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Comparative study of long-term effects of atorvastatin and rosuvastatin on fasting glucose and hemoglobin A1c in patients with cardiovascular diseases

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ABSTRACT

Introduction: Statins are lipid lowering medications, used for the prevention of cardiovascular diseases (CVD), but have shown to increase the risk of Type 2 diabetes mellitus. The aim of this study was to investigate the effects of high-potency statins, atorvastatin, and rosuvastatin on fasting glucose (FG) and hemoglobin A1c (HbA1c) in CVD patients.

Methods: The case–control study included 123 patients from Tuzla Canton, Bosnia, and Herzegovina, with a diagnosis of CVD, treated in three health centers: Public Health Center Gračanica, Banovići, and Čelić. Of total patients, 84 were statin users (39 atorvastatin users and 45 rosuvastatin users) and 39 were not. Demographic data, diagnosis, and data of the therapy were taken from the medical records, as well as data of the FG and HbA1c, measured before or within 3 months of the statin therapy introduction. For the same patients, FG and HbA1c were also measured at least 3 months after the introduction of therapy.

Results: Obtained results have shown a significant increase of FG in CVD patients on statin therapy in relation to control ($p = 0.034$). Comparing the diabetogenic effects of atrovastatin and rosuvastatin, it was found that the HbA1c in patients on atorvastatin therapy was significantly higher comparing to those on rosuvastatain therapy ($p = 0.028$). The FG was significantly increased ($p = 0.027$) after atrovastatin therapy. Similar results were obtained in diabetogenic CVD patients, where HbA1c on atorvastatin therapy was significantly higher comparing to HbA1c in those on rosuvastatain therapy ($p = 0.039$). A significant correlation was found between the increase in FG and HbA1c with the duration of atorvastatin therapy ($p = 0.001$ and $p = 0.033$), and between the increase in HbA1c and the duration of rosuvastatin therapy ($p = 0.001$).

Conclusion: Long-term therapy with high-potency statins, atorvastatin, and rosuvastatin, may increase levels of FG and HbA1c in patients with CVD, where atorvastatin shows more significant effects.

Keywords: Cardiovascular disease; fasting glucose; hemoglobin A1c; statins

INTRODUCTION

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) inhibitors, are class of lipid-lowering medications, widely used for the primary and secondary prevention of cardiovascular diseases (CVDs) (1). Although, numerous studies have shown that statin treatment may induce the development of Type 2 diabetes (2-6), the precise mechanism of their diabetogenic effects is not completely known. Experimental and clinical studies suggest that statins may lead to an increase of insulin-resistance and hyperglycemia (7,8). A large nationwide population-based health examination in Korea have shown that the use of statins had significant associations with the increase in fasting glucose (FG) (4), which may be associated with statin-induced hepatic gluconeogenesis (5).

Different types of statins may have different effects on the glucose metabolism (5,9-12). In general, statins are classified according to their hydophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin) which have different pharmacological properties (13,14). Although the target of both types of statins is HMG-CoA reductase, the inhibitory mechanisms are distinct. Hydrophilic statins target the liver more efficiently because their uptake is carrier-mediated, while lipophilic statins passively diffuse through the hepatocellular

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membrane and also in extrahepatic tissues, thus showing reduced hepatoselectivity (14,15), which may explain their higher incidence of adverse effects. Exception to this is rosuvastatin, which is a hydrophilic statin, but has a similar activity profile to lipophilic statins (16).

A recent studies have shown that statin treatment was associated with the increase of hemoglobin A1c (HbA1c) and altered glycemic control (17-22). A large retrospective and cohort study has shown that the use of high-potency statins, atorvastatin and rosuvastatin, may increase HbA1c levels in patients with or without diabetes (17). Furthermore, a recent meta-analysis has showed that statin treatment was associated with increase of HbA1c in individuals with adequate or altered glycemic control (18). Similar, a randomized and controlled study in patients with Type 2 diabetes conducted in Taiwan found that HbA1c was significantly increased after 3 months in patients receiving atorvastatin (21). On the other hand, in a randomized study of non-diabetic patients, neither of high-potency statins investigated (atorvastatin and rosuvastatin) had a significant effect on HbA1c (23).

