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SHORT COMMUNICATION

Comparative effects of rosuvastatin and atorvastatin on glucose metabolism and adipokine levels in non-diabetic patients with dyslipidaemia: a prospective randomized open-label study

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Abstract

Aims: The impact of statins on glucose metabolism and adipokines remains controversial. We compared the effects of rosuvastatin and atorvastatin on glucose homeostasis, insulin sensitivity (IS), adiponectin and leptin levels as well as systemic inflammation in non-diabetic patients with dyslipidaemia.

Methods: Thirty-six patients were randomly assigned to 10 mg/day of rosuvastatin (n=18) or 20 mg/day of atorvastatin (n=18) for 12 weeks. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), fasting plasma glucose, insulin, homeostasis model assessment-insulin resistance (HOMA-IR), quantitative IS check index (QUICKI), adiponectin, leptin and high-sensitivity C-reactive protein (hsCRP) were measured at baseline and after 4 and 12 weeks.

Results: Both statins significantly lowered TC, LDL-C, non-HDL-C and TG compared with baseline. Only rosuvastatin caused a significant reduction in insulin and HOMA-IR levels (-35%, $p=0.005$ and -33%, $p=0.011$, respectively) and a significant increase in QUICKI (+11%, $p=0.003$) at 12 weeks. In terms of adipokines and hsCRP, no difference was observed after 4 and 12 weeks of treatment with either statin.

Conclusions: Rosuvastatin compared with atorvastatin resulted in significant improvements in IS indices. No significant changes in adiponectin, leptin or hsCRP levels were observed at 4 and 12 weeks of treatment with either statin.

Keywords: rosuvastatin, atorvastatin, glucose, adiponectin, leptin

What’s known?

- Conflicting data exist regarding the impact of statins on glucose metabolism, insulin resistance and adipokine levels
- The JUPITER trial has raised concern about the risk for new onset diabetes mellitus (NODM) following statin therapy, an issue that was also addressed by a recent meta-analysis, which reported a 9% increased risk in NODM, especially for older participants

What’s new?

- This is the first study showing a beneficial effect of rosuvastatin on insulin resistance in non-diabetic patients with dyslipidaemia, compared with atorvastatin at equivalent dosage, in contrast to previous reports
- The effect of both statins on fasting glucose and HbA_{1c} levels was neutral
- Treatment with both statins had no impact on adiponectin and leptin levels compared with baseline.

Introduction

Conflicting data exist regarding the impact of statins on glucose metabolism, insulin resistance (IR) and adipokines [1,2]. Statins might increase the risk for new onset diabetes mellitus (NODM) [3,4], although small studies evaluating their effect on insulin sensitivity (IS) reported conflicting results [5-9].

We evaluated the effect of rosuvastatin and atorvastatin on glucose metabolism, IS, leptin, adiponectin and high-sensitivity C-reactive protein (hsCRP) levels in non-diabetic patients with dyslipidaemia, not meeting goals [10] for low-density lipoprotein cholesterol (LDL-C).

Patients and methods

Study design and subjects

A 12-week prospective randomized open-label single-dose study was conducted from April 2009 to May 2010 in the Department of Endocrinology, Hippokration General Hospital (Thessaloniki, Greece), a tertiary referral center. We included patients with dyslipidaemia not meeting goals for LDL-C [10]. Exclusion criteria were: DM, malignancy, thyroid dysfunction, any lipid-lowering or anti-obesity agents. At screening, physical examination and basal laboratory assessment were performed.

Patients were randomly assigned to receive either rosuvastatin 10 mg or atorvastatin 20 mg once daily for 12 weeks. Randomization was performed by Microsoft Excel. Patients were reassessed at 4 and 12 weeks in terms of adverse events. The statin was discontinued and the subjects were withdrawn from the study in case of drug intolerance, pregnancy, transaminase elevation $>3\times$ or creatine kinase $>10\times$ upper limit of normal.

