NDT Plus (2009) 2: 392–394
doi: 10.1093/ndtplus/sfp058
Advance Access publication 18 May 2009

NDT PLUS
Nephrology Dialysis Transplantation

Case Report

Worsening of hyperglycemia due to atorvastatin in a renal transplant patient

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Abstract

New-onset diabetes mellitus post-renal transplantation [post-transplantation diabetes mellitus (PTDM)] and impaired glucose tolerance are among the most serious adverse metabolic disturbances of kidney transplants. We report a renal transplant patient whose mild post-transplant hyperglycaemia considerably worsened upon substituting atorvastatin for pravastatin. The patient was a 58-years-old Caucasian man who underwent living, non-related kidney transplantation. The mean blood sugar level (BSL) following transplantation was 113.8 mg/dl. In an attempt to reduce LDL cholesterol, atorvastatin 40 mg/day was substituted for pravastatin. Soon after commencement of atorvastatin, polydipsia and polyuria appeared. Both fasting and 2-h post-prandial BSL values increased, while there was no change in the patient's medications, dietary habits and renal function. Upon reverting back to pravastatin, BSL promptly declined to the previously mentioned baseline values. Since PTDM is a strong independent factor of graft failure, cardiovascular events and mortality, physicians should be made aware of this possible adverse effect of atorvastatin on glucose tolerance.

Keywords: atorvastatin; kidney transplantation; post-transplantation diabetes mellitus; statins

Introduction

New-onset diabetes mellitus post-renal transplantation [post-transplantation diabetes mellitus (PTDM)] and impaired glucose tolerance are among the most serious adverse metabolic disturbances of kidney transplants [1]. The cumulative incidence in US Medicare beneficiaries with kidney transplants between 1996 and 2000 was 9.1, 16.0 and 24.0% at 3, 12 and 36 months post-transplant, respectively [1]. PTDM is a strong independent factor of graft failure, cardiovascular events and mortality [1]. Risk factors for PTDM include age, race (African American, Hispanic), male donor, increased HLA mismatches, obesity and tacrolimus [1].

HMG-CoA reductase inhibitors are frequently administered to kidney transplant patients. Although the lipid-lowering effect of statins is well recognized, their influence on glucose tolerance is controversial. In the WOSCOPS (West of Scotland Coronary Prevention Study), pravastatin therapy resulted in a 30% hazard reduction of becoming diabetic [2]. In contrast, a marked deterioration of glycaemic control has been reported in some patients (in particular, Japanese) treated with atorvastatin [3,4].

We describe a renal transplant patient whose mild post-transplant hyperglycaemia considerably worsened upon substituting atorvastatin for pravastatin and present a review of the pertinent literature.

Case description

A 57-year-old Caucasian man developed end-stage renal disease (ESRD) due to membranous nephropathy that had been diagnosed in 1995. A relevant past history included bronchial asthma (mild, intermittent type), well-controlled hypertension (120/70 mmHg) and hypercholesterolaemia for which he was being treated with pravastatin 40 mg od. In December 2006, he was commenced on continuous ambulatory peritoneal dialysis (CAPD). Fasting blood sugar levels (BSL) prior to the beginning of dialytic therapy had always been <100 mg/dl. With the advent of CAPD, BSL increased to a mean of 110.9 mg/dl (range 88–144), calculated from routine monthly blood tests. No hypoglycaemic drugs were given. In December 2007, the patient received a living, non-related kidney transplant (female donor). Serum creatinine on the third post-operative day was found to be 1.2 mg/dl. Immunosuppressive treatment included prednisone, tacrolimus and mycophenolate. The mean BSL following transplantation was 113.8 mg/dl with an HbA1C level of 6.2%. Total and LDL cholesterol averaged, respectively, 205 and 119 mg/dl. In an attempt to reduce LDL cholesterol to <100 mg/dl, atorvastatin 40 mg/day was substituted for pravastatin. A day after beginning atorvastatin,

the patient noticed increased thirst and polyuria. For the following week, he self-monitored both fasting and 2-h post-prandial BSL. Values recorded averaged 140 and 170 (140–230) mg/dl, respectively. During the period of atorvastatin administration, there was no change in the patient's medications, dietary habits and renal function. Tacrolimus levels for the week of atorvastatin treatment and 1 week thereafter increased from a mean of 7.0 (pre-atorvastatin) to 9.9 ng/ml after which they declined to the previous mean. Upon reverting back to pravastatin, BSL promptly declined to the above-mentioned baseline values.

