Treatment With Rosuvastatin for Severe Dyslipidemia in Patients With Schizophrenia and Schizoaffective Disorder

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Background: Mortality rates in patients with schizophrenia are double compared to those in the general population, with cardiovascular disease causing 50% of the excess. Lowering low-density lipoprotein (LDL) cholesterol is recognized as a primary target for the prevention of cardiovascular mortality according to the National Cholesterol Education Program–Adult Treatment Panel III. Use of lipid-lowering drugs such as statins is recommended when lifestyle changes are not sufficient to reach the LDL goal. The efficacy and safety of rosuvastatin treatment were evaluated in schizophrenic patients.

Method: 100 schizophrenic patients with severe dyslipidemia were identified. All were treated with antipsychotics. Fifty-two patients were treated with rosuvastatin and compared with 48 who did not receive statin treatment. All patients were screened for cardiovascular risk factors and examined at baseline. The effects of lipid-lowering medication on lipid profile, glucose homeostasis, and components of metabolic syndrome were evaluated at 3-month follow-up. The study began in 2003, and all data available until December 2005 are reported.

Results: After 3 months of statin therapy, a significant decrease in triglycerides, total cholesterol, LDL cholesterol, and non–high-density lipoprotein (non-HDL) cholesterol and in associated ratios (LDL/HDL, total cholesterol/HDL) was observed. The difference was highly significant compared to patients not receiving statin treatment. No significant changes occurred in HDL cholesterol, body mass index and waist circumference, or glucose homeostasis. The only component of metabolic syndrome affected by statin therapy was the serum triglyceride level.

Conclusion: Rosuvastatin proved effective in the management of dyslipidemia in patients with schizophrenia treated with antipsychotics. More complex treatment may be required for associated metabolic disturbances.

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Cardiovascular disease (CVD) is recognized as a leading cause of global mortality and is responsible for the majority of premature deaths in European countries. It is also responsible for rising costs of health care and disability.

Research outcomes, based on animal studies, laboratory investigations, epidemiology, and studies of genetic forms of hypercholesterolemia, indicate that elevated low-density lipoprotein (LDL) cholesterol is a major cause of coronary heart disease, and recent clinical trials suggest that LDL-lowering therapy reduces risk for CVD and can slow progression of atherosclerosis.[1,2] On the basis of this knowledge, both the National Cholesterol Educational Program–Adult Treatment Panel III (ATP-III)[3] and the Joint Task Force of European and Other Societies[4] established guidelines to reduce risk of coronary artery disease. Because CVD is due to a combination of several risk factors and has a multifactorial nature, the European Task Force developed the SCORE risk assessment system, based on a large dataset of prospective studies, which predicts 10-year probability of developing a fatal cardiovascular event.[5,6] SCORE integrates the following risk factors: gender, age, smoking, systolic blood pressure, and

either total cholesterol or the cholesterol/high-density lipoprotein (HDL) ratio. Recommendations for therapeutic interventions include lifestyle changes, smoking cessation, and either nonpharmacologic or pharmacologic correction of high blood pressure and hyperlipidemia.[3,4,6]

The metabolic syndrome is another independent risk factor for CVD that is more and more prevalent and plays an increasing role in atherosclerosis.[7] According to results from large observational as well as prospective trials, the metabolic syndrome appears to have higher prevalence in patients with schizophrenia.[8–12] Today, the most commonly used definitions for the metabolic syndrome are the ATP-III[3] and the adapted ATP-III criteria (ATP-III A).[13] The ATP-III criteria recognized the association of the factors of metabolic syndrome and both proinflammatory and prothrombotic states, but these are not required for the diagnosis of the syndrome.[14] The International Diabetes Federation recently produced a reviewed consensus definition of the metabolic syndrome[15–17] using waist circumference as an obligatory criterion and applying more stringent and ethnicity-specific criteria.