All blood samples were obtained between 8:00 and 9:00 am after an overnight fast. Basal laboratory parameters, serum insulin, leptin and hsCRP levels were assessed at

baseline, at 4 and 12 weeks. Total serum adiponectin was assessed at baseline and at 12 weeks. IS was estimated at the same intervals using the homeostasis model assessment-IR (HOMA-IR) and the quantitative IS check index (QUICKI). HOMA-IR was calculated based on the formula: [fasting serum insulin (μ IU/L) x fasting plasma glucose (mmol/L)]/22.5, while QUICKI was based on the logarithmic transformation: $1/[\log \text{ glucose (mg/dL)} + \log \text{ insulin (}\mu\text{U/mL)}]$ [11,12]. Insulin was measured using an immunochemiluminometric (ICMA) assay (Immulite 2500, DPC, Los Angeles, USA). Enzyme-linked immunosorbent assays (ELISA) were used to measure total circulating adiponectin (Biovendor, Heidelberg, Germany) and leptin levels (Mercodia, Uppsala, Sweden). HsCRP was measured by nephelometry (Dade, Behring, BN II, Germany).

Statistical analysis

Data for continuous variables are presented as mean \pm standard deviation (SD). Data for categorical variables are presented as numbers and/or percentages. The Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variables. Repeated measures analysis of variance (ANOVA) was used to test for differences within the levels of continuous variables, in cases of more than 2 serial measurements. Wilcoxon Signed Ranks Test was used to test for differences within the levels of continuous variables, in cases with 2 serial measurements. The independent t-test or Mann-Whitney test was used for between group differences. Pearson's (r) or Spearman's (rs) correlation coefficients were used. A $p < 0.05$ (two-tailed) was considered significant. Statistical analysis was performed using SPSS for Windows version 13 (SPSS Inc., Illinois, USA). Power analysis was performed with GPower 3.0.8 (University of Kiel, Germany).

Results

Thirty-six patients completed the study, 18 (3 males/15 females, age 54.7 ± 11.3 years) received rosuvastatin and 18 (3 males/15 females, age 59.8 ± 10.3 years) atorvastatin. The 2 groups were comparable at baseline regarding anthropometric parameters including age, gender, weight, blood pressure, body mass index, waist and hip circumference. No significant differences in these parameters were noted after treatment.

The 2 groups did not differ in baseline fasting plasma glucose, haemoglobin A_{1c} (HbA_{1c}), insulin, HOMA-IR and QUICKI. No difference was observed in fasting plasma glucose and HbA_{1c} after treatment within either group (table 1). Compared with baseline, only rosuvastatin caused a significant reduction in insulin and HOMA-IR ($p=0.005$ and $p=0.011$, respectively) and a significant increase in QUICKI at 12 weeks ($p=0.003$) (table 1). These differences were greater with rosuvastatin compared with atorvastatin at 12 weeks [-35% vs $+17\%$, ($p = 0.032$) for insulin, -33% vs $+17\%$ ($p = 0.008$) for HOMA-IR and $+11\%$ vs 6% ($p = 0.015$) for QUICKI, respectively]. Differences in insulin and HOMA-IR remained significant ($p = 0.012$ and $p = 0.007$, respectively) at the end of study after adjustment for age, gender and deltas in waist circumference, adiponectin, leptin and TG. However, differences in QUICKI did not remain significant after similar adjustment. Regarding insulin and HOMA-IR at 12 weeks, the between groups difference remained significant after adjustment for baseline insulin ($p=0.043$ and $p=0.029$, respectively) Baseline HOMA-IR did not significantly affect the 12-week HOMA-IR ($p=0.665$). The between groups difference remained significant ($p=0.043$) after adjustment for age, gender, and baseline insulin and waist circumference. Modification of log-transforming HOMA using $\log(\text{glucose} \times \text{insulin})/\log(22.5)$ led to similar results (table 1).

We did not perform a priori power analysis, because this is a pilot study. However, a post-hoc power analysis for actual differences of QUICKI regarding the within-between group interaction (repeated measures ANOVA) provided a power of 87% for a type I error probability 0.05.