Discussion

Given the known negative prognostic impact of PTDM, prevention is of utmost importance. Of the risk factors for PTDM outlined above, only two are potentially modifiable: obesity and tacrolimus. However, obesity is notoriously difficult to control and tacrolimus is incorporated into most immunosuppressive regimens. Due to their lipid-lowering effect, statins are commonly included among the medications administered to kidney transplant patients. Beyond their ability to decrease serum cholesterol, statins have been attributed a multitude of pleiotropic effects such as reduced expression of adhesion molecules, inhibition of the proliferation and migration of vascular smooth muscle cells [5], anti-thrombotic and anti-inflammatory properties [6]. Thus, specific to the transplant population, they have been shown to favourably influence cardiac events [7], chronic and acute rejection [8] and be associated with improved bone density [9] and patient survival [10]. Their effect on glucose tolerance and/or the development of new-onset PTDM remains an open question.

In a retrospective study on renal transplant patients, Prasad *et al*. found a reduced incidence of PTDM with statin therapy, independent of the lipid-lowering effect of statins [11]. Of 49 patients who developed new-onset diabetes events during the follow-up (overall incidence rate 16%), there were 9 in the statin group versus 40 in the non-statin group (incidence rates of 7 and 22%, respectively). Of note, the statin preparations used were atorvastatin (85%), pravastatin (7%), simvastatin (4%) and fluvastatin (4%). In a non-transplant population, the only study that showed a possible preventive effect on new-onset diabetes mellitus was a sub-analysis of WOSCOPS that used pravastatin [2]. In the Collaborative Atorvastatin Diabetes Study (CARDS), designed to examine the ability of atrovastatin to suppress the development of cardiovascular events in patients with type 2 diabetes mellitus, the mean follow-up survey of 4 years revealed an increase in HbA1c in the atrovastatin group (7.87–8.3%), a change that appeared to be greater than that in the placebo group (7.81 to 8.1%), although statistically insignificant. Moreover, after 4 years of follow-up, the number of patients switched to insulin therapy or insulin plus hypoglycaemic drugs was higher in the atrovastatin group versus the placebo group [12]. Sabatine *et al*., in a sub-study of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI-22) trial, among patients with pre-existing diabetes, reported that HbA1c increased by $0.30 \pm 0.56\%$ in atorvastatin-treated patients and by $0.12 \pm 1.41\%$ in patients treated by pravastatin ($P < 0.0001$) [13]. In the much publicized recently published JUPITER study in non-diabetic patients, the rosuvastatin group had significantly higher HbA1c levels and physician-reported incident diabetes (3.0% versus 2.4% in the placebo group, $P < 0.01$) [14]. Sporadic case reports originating mainly from Japan have been described in which the administration of atorvastatin resulted in a marked deterioration of glycaemic control in type 2 diabetics [3,4] or in new-onset diabetes in a patient with no prior history of hyperglycaemia [15]. The above data seem to implicate statin therapy and, in particular, atorvastatin, in the induction of impaired glucose tolerance. Whether this is a class effect or is preferentially seen with some types of statin, notably atorvastatin, is, as yet, unclear. To examine this issue, Takano *et al*. retrospectively compared the effect of atorvastatin and pravastatin on glucose tolerance in type 2 diabetics, from the onset of administration to 3 months thereafter [16]. BSL levels significantly increased from 147 ± 50 to 177 ± 70 mg/dl in the atorvastatin group while remaining unchanged in the pravastatin group (141 ± 38 to 141 ± 32 mg/dl). Accordingly, HbA1c increased from 6.8 ± 0.9 to 7.2 ± 1.1 in the atorvastatin group versus 6.9 ± 0.9 to $6.9 \pm 1.0\%$ in the pravastatin group. These results suggest a predisposition to a deterioration of glycaemic control in type 2 diabetic patients treated with atorvastatin. In a similar but prospective study using the oral glucose tolerance test (OGTT), Mita *et al*. found that HbA_{1c} and 2-h glucose levels during OGTT in the pravastatin treatment were significantly lower than those in the atorvastatin treatment [17]. In addition, the disposition index (product of a validated insulin secretion parameter and sensitivity) was significantly higher after pravastatin treatment. These authors concluded that compared to atorvastatin, pravastatin has a favourable effect on pancreatic beta-cell function.