Lifestyle has a strong influence on all components of metabolic syndrome.[18] Lifestyle changes leading to body weight reduction and increase in physical activity should therefore be considered as the first steps in treatment.[6] With respect to pharmacotherapy, rosuvastatin showed a benefit in the management of the metabolic syndrome.[2,19]

Among the drugs studied in association with CVD, statins have proven to be most effective for the prevention of CVD morbidity and mortality and are recommended when lifestyle changes are not sufficient to manage hypercholesterolemia. Statins are lipid-lowering drugs that mainly reduce the LDL cholesterol subfraction but can also achieve a 22% to 45% reduction in triglyceride levels and a minor increase (5%–10%) in HDL cholesterol levels.[1,20–22] They inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, with stimulation of LDL receptor expression on hepatocytes and enhanced removal of LDL cholesterol from the circulation as a consequence. The statins differ in their absorption, plasma protein binding, excretion, solubility, and dose-related efficacy in reducing LDL cholesterol, with rosuvastatin showing the highest efficacy in comparative studies.[1,20–22] The high potency of rosuvastatin relative to other statins is probably due to its low lipophilicity and high hepatocyte selectivity. Additionally, recent clinical trial outcomes suggest that rosuvastatin is also effective in treatment of metabolic syndrome and carries immunomodulatory properties independent of LDL cholesterol.[19,23–25] A high dose of rosuvastatin (40 mg/day) has recently been shown, using intravascular ultrasound, to induce a significant regression of coronary atherosclerosis.[26]

Risk for CVD and overall mortality due to CVD is elevated in patients suffering from schizophrenia compared to the general population, with mortality rates in this population being 2 times higher than in the general population[27–29] and CVD being responsible for as much as 50% of the excess mortality.[30] These data are in accordance with the results from large observational as well as prospective trials showing higher prevalence of metabolic syndrome, diabetes mellitus, and dyslipidemia in patients with schizophrenia, all conditions predisposing to cardiovascular morbidity and mortality.[8–12] With regard to treatment in this specific population, several factors must be taken into account. Patients with schizophrenia appear to have unhealthy lifestyles and are considered to be resistant to lifestyle interventions due to negative symptoms, lack of insight, and lack of adherence.[31–33] In most cases, patients with schizophrenia are treated with antipsychotic drugs that themselves can cause or worsen lipid and glucose abnormalities as well as the metabolic syndrome.[10–12,34–36] In addition, these drugs can increase the risk of pharmacokinetic interactions when administered in combination with other drugs.

The efficacy of statins in non–psychiatrically ill patients is well established, but there are no data on the use and the efficacy of statins in patients suffering from schizophrenia. Whether statins are effective in dyslipidemia that is partly due to the metabolic effects of antipsychotic medication also needs to be evaluated. To our knowledge, this is the first study evaluating the effects of treatment of severe hyperlipidemia with a high-potency statin, rosuvastatin, in patients with schizophrenia compared to a control group with dyslipidemia not receiving statin treatment.

METHOD

All consecutive patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, both outpatients and inpatients, of a university psychiatric hospital and affiliate services were asked to participate in an extensive screening and prospective follow-up study of their metabolic parameters. The prospective inclusions started in November 2003, and all data available until December 2005 are reported. At baseline, patients received a full fasting laboratory screening, clinical measurements, and an electrocardiogram. A 75-g glucose load oral glucose tolerance test (OGTT) was performed in all patients. Patients were initiated on an overnight fast and were monitored during the OGTT. All laboratory analyses were performed in the same laboratory.

The study sample consisted of 100 patients with severe dyslipidemia meeting SCORE criteria[6] who were continued on treatment with the same antipsychotic drug. In 52 patients, treatment with rosuvastatin was started (statin group). They were compared with 48 patients in whom no treatment apart from dietary advice was given (control group; advice to start a statin was given to the treating psychiatrist, but no treatment was started).