Although the diabetogenic effects of statins have been extensively investigated over the past decade, and there is accumulating evidence indicating that patients treated with statins have an increased risk of developing new-onset diabetes, only a few studies in mice (24) and a few in patients (17,22,23) have compared the diabetogenic effects of atorvastatin and rosuvastatin, high-potency statins but with different hydrophobicity.

Based on this background, the present study was designed to investigate and compare diabetogenic effects of widely used high-potency statins rosuvastatin and atorvastatin. We conducted a case–control, observational study to analyze their diabetogenic effects through changes in FG and HbA1c in patients with CVDs on long-term atorvastatin or rosuvastatin therapy.

METHODS

The retrospective case–control, observational study conducted during 2022, included 123 patients from Tuzla Canton, Bosnia, and Herzegovina, with a diagnosis of CVD treated in three health centers (Public Health Center Gračanica, Public Health Center Banovići, and Public Health Center Čelić). The study is designed with the primary goal to retrospectively determine whether long-term statin therapy leads to an increase in FG and HbA1c and whether there is a difference in the increase in FG and HbA1c between patients treated with atorvastatin versus those treated with rosuvastatin. Of the total number of patients included in the study, 84 were CVD patients on long-term statin therapy for more than 3 months, and 39 were CVD patients who were not treated with statins.

Each patient included in the study signed an informed consent, thus permissions were obtained from the ethics committees of the centers where the patients were treated (Ethics Committee's Approval of Health Center Gračanica dated April 15, 2022; Ethics Committee's Approval of Health Center Banovići, number 05-240/22, dated May 13, 2022; Ethics Committee's Approval of Health Center Čelić number 01-747-04/22, dated April 8, 2022).

The including criteria were: A confirmed diagnosis of CVD (essential hypertension and hypertension with conditions such as abnormal heart rhythms, angina pectoris, heart failure, ischemic heart disease, cardiomyopathy, acute myocardial infraction, etc.) and/or a confirmed diagnosis of diabetes mellitus (DM) Type 2 and duration of statin therapy longer than 3 months (for patients on statin therapy). The criteria for excluding patients were: Patients with a confirmed diagnosis of DM Type 1, patients with a confirmed diagnosis of DM Type 2 on insulin therapy, confirmed diagnosis of CVD on non-statin lipid-lowering therapy, pregnancy, or patients with other significant comorbidity (solid and hematological malignancies, chronic kidney failure, chronic alcoholism, and liver cirrhosis). All the DM Type 2 patients were on oral anti-diabetic therapy.

Two main groups of patients were formed, the test group and the control group. The test group consisted of 84 patients with CVD on long-term statin therapy, and the control group consisted of 39 patients with CVD who were not on statin therapy. In the test group, two subgroups were formed, namely, the subgroup of patients on atorvastatin therapy (39 patients) and a subgroup of patients on rosuvastatin therapy (45 patients). In addition, the test group was also divided in subgroups as follows: Diabetic patients on atorvastatin therapy, non-diabetic patients on atorvastatin therapy, diabetic patients on rosuvastatin therapy, and non-diabetic patients on rosuvastatin therapy.

Demographic data, diagnosis, and data of the therapy included were taken from the medical records for all patients. Furthermore, the data of the measured values of FG and HbA1c were taken from the medical records. Those were measured before the introduction of the therapy or within 3 months of the introduction of the therapy for statin-treated patients. For all patients, FG and HbA1c values were measured at the last routine biochemical treatment of the patient, at least 3 months after the introduction of the therapy for the test group, or 3 months after the diagnosis of CVD for the control group. To determine whether statins, Atorvastatin, and Rosuvastatin have diabetogenic effects, FG and HbA1c values that were measured at the last routine biochemical treatment were compared among the test and the control group. Furthermore, FG and HbA1c measured before the introduction of the therapy or within 3 months of the introduction of the therapy for statin-treated patients were compared to those measured at the last routine biochemical treatment of the same patients. To determine if there is a difference in diabetogenic effects between atorvastatin and rosuvastatin, FG and HbA1c values that were measured at the last routine biochemical treatment atorvastatin-treated patients were compared to those in rosuvastatin-treated patients. In addition, to examine whether pre-existing diabetes has an effect on changes in FG and HbA1c in statin-treated CVD patients, we compared these values between diabetic and non-diabetic CVD patients.

