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**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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**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<sub>1c</sub> 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  $>3x$  or creatine kinase  $>10x$  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

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

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

Thirty-six patients completed the study, 18 (3 males/15 females, age  $54.7 \pm 11.3$  years) received rosuvastatin and 18 (3 males/15 females, age  $59.8 \pm 10.3$  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<sub>1c</sub> (HbA<sub>1c</sub>), insulin, HOMA-IR and QUICKI. No difference was observed in fasting plasma glucose and HbA<sub>1c</sub> 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).



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3 We did not perform a priori power analysis, because this is a pilot study. However, a  
4 post-hoc power analysis for actual differences of QUICKI regarding the within-between  
5 group interaction (repeated measures ANOVA) provided a power of 87% for a type I  
6 error probability 0.05.  
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12 No differences within the 2 groups were observed regarding the levels of  
13 adiponectin, leptin and hsCRP at baseline, 4 and 12 weeks of treatment (table 1).  
14 However, compared with atorvastatin, rosuvastatin significantly increased adiponectin (p  
15 = 0.016) and decreased leptin levels (p = 0.009) compared with atorvastatin at 12 weeks.  
16 These differences did not remain significant after adjustment for age, gender and deltas in  
17 waist circumference, HOMA-IR, TG and leptin or adiponectin levels, respectively.  
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## 29 Discussion

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32 Our study demonstrates for the first time that rosuvastatin may improve IS in non-  
33 diabetic patients compared with atorvastatin. Other comparative studies did not show  
34 changes in IR [5, 6]. The 2 statins had neutral impact on HbA<sub>1c</sub> in our study with a trend  
35 towards reducing fasting plasma glucose levels (mainly with rosuvastatin). It is not clear  
36 if the statin-related risk of NODM is a 'class effect' [13,14]. Furthermore, data from  
37 randomized studies have shown that the CVD risk reduction by statins is greater in  
38 patients with type 2 DM than in non-diabetics, thus counteracting a potential increase in  
39 CVD risk related to NODM [13,14].  
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51 With respect to their impact on IS, previous reports of rosuvastatin showed no effect  
52 [15-17] or even worsening of IR [18]. Atorvastatin was neutral in our study which is  
53 consistent with most previous reports [8,19], although some demonstrated amelioration  
54 [20] or worsening of IR [21]. We cannot exclude a dose-dependent effect of statins on IR.  
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3 We found no change in adipokines after treatment. There are limited data regarding  
4 the effects of rosuvastatin on adiponectin and leptin levels. Rosuvastatin [22], as well as  
5 atorvastatin increase adiponectin levels in patients with dyslipidaemia [23,24]. In terms  
6 of leptin, conflicting data exist, since atorvastatin reduced plasma leptin levels in diabetic  
7 patients [25] but had no effect in patients with dyslipidemia [21,24]. Regarding systemic  
8 inflammation, rosuvastatin and atorvastatin have been shown to reduce hsCRP levels  
9 [3,23,25]. The lack of reduction in hsCRP levels in our study may be attributed to the  
10 average baseline levels of hsCRP of 3 mg/L or the small number of patients.  
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15 One advantage of the present study is that we evaluated the impact of both statins at  
16 equivalent doses on IS at 2 intervals (4 and 12 weeks). However, we acknowledge  
17 limitations. First, there was unequal distribution between males and females and a non-  
18 significant difference in mean age of patients (about 5 years older in the atorvastatin  
19 group). However, we performed adjustments for several parameters including age and  
20 gender. We also acknowledge that HOMA and QUICKI have high variability and should  
21 be regarded more as derivatives of the insulin level than as truly reflecting IS. We were  
22 not able to perform a trapezoidal/frequently sampled glucose tolerance test (with  
23 measurement of insulin) (which would be better) or the euglycaemic clamp (which is the  
24 gold standard), but a good and strong correlation between estimates of IR derived from  
25 HOMA or QUICKI and from the euglycemic clamp has been reported [26,27], despite  
26 coefficients of variation (CV) of 24-28% for HOMA-IR, and 4-8% for QUICKI in 1  
27 study [27, 28]. It should be recognized that HOMA is a measure of basal insulin  
28 sensitivity and  $\beta$ -cell function and, in contrast to euglycemic clamp, it does not give  
29 information about the stimulated state. QUICKI is actually a  $\log$ HOMA-IR, displaying an  
30 acceptable correlation and having the same limitations with HOMA [26]. In addition,  
31 using log-transforming HOMA by  $\log(\text{glucose} \times \text{insulin})/\log(22.5)$  and log-transforming  
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3 HOMA without transforming the constant denominator may improve CV, as previously  
4 reported [28].  
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9 In conclusion, rosuvastatin compared with atorvastatin exerted beneficial effects on  
10 carbohydrate metabolism in non-diabetic patients with dyslipidaemia. Larger trials are  
11 needed to validate the impact of statins on glucose metabolism, IS and adipokine levels.  
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### 15 16 17 18 19 **Conflict of interest**

20 This article was written independently. The authors did not receive financial or  
21 professional help with the preparation of the manuscript. The authors have given talks,  
22 attended conferences and participated in advisory boards and trials sponsored by  
23 various pharmaceutical companies.  
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### 33 34 **Authors' contributions**

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

	<b>Rosuvastatin</b>	16.5 ± 11.1	-	17.7 ± 12.3 *	0.286
Leptin (ng/mL)	<b>Atorvastatin</b>	40.5 ± 24.0	40.0 ± 22.1	42.9 ± 22.7	0.775
	<b>Rosuvastatin</b>	30.9 ± 24.5	28.2 ± 22.4	27.9 ± 24.0 *	0.626
hsCRP (mg/L)	<b>Atorvastatin</b>	3.1 ± 2.3	2.5 ± 1.8	2.7 ± 2.4	0.155
	<b>Rosuvastatin</b>	2.8 ± 2.5	3.1 ± 3.7	2.2 ± 2.1	0.582
Log(insulin)	<b>Atorvastatin</b>	0.96 ± 0.11	0.82 ± 0.08	0.83 ± 0.08	0.361
	<b>Rosuvastatin</b>	0.83 ± 0.05	0.75 ± 0.06 (a)	0.59 ± 0.07 *(a)	0.001
Log (HOMA-IR)	<b>Atorvastatin</b>	3.4 ± 3.8	2.1 ± 2.3	2.1 ± 1.7	0.323
	<b>Rosuvastatin</b>	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