Table 1. Demographic and Clinical Data at Baseline

Characteristic	Statin (N = 52)	Control (N = 48)	p
Age, mean (SD), y	39.4 (± 10.1)	37.5 (± 10.1)	NS
Sex, % (N)			NS
Male	84.6 (44)	70.8 (34)	
Female	15.4 (8)	29.2 (14)	
GAF score, mean (SD)	58.8 (± 9.5)	61.8 (± 9.7)	NS
No. of admissions, mean (SD)	5.9 (± 4.6)	5.3 (± 4.1)	NS
Duration of illness, mean (SD), y	14.2 (± 9.8)	11.9 (± 9.3)	NS
No. of medications, mean (SD)	3.4 (± 1.4)	3.1 (± 1.0)	NS
BMI, mean (SD)	28.2 (± 4.7)	27.2 (± 4.9)	NS
BMI segmentation, % (N)			NS
Normal	26.9 (14)	43.7 (21)	
Overweight	46.2 (24)	27.1 (13)	
Obese	26.9 (14)	29.2 (14)	
Waist circumference, mean (SD), cm	103.2 (± 13.8)	98.0 (± 12.0)	NS
Weight, mean (SD), kg	86.8 (± 16.8)	81.0 (± 14.0)	NS
Metabolic syndrome criteria met, % (N)			
ATP-III	55.8 (29)	41.7 (20)	NS
ATP-III A	55.8 (29)	45.8 (22)	NS
IDF	59.6 (31)	56.2 (27)	NS
Family history, % (N)			
Cardiovascular disease	53.8 (28)	54.2 (26)	NS
Diabetes	32.7 (17)	33.3 (16)	NS
Lipid disorder	36.5 (19)	45.8 (22)	NS

Abbreviations: ATP-III = National Cholesterol Education Program–Adult Treatment Panel III, ATP-III A = National Cholesterol Education Program–Adult Treatment Panel III adapted criteria, BMI = body mass index, GAF = Global Assessment of Functioning, IDF = International Diabetes Federation, NS = nonsignificant.

The patients were evaluated with a full metabolic screening: 3 months prior to the start of statin treatment, at baseline when statin treatment was started, and 3 months after statin treatment was initiated for the statin group and at baseline and 3 months for the control group.

The diagnosis of hyperlipidemia, evaluation of the CVD risk, and subsequent pharmacotherapy were assessed according to European guidelines developed by the Third Joint Task Force, using the SCORE chart for low-risk countries.[6] The presence of the metabolic syndrome was assessed using the ATP-III A criteria.[13] This is a recent commentary on the original ATP-III criteria that proposes to use a fasting glucose limit of 100 instead of 110 mg/dL and to include drug treatment for hypertension, hyperlipidemia, and hyperglycemia as criteria for the metabolic syndrome. For the diagnosis of diabetes and prediabetic abnormalities, we used the criteria of the American Diabetes Association (impaired fasting glucose [glucose ≥ 100 mg/dL] and impaired glucose tolerance [glucose ≥ 140 mg/dL at 2 hours in the OGTT]).[37]

Descriptive statistics were computed for the basic demographic and clinical variables as well as for the variables relevant for the evaluation of metabolic abnormalities. The influence of statin therapy on continuous dependent variables was calculated by means of an analysis of variance with repeated measures. The association between categorical variables was evaluated by a χ^2 test.

The study was approved by an ethical committee, and all patients gave written informed consent.

RESULTS

One hundred patients participated in the study. Seventy-eight percent of patients were male. Ninety-eight percent were white and Belgian natives. The mean age of the patients was 38.5 years (SD = 10.1), and the mean duration of illness was 13.1 years (SD = 9.5). Their mean Global Assessment of Functioning score was 60.3 (SD = 9.6). The studied population consisted of 80% patients with schizophrenia and 20% with schizoaffective disorder.

There was no significant difference between the patients in the experimental group compared with the control group on any demographic variable, medication regimen, or percentage of patients with abnormal lipid parameters at baseline (Table 1 and Table 2).

