of Cardiology Foundation. Circulation. 2010;121:1868-77.
15. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457-71.
16. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-35.
17. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-89.
18. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731.
19. Gerstein HC, Ratner RE, Cannon CP, Serruys PW, Garcia-Garcia HM, van Es GA, et al. Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. Circulation. 2010;121(10):1176-87.
20. Wang AT, McCoy CP, Murad MH, Montori VM. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. BMJ. 2010;340:c1344.