No differences within the 2 groups were observed regarding the levels of adiponectin, leptin and hsCRP at baseline, 4 and 12 weeks of treatment (table 1). However, compared with atorvastatin, rosuvastatin significantly increased adiponectin ($p = 0.016$) and decreased leptin levels ($p = 0.009$) compared with atorvastatin at 12 weeks. These differences did not remain significant after adjustment for age, gender and deltas in waist circumference, HOMA-IR, TG and leptin or adiponectin levels, respectively.

Discussion

Our study demonstrates for the first time that rosuvastatin may improve IS in non-diabetic patients compared with atorvastatin. Other comparative studies did not show changes in IR [5, 6]. The 2 statins had neutral impact on HbA_{1c} in our study with a trend towards reducing fasting plasma glucose levels (mainly with rosuvastatin). It is not clear if the statin-related risk of NODM is a ‘class effect’ [13,14]. Furthermore, data from randomized studies have shown that the CVD risk reduction by statins is greater in patients with type 2 DM than in non-diabetics, thus counteracting a potential increase in CVD risk related to NODM [13,14].

With respect to their impact on IS, previous reports of rosuvastatin showed no effect [15-17] or even worsening of IR [18]. Atorvastatin was neutral in our study which is consistent with most previous reports [8,19], although some demonstrated amelioration [20] or worsening of IR [21]. We cannot exclude a dose-dependent effect of statins on IR.

We found no change in adipokines after treatment. There are limited data regarding the effects of rosuvastatin on adiponectin and leptin levels. Rosuvastatin [22], as well as atorvastatin increase adiponectin levels in patients with dyslipidaemia [23,24]. In terms of leptin, conflicting data exist, since atorvastatin reduced plasma leptin levels in diabetic patients [25] but had no effect in patients with dyslipidemia [21,24]. Regarding systemic inflammation, rosuvastatin and atorvastatin have been shown to reduce hsCRP levels [3,23,25]. The lack of reduction in hsCRP levels in our study may be attributed to the average baseline levels of hsCRP of 3 mg/L or the small number of patients.

One advantage of the present study is that we evaluated the impact of both statins at equivalent doses on IS at 2 intervals (4 and 12 weeks). However, we acknowledge limitations. First, there was unequal distribution between males and females and a non-significant difference in mean age of patients (about 5 years older in the atorvastatin group). However, we performed adjustments for several parameters including age and gender. We also acknowledge that HOMA and QUICKI have high variability and should be regarded more as derivatives of the insulin level than as truly reflecting IS. We were not able to perform a trapezoidal/frequently sampled glucose tolerance test (with measurement of insulin) (which would be better) or the euglycaemic clamp (which is the gold standard), but a good and strong correlation between estimates of IR derived from HOMA or QUICKI and from the euglycemic clamp has been reported [26,27], despite coefficients of variation (CV) of 24-28% for HOMA-IR, and 4-8% for QUICKI in 1 study [27, 28]. It should be recognized that HOMA is a measure of basal insulin sensitivity and β -cell function and, in contrast to euglycemic clamp, it does not give information about the stimulated state. QUICKI is actually a logHOMA-IR, displaying an acceptable correlation and having the same limitations with HOMA [26]. In addition, using log-transforming HOMA by $\log(\text{glucose} \times \text{insulin})/\log(22.5)$ and log-transforming

HOMA without transforming the constant denominator may improve CV, as previously reported [28].

In conclusion, rosuvastatin compared with atorvastatin exerted beneficial effects on carbohydrate metabolism in non-diabetic patients with dyslipidaemia. Larger trials are needed to validate the impact of statins on glucose metabolism, IS and adipokine levels.

Conflict of interest

This article was written independently. The authors did not receive financial or professional help with the preparation of the manuscript. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies.

Authors' contributions

Concept/design, PA and DS; Data analysis/interpretation, SAP, AP, AS, and AP; Critical revision of article, VGA, AK; Approval of article, MK, DPM.

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Table 1. Effects of 4-and 12-week treatment of atorvastatin and rosuvastatin on glucose metabolism, adipokines and systemic inflammation.