All patients were treated with antipsychotic medication. Duration of treatment with the same antipsychotic was longer than 6 months in 69% of patients; 28% were treated for less than 3 months. Ninety-two percent of patients were treated with second-generation antipsychotics, and 18% were treated with first-generation antipsychotics. At baseline, the majority of patients were treated with only 1 antipsychotic (84%, of which 92.8% were second-generation and 7.2% were first-generation antipsychotics). The remaining patients took a combination of 2 antipsychotics. The overall distribution of second-generation antipsychotics at baseline was as follows: 6% amisulpride, 24% clozapine, 30% olanzapine, 14% quetiapine, and 26% risperidone.

Antipsychotics were combined with anticholinergics (20%), antidepressants (48%), benzodiazepines (40%), and mood stabilizers (19%). Forty-one percent of patients were using somatic medication at the time of screening. At baseline, 4% of patients were being treated for diabetes, and 20% of patients were being treated for hypertension.

All experimental patients were started on rosuvastatin treatment at baseline (all remained on a 10-mg daily dose during the follow-up). Both groups received dietary advice.

Fifty-one percent of patients fulfilled the criteria for metabolic syndrome at baseline. There was no significant difference between the experimental group and controls.

The statin group was evaluated on lipid parameters 3 months prior to baseline. All lipid values worsened during this period before statin treatment. Changes were significant for total cholesterol ($p < .0020$), LDL cholesterol ($p < .0020$), non-HDL cholesterol ($p < .0020$), triglycerides ($p < .0434$), and total cholesterol/HDL ($p < .0123$) (Table 3). These changes are similar to the deterioration of lipid parameters observed in the control group during

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Table 2. Frequency of Abnormal Lipid Values at Baseline and Follow-Up in Patients With Hyperlipidemia

Measure	Statin (N = 52), (%) N	Control (N = 48), (%) N	p
Baseline			
Elevated total cholesterol (≥ 190 mg/dL)	98.1 (51)	100 (48)	NS
Elevated triglycerides (≥ 150 mg/dL)	69.2 (36)	79.2 (38)	NS
Low HDL (men, < 40 mg/dL; women, < 50 mg/dL)	38.5 (20)	39.6 (19)	NS
Elevated LDL (≥ 115 mg/dL)	90.4 (47)	85.4 (41)	NS
Total cholesterol/HDL (≥ 4)	88.5 (46)	83.3 (40)	NS
LDL/HDL (≥ 3)	78.8 (41)	62.5 (30)	NS
3-Month follow-up			
Elevated total cholesterol (≥ 190 mg/dL)	15.4 (8)	100 (48)	.0001
Elevated triglycerides (≥ 150 mg/dL)	34.6 (18)	91.7 (44)	.0001
Low HDL (men, < 40 mg/dL; women, < 50 mg/dL)	38.5 (20)	45.8 (22)	NS
Elevated LDL (≥ 115 mg/dL)	17.3 (9)	81.3 (39)	.0001
Elevated total cholesterol/HDL (≥ 4)	34.6 (18)	89.6 (43)	.0001
Elevated LDL/HDL (≥ 3)	19.2 (10)	64.6 (31)	.0001

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = nonsignificant.

Table 3. Changes in Lipid Levels in the Rosuvastatin Group

Measure	3 Months Prior to Baseline, Mean (SD)	Baseline, Mean (SD)	3-Month Follow-Up, Mean (SD)	p[a]
Total cholesterol, mg/dL	250.0 (± 50.5)	263.6 (± 59.3)	163.1 (± 38.4)	.0001
Triglycerides, mg/dL	239.6 (± 222.7)	273.9 (± 260.5)	164.0 (± 129.3)	.0011
HDL, mg/dL	46.7 (± 14.0)	43.8 (± 12.4)	45.7 (± 14.0)	NS
LDL, mg/dL	160.9 (± 32.9)	164.3 (± 36.2)	88.9 (± 2.9)	.0001
Non-HDL cholesterol, mg/dL	204.4 (± 53.6)	219.8 (± 63.4)	117.4 (± 41.8)	.0001
LDL/HDL	3.9 (± 1.6)	4.1 (± 1.6)	2.2 (± 1.0)	.0001
Total cholesterol/HDL	6.0 (± 2.3)	6.7 (± 3.3)	4.0 (± 1.9)	.0001

[a]Baseline vs. 3 months.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = nonsignificant.

the 3-month follow-up without treatment. In the controls, there was a significant worsening of total cholesterol ($p < .0013$), non-HDL cholesterol ($p < .0001$), triglycerides ($p < .0002$), and total cholesterol/HDL ($p < .0013$) over the 3-month follow-up period.