The mechanism by which atorvastatin might adversely affect glycaemic control remains unknown. Published experimental data suggest that statins might deteriorate glucose tolerance via inhibition of insulin secretion from the pancreatic β-cell and a reduction of glucose uptake. Thus, using the rat islet β-cell, Yada *et al*. showed that simvastatin dose-dependently inhibited glucose-induced cytosolic calcium signalling and insulin secretion due to the blockade of L-type calcium channels [18]. Such inhibition was not observed with pravastatin. Another study, in which adipose cells were pretreated with lovastatin to observe glucose uptake after the addition of insulin, reported that a decrease in GLUT4 lowered glucose uptake into the cell and that the addition of mevalonic acid recovered the uptake [19]. Of note is the fact that the unfavourable effects on glucose metabolism of statins, both *in vivo* and *in vitro*, have been limited to the lipophilic statins. These include lovastatin, simvastatin, pitavastatin and atorvastatin whereas pravastatin is hydrophilic. Lipophilic statins may be incorporated into various organs such as the pancreas, adipose tissue and muscle, while hydrophilic statins are incorporated mainly into the liver. This differential distribution coupled with the specific target organ pleitropic actions may offer, at least a partial explanation for the adverse effect on glucose tolerance of atorvastatin.

In the case presented, a marked worsening of hyperglycaemia was seen upon substituting atorvastatin for pravastatin on a 1:1 basis. We are aware that the dose of atorvastatin employed, namely 40 mg/day, is above the one that was recommended in transplanted patients. This dose was decided upon in an attempt to reduce the patient's LDL cholesterol to <100 mg/dl, a target that was not achieved with an equivalent dose of pravastatin. The recommendation to decrease statin dose in transplanted patients stems from the known pharmacokinetic interaction of these drugs with the calcineurin inhibitors (CIN) as both are metabolized by the cytochrome P450 pathway. Statins differ, however, in their pharmacokinetic properties. Whereas atorvastatin is metabolized by the CYP3A4 isoenzyme, pravastatin does so only to a small extent (most of the drug is excreted unchanged), and fluvastatin is a CYP2C9 substrate. Consequently, most transplant physicians prefer to use the latter two drugs for the treatment of hypercholesterolaemia in transplanted patients. Pravastatin is actually the only statin approved by the US Food and Drug Administration for combination therapy with cyclosporin. The interaction between statins and CIN has the potential of bilaterally affecting the levels of both drugs. Thus, cyclosporin-treated patients show several folds higher systemic exposure of all statins. The opposite effect is somewhat controversial; some studies report a decrease in systemic exposure of cyclosporin whereas others demonstrate up to a 10% increase in concentration [20]. Similar data on tacrolimus are much less available. With regard to our patient, atorvastatin did seemingly increase his tacrolimus levels. This coupled with the high dose of atorvastatin may have been contributing factors to the development of hyperglycaemia. However, as far as dose is concerned, it must be noted that in the studies of Takano [16] and Mita [17] quoted above, the atorvastatin dose employed was 10 mg daily. Furthermore, our patient's BSL returned to baseline on reverting back to pravastatin at an equivalent dose of 40 mg/day. Although a temporal coincidence cannot be entirely ruled out, given the available data, it does appear that atorvastatin might have played, at least, a partial role in our patient's hyperglycaemia.

In this predisposed kidney transplant population, atorvastatin (or other lipophilic statins) should be considered as an additional modifiable risk factor for the development of PTDM. The physician is thus faced with the dilemma of choosing between an optimal lipid profile and an impairment of glucose metabolism. Obviously, one should aspire to obtain the best possible control of both hyperlipidaemia and hyperglycaemia. There are no available data, nor are there likely to be, comparing the adverse prognostic implications of the two in the renal transplant patient. This is particularly true in view of the fact that they often coexist. As stated above, the use of hydrophilic rather than lipophilic statins should perhaps be encouraged or preferred. An alternative option is to use the lowest dose of statin in combination with a second-line lipid-lowering agent such as ezetimibe. In any case, considering the frequent use of statins in this population, physicians should be made aware of the potential adverse effect of these drugs on glucose homeostasis.

Conflict of interest statement. None declared.

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Received for publication: 19.2.09; Accepted in revised form: 27.4.09