Parameter	Group	Baseline	4 weeks	12 weeks	<i>p</i> -value #
Total Cholesterol (mg/dL)	Atorvastatin	272 ± 41	178 ± 27 (a)	182 ± 25 (a)	<0.001
	Rosuvastatin	278 ± 35	177 ± 41 (a)	176 ± 33 (a)	<0.001
Triglycerides (mg/dL)	Atorvastatin	167 ± 90	126 ± 56	115 ± 44 (a)	0.021
	Rosuvastatin	149 ± 79	118 ± 51	104 ± 46 (a)	0.041
HDL-C (mg/dL)	Atorvastatin	58 ± 8	53 ± 10	55 ± 10	0.098
	Rosuvastatin	62 ± 17	58 ± 17	60 ± 14	0.132
LDL-C (mg/dL)	Atorvastatin	183 ± 34	99 ± 24 (a)	106 ± 18 (a)	<0.001
	Rosuvastatin	187 ± 24	95 ± 32 (a)	95 ± 26 (a)	<0.001
Non-HDL-C (mg/dL)	Atorvastatin	214 ± 39	124 ± 29 (a)	127 ± 24 (a)	< 0.001
	Rosuvastatin	217 ± 28	119 ± 34 (a)	116 ± 25 (a)	< 0.001
Glucose (mg/dL)	Atorvastatin	98 ± 11	95 ± 11	96 ± 9	0.298
	Rosuvastatin	90 ± 13	89 ± 13	88 ± 10 *	0.856
Insulin (μIU/mL)	Atorvastatin	11.5 ± 6.1	8.9 ± 8.6	8.8 ± 6.6	0.202
	Rosuvastatin	7.5 ± 3.4	6.4 ± 3.9	4.9 ± 3.6 *(a)	0.005
HOMA-IR	Atorvastatin	3.4 ± 3.8	2.1 ± 2.3	2.1 ± 1.7	0.188
	Rosuvastatin	1.7 ± 0.9	1.4 ± 0.8	1.1 ± 0.8 *(a)	0.011
QUICKI	Atorvastatin	0.35 ± 0.06	0.36 ± 0.04	0.36 ± 0.04	0.440
	Rosuvastatin	0.36 ± 0.03	0.37 ± 0.04	0.40 ± 0.05 *(a)	0.003
HbA1c (%)	Atorvastatin	5.6 ± 0.4	-	5.7 ± 0.4	0.331
	Rosuvastatin	5.4 ± 0.3	-	5.5 ± 0.3	0.066
Adiponectin (μg/mL)	Atorvastatin	10.2 ± 3.9	-	10.5 ± 4.7	0.828

	Rosuvastatin	16.5 ± 11.1	-	17.7 ± 12.3 *	0.286
Leptin (ng/mL)	Atorvastatin	40.5 ± 24.0	40.0 ± 22.1	42.9 ± 22.7	0.775
	Rosuvastatin	30.9 ± 24.5	28.2 ± 22.4	27.9 ± 24.0 *	0.626
hsCRP (mg/L)	Atorvastatin	3.1 ± 2.3	2.5 ± 1.8	2.7 ± 2.4	0.155
	Rosuvastatin	2.8 ± 2.5	3.1 ± 3.7	2.2 ± 2.1	0.582
Log(insulin)	Atorvastatin	0.96 ± 0.11	0.82 ± 0.08	0.83 ± 0.08	0.361
	Rosuvastatin	0.83 ± 0.05	0.75 ± 0.06 (a)	0.59 ± 0.07 *(a)	0.001
Log (HOMA-IR)	Atorvastatin	3.4 ± 3.8	2.1 ± 2.3	2.1 ± 1.7	0.323
	Rosuvastatin	1.7 ± 0.9	1.4 ± 0.8	1.1 ± 0.8 *(a)	0.003
#: p for within groups comparisons (repeated measures ANOVA or Wilcoxon Signed Ranks Test)					
*: p<0.05 for between groups comparison (independent T-test or Mann-Whitney test)					
a: p<0.05 compared to baseline; (Bonferroni post-hoc analysis)					

Abbreviations: LDL-C: low density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment-insulin resistance, QUICKI: quantitative insulin-sensitivity check index, HbA1c: haemoglobin A1c, hsCRP: high sensitivity C-reactive protein