At baseline (all patients, N = 100), 99% of patients had elevated total cholesterol levels (≥ 190 mg/dL), 88% had high LDL levels (≥ 115 mg/dL), and 39% had low HDL levels (men, < 40 mg/dL; women, < 50 mg/dL), with corresponding elevation of total cholesterol/HDL in 86% and LDL/HDL ratios in 71%. Seventy-four percent of patients had hypertriglyceridemia (≥ 150 mg/dL) (Table 2). The frequency of abnormal values increased over time in controls and significantly decreased in patients treated with a statin. The difference between patients in the statin and control groups was highly significant for all values except HDL cholesterol (Table 2).

After 3 months of statin therapy, there was a significant decrease in total cholesterol levels, triglyceride levels, and LDL cholesterol levels, as well as non-HDL cholesterol and total cholesterol/HDL and LDL/HDL ratios (Table 3). There was a nonsignificant increase in HDL cholesterol.

There was a highly significant difference between the statin and the control groups on all lipid parameters evaluated, except HDL (all $p < .0001$, Figure 1). In the control group, lipid parameters worsened during the follow-up. Figure 2 shows the absolute and percentage change from baseline in the statin group. The changes from baseline were most pronounced in LDL (45.9%), followed by triglycerides (41.1%) and total cholesterol (38.1%).

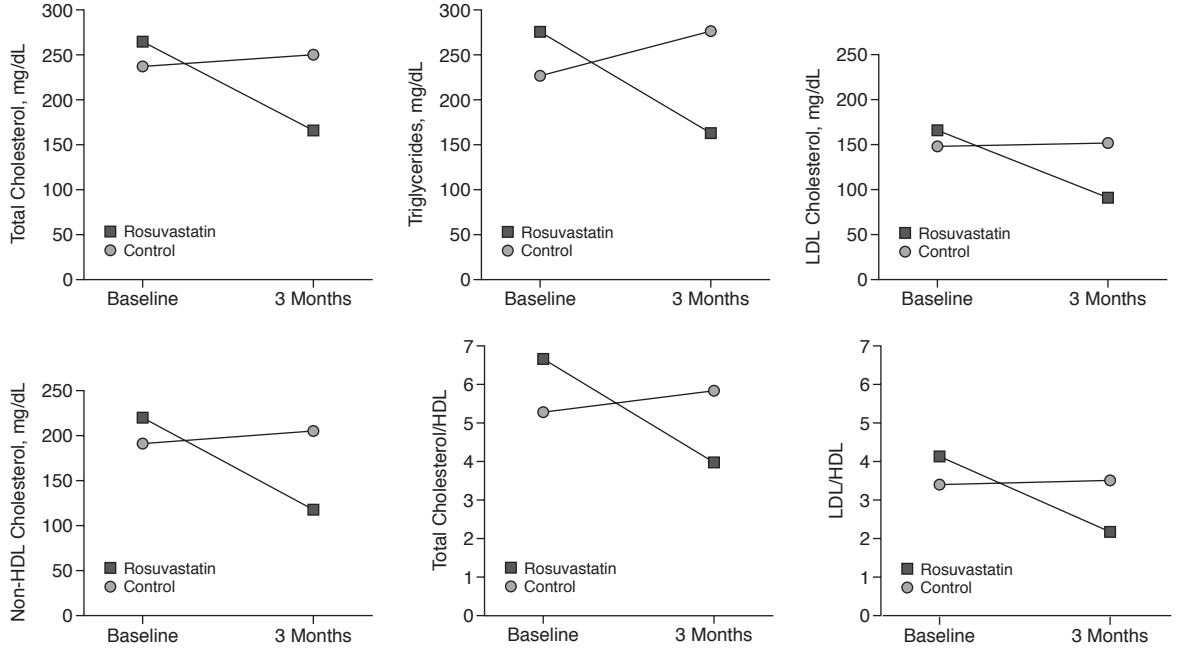
Statin therapy had no effect on weight, waist circumference, or body mass index (BMI). In both groups, statins and controls, there was a nonsignificant increase in all measures.