FG levels were measured using colorimetric method with glucose oxidase (GOD - PAP) on biochemical analyzer (Biochemical analyzer XL640, Erba, Czech Republic in Public Health Center Gračanica, Biochemical analyzer BT 1500, Biotehnica Instruments, Italy in Public Health Center Čelić and Biochemical analyzer Autolyser 100,

Dialb, Austria). HbA1c levels were measured using turbidimetric immunoassay on biochemical analyzer Architect ci 8200, Abbot for all three health centers.

After checking the normality of the data using Shapiro–Wilk test, non-parametric statistical tests were used for data processing. Wilcoxon test was used for a dependent sample, the Mann–Whitney U test for an independent sample, and Spearman's test for sample correlations. All statistical tests were performed using the SPSS/WIN program. (Release 26.0 SPSS Inc., Chicago, IL, USA). In all tests, values of $p \leq 0.05$ were considered statistically significant.

RESULTS

In total 123 CVD patients were examined (86.18% with essential hypertension, 5.69% with hypertension and angina pectoris, 2.44% with hypertension and abnormal heart rhythms, 1.63% with hypertension and acute myocardial infraction, 1.63% with hypertension and ischemic heart disease, 0.81% with hypertension and cardiomyopathy, 0.81% with hypertension and varicose vains, and 0.81% with hypertension and heart failure). Of these, 84 were high-potency statins, atorvastatin (46.43%) or rosuvastatin (53.57%) users. Of the CVD patients receiving statins, 66 (78.57%) were diabetic and 18 (21.43%) were non-diabetic patients. Of the CVD patients receiving statins, 19 (28.79%) have developed diabetes after the introduction of statin therapy, 11 (57.89%) atorvastatin users, and 8 (42.10%) rosuvastatin users. Age and monitored parameters for all the patients included in the study are presented in Tables 1 and 2.

Table 1 also shows changes in FG or HbA1c values after long-term statin therapy in the same CVD patients and the differences of FG or HbA1c between CVD patients on long-term statin therapy and CVD patients who are not on statin therapy. Statistically significant increase was found in FG values in CVD patients on long-term atorvastatin therapy ($p = 0.027$). Values of FG were significantly higher in CVD patients on atorvastatin therapy compared to those who were not statin users ($p = 0.034$). Furthermore, HbA1c values were significantly higher in CVD patients on atorvastatin therapy compared to those on long-term rosuvastatin therapy ($p = 0.028$).

Table 2 shows changes in FG or HbA1c values after long-term statin therapy in the same CVD patients with DM and differences of FG or HbA1c between CVD patients with DM Type 2 on long-term statin therapy and CVD patients who are not on statin therapy.

HbA1c values were significantly higher in CVD patients with DM Type 2 on atorvastatin therapy compared to those on long-term rosuvastatin therapy ($p = 0.039$).

As the CVD patients included in this study were under statin therapy in the intervals from 5 to 216 months for patients on atorvastatin, and 5-174 months for rosuvastatin, the correlation between duration of statin therapy and monitored parameters (FG and HbA1c) were tested (Table 3). Table 3 shows a significant correlation between FG and the duration of atorvastatin therapy ($p = 0.001$), but not a significant correlation with the duration of rosuvastatin therapy. A significant correlation was found between HbA1c and both, duration of atorvastatin therapy ($p = 0.033$) and rosuvastatin therapy ($p = 0.001$).

The same correlations were tested in CVD patients with DM Type 2 (Table 4). A significant correlation was found between both FG and HbA1c with the duration of atrovastatin therapy ($p = 0.001$, $p = 0.028$, respectively) and rosuvastatin therapy ($p = 0.031$, $p = 0.001$, respectively).