Rosuvastatin treatment had no significant effect on fasting glucose levels or any other parameter evaluated in the OGTT (Table 4). No significant between-group effect was observed.

In the statin group, there was a nonsignificant difference in the prevalence of metabolic syndrome between baseline and 3-month follow-up (55.8% vs. 42.3%); the only component of the syndrome that changed significantly was triglyceride level (Table 5). After statin treatment, 7 patients (13.5%) no longer met criteria for metabolic syndrome. In the control group, 5 additional patients (10.4%) developed metabolic syndrome.

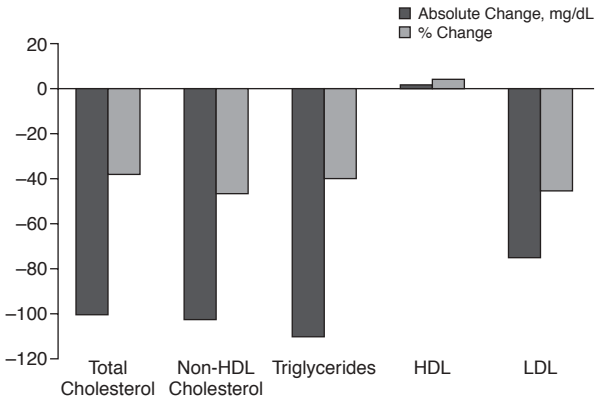
Statin treatment was well tolerated. There were no subjective complaints and there was no significant rise in creatine kinase (CK; mean change from baseline = 26 U/L) or liver enzymes at 3-month follow-up. Statin

Figure 1. Effects of Rosuvastatin: Comparison With Control Subjects



Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Figure 2. Absolute Change and Percentage Change in Lipid Parameters With Rosuvastatin From Baseline to 3 Months



Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 4. Effect of Rosuvastatin on Glucose and Insulin Homeostasis in an Oral Glucose Tolerance Test

Measure	Baseline, Mean (SD)	3-Month Follow-Up, Mean (SD)	p
Glucose			
Fasting glucose, mg/dL	99.4 (± 31.5)	97.6 (± 27.5)	NS
Glucose 30 min, mg/dL	157.3 (± 42.2)	160.4 (± 40.9)	NS
Glucose 60 min, mg/dL	159.2 (± 55.5)	148.4 (± 51.2)	NS
Glucose 120 min, mg/dL	102.6 (± 42.0)	96.6 (± 33.3)	NS
Glucose AUC	16.3 (± 3.9)	15.8 (± 4.1)	NS
Insulin			
Fasting insulin, μIU/mL	12.4 (± 7.2)	13.5 (± 10.5)	NS
Insulin 30 min, μIU/mL	88.1 (± 57.7)	86.7 (± 54.7)	NS
Insulin 60 min, μIU/mL	102.3 (± 58.0)	98.6 (± 65.7)	NS
Insulin 120 min, μIU/mL	53.6 (± 55.1)	46.9 (± 43.6)	NS
Insulin AUC	9.0 (± 5.8)	8.6 (± 6.3)	NS
HOMA-IR	3.2 (± 1.7)	3.1 (± 2.4)	NS

Abbreviations: AUC = area under the curve, HOMA-IR = homeostasis model assessment–insulin resistance index, NS = nonsignificant.

treatment was stopped in 1 patient who developed abnormal liver enzyme levels and high CK levels (769 U/L) after 5 months of treatment with rosuvastatin.

DISCUSSION

To our knowledge, this is the first study directly addressing treatment with rosuvastatin of hyperlipidemia as pharmacologic treatment and for prevention of cardiovascular disease in patients with schizophrenia compared to a control group.

Treatment with rosuvastatin resulted in a significant decrease in total cholesterol levels, triglyceride levels, and LDL cholesterol levels, as well as non-HDL cholesterol and CHOL/HDL and LDL/HDL ratios. The differences between this group and the control group not receiving statin treatment were highly significant. All lipid parameters worsened in the control group.

Table 5. Effect of Rosuvastatin on Metabolic Syndrome Prevalence and Individual Criteria

Measure	Baseline, % (N)	3-Month Follow-Up, % (N)	p
ATP-III A criteria fulfilled	55.8 (29)	42.3 (22)	NS
Increased waist circumference (men, > 102 cm; women, > 88 cm)	57.7 (30)	59.6 (31)	NS
Elevated blood pressure (≥ 130/85 mm Hg)	65.4 (34)	57.7 (30)	NS
Low HDL (men, < 40 mg/dL; women, < 50 mg/dL)	38.5 (20)	38.5 (20)	NS
Elevated triglycerides (≥ 150 mg/dL)	69.2 (36)	34.6 (18)	.0004
Elevated glucose (≥ 100 mg/dL)	26.9 (14)	25.0 (13)	NS

Abbreviations: ATP-III A = National Cholesterol Education Program–Adult Treatment Panel III adapted criteria, HDL = high-density lipoprotein, NS = nonsignificant.

The results suggest that the use of statins can improve hyperlipidemia even in patients with chronic antipsychotic treatment. These findings are comparable to those seen in the general population[2] and also to those reported by Osser et al.[36] In the latter study, the use of simvastatin, pravastatin, and gemfibrozil prevented hypertriglyceridemia caused by olanzapine treatment. Unfortunately, the study group consisted of only 6 patients, and the effect of statin therapy was not the main outcome of the study. Our study evaluated a much larger group of patients with schizophrenia receiving various antipsychotics. All of the patients in the statin group were treated with rosuvastatin, the statin with the most potent cholesterol-lowering activity and the most important effect on dyslipidemia associated with the metabolic syndrome.[1,21,22,24]

Statin therapy had no significant influence on weight, waist circumference, BMI, or glucose homeostasis. Protective properties of statins in the development of new diabetes mellitus as well as their influence on insulin action remain unclear. According to the results of the West of Scotland Coronary Prevention Study, treatment with pravastatin resulted in a 30% reduction in the risk of developing diabetes[38]; however, 2 other studies based on large databases failed to find similar benefit.[39,40] A direct influence of statins on improvement in insulin sensitivity was found to be significant in 2 randomized, placebo-controlled studies[41,42] but not in a third.[43] In our study, no significant changes in fasting or post-glucose load plasma glucose or insulin levels were observed. These observations are not in support of a positive effect of statins on insulin sensitivity (no significant change in the homeostasis model assessment [HOMA]-insulin resistance index) in patients with schizophrenia treated with antipsychotic medication. More sensitive measures of insulin sensitivity could perhaps have detected differences within 3 months, and it is possible that some effects could be detected only over longer periods of time.

We did not find a significant influence on the global prevalence of metabolic syndrome in the statin-treated group, other than a significant decrease in the triglyceride criterion. Nevertheless, more patients in the control group met criteria for metabolic syndrome at 3-month follow-up than at baseline, whereas fewer patients in the rosuvastatin group met these criteria at follow-up than at baseline. The impact of statins might have been underestimated because we did not measure prothrombotic or proinflammatory markers. These markers are associated with the metabolic syndrome and are thought to be positively affected through the so-called pleiotropic effect of statins.[2,25]

Statins have a relatively good safety profile. Two adverse effects with possibly serious consequences have been observed. Myotoxicity can occur, ranging from muscle pain without CK elevation to rhabdomyolysis, with CK values exceeding 10,000 U/L and renal failure as a consequence. This condition is potentially fatal, but the incidence is low (< 0.1%).[1] The second observed adverse effect is hepatotoxicity ranging from asymptomatic transient elevations in transaminase values to liver failure. Shepherd et al.[44] assessed the tolerability and safety of rosuvastatin using data from 12,400 patients who received 5 to 40 mg of rosuvastatin. According to their results, clinically significant elevations in alanine aminotransferase and CK were uncommon (< 0.2%), and myopathy that was possibly related to treatment occurred in < 0.03% of patients who took rosuvastatin at doses < 40 mg. No rhabdomyolysis occurred, and no deaths in the program were attributed to rosuvastatin.

A variety of factors such as female sex, older age, hypothyroidism, or preexisting liver disease may contribute to the risk of statin-induced adverse effects. Pharmacokinetic interactions with concomitant medication must also be considered. All statins except pravastatin are metabolized by the cytochrome P450 (CYP) liver system, with various affinities to different isoenzymes. Drug-drug interactions can occur when drugs with stronger binding affinity for the CYP isoenzyme are given together. The most frequent interactions are observed with gemfibrozil, niacin, warfarin, cyclosporine, amiodarone, verapamil, and macrolide antibiotics. Of all statins, those that depend on the CYP 3A4 isoenzyme, such as atorvastatin, simvastatin, and lovastatin, have the highest propensity for causing toxicity as a result of pharmacokinetic interactions.[1,45,46]

When treating patients with schizophrenia, one should be aware that clozapine, olanzapine, quetiapine, and risperidone are also metabolized by CYP 450 isoenzymes, and some antidepressants are known to act as CYP 450 inhibitors. There were no subjective complaints of any kind in patients treated with rosuvastatin in this study, nor

was a clinically significant elevation in CK or liver isoenzymes seen during the follow-up period. Statin treatment was stopped in 1 patient due to hepatotoxicity and elevated CK levels after 5 months of treatment.

Our study shows that the screening process and subsequent treatment of somatic comorbidity can be effective in patients with schizophrenia.[29,47] This issue should be emphasized in the literature as well as in educational activities. Two recent surveys indicate that screening for metabolic side effects is not yet common practice.[48,49] Having elaborate guidelines[34,50–52] as such is not sufficient to change daily clinical practice.

Some recent guidelines propose a switch to an antipsychotic with a safer metabolic profile when severe dyslipidemia or other metabolic side effects occur, but this strategy has not been evaluated systematically.[50,51] A recent switch study to aripiprazole showed highly significant reduction in serum lipids and a 50% reduction in metabolic syndrome prevalence over 3 months.[53] It remains unclear which strategies are most clinically effective and cost-effective in schizophrenia patients.

Limitations of our study include its open design in which patients were not randomized. Patient recruitment was restricted to 1 site, which could have influenced our results. In addition, not all of the patients with hyperlipidemia consecutively entering the prospective naturalistic study were involved in our analysis. Only those who remained on treatment with the same antipsychotic were included. We included only patients treated with rosuvastatin; patients treated with other lipid-lowering medication were excluded. We failed to explore other factors influencing dyslipidemia, such as dietary habits, physical activity level, or pharmacotherapy other than statins. Future research should address these issues more specifically in large, multisite samples.

In conclusion, in patients with severe dyslipidemia for whom a switch to an antipsychotic with a safer metabolic profile is not possible or lifestyle interventions are not feasible, treatment with statins should be considered.

Drug names: amiodarone (Cordarone, Pacerone, and others), aripiprazole (Abilify), atorvastatin (Lipitor), clozapine (Fazaclo, Clozaril, and others), cyclosporine (Gengraf, Neoral, and others), gemfibrozil (Lopid and others), lovastatin (Mevacor, Altoprev, and others), olanzapine (Zyprexa), pravastatin (Pravachol and others), quetiapine (Seroquel), risperidone (Risperdal), rosuvastatin (Crestor), simvastatin (Zocor and others), verapamil (Isoptin, Verelan, and others), warfarin (Coumadin, Jantoven, and others).

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