DISCUSSION

Numoreous studies have shown association of glucose metabolism and use of statins (2-8,17-26). Therapy with

TABLE 1. Age, duration of the therapy, and monitored parameters (FG and HbA1c) of CVD patients

Variable	CVD patients on statin therapy (n=84)		Differences, $p \leq 0.05$ Mann–Whitney test	CVD patients not on statin therapy (n=39)	Differences, $p \leq 0.05$ Mann–Whitney test
	atorvastatin	rosuvastatin			
Number of patients	39	45		39	
Age, years, mean±SE, SD (min-max)	67.154±1.308, 8.171 (51-85)	64.91±1.354, 9.08 (41-84)		67.512±1.780, 11.12 (45-90)	
Duration of therapy, months, mean±SE, SD (min-max)	98.77±8.76, 54.71 (5-216)	61.733±7.148, 47.95 (5-174)		-	
Male, %	33.33	53.33		38.46	
A) FG mmol/L, mean±SE, SD (min-max)	7.531±0.294, 1.83 (4.20-12.80)	8.726±0.534, 3.58 (3.60-20.00)	p=0.319	-	
B) FG mmol/L, mean±SE, SD (min-max)	8.826±0.496, 3.10 (5.40-19.00)	7.91±0.310, 2.1 (4.80-14.20)	p=0.277	7.535±0.377, 2.35 (4.50-15.60)	p=0.034*
Differences, $p \leq 0.05$ Wilcoxon test	p=0.027*	p=0.447			
A) HbA1c %, mean±SE, SD (min-max)	7.180±0.191, 0.957 (5.70-9.80)	7.175±0.271, 1.39 (5.00-10.80)	p=0.658	-	
B) HbA1c %, mean±SE, SD (min-max)	7.881±0.404, 1.98 (5.85-11.80)	6.680±1.198, 1.03 (5.02-9.10)	p=0.028*	7.13±0.280, 1.44 (4.60-10.20)	p=0.911
Differences, $p \leq 0.05$ Wilcoxon test	p=0.308	p=0.319			

A) Values of FG or HbA1c measured before the introduction of therapy or immediately (within 3 months) after the introduction of therapy. B) Values of FG or HbA1c measured at the patient's last follow-up examination (after at least 3 months on statin therapy), Values of FG and HbA1c for CVD patients who are not on statin therapy were measured at last biochemical follow-up (minimum 3 months after diagnosis), CVD: Cardiovascular diseases, FG: Fasting glucose, HbA1c: Hemoglobin A1c

TABLE 2. Age, duration of the therapy, and monitored parameters (FG and HbA1c) of diabetic and non-diabetic patients on long-term statin therapy

Variable	Diabetic patients		Differences $p \leq 0.05$ Mann-Whitney test	Non-diabetic patients	
	Atorvastatin	Rosuvastatin		Atorvastatin	Rosuvastatin
Number of patients	31	35		8	10
Age, years, mean±SE, SD (min-max)	68.290±1.307, 7.28 (52-82)	65.171±1.550, 9.17 (41-84)		63.222±3.265, 9.79 (34-51)	64.00±2.91, 9.20 (49-76)
Duration of therapy, months, mean±SE, SD (min-max)	106.129±9.802, 54.58 (5-216)	60.714±8.312, 49.17 (5-173)		73.778±15.401, 46.20 (6-144)	65.300±14.452, 45.70 (28-174)
Male, %	41.93	54.28		12.5	50.00
A) FG mmol/L, mean±SE, SD (min-max)	8.432±0.404, 2.25 (4.80-7.00)	9.525±0.618, 3.66 (5.10-20)	p=0.559	5.478±0.194, 0.58 (4.20-6.10)	5.930±0.340, 1.07 (3.60-7.70)
B) FG mmol/L, mean±SE, SD (min-max)	9.623±0.404, 3.02 (6.00-19.00)	8.441±0.343, 2.03 (5.80-14.20)	p=0.126	6.00±0.107, 0.32 (5.40-6.60)	6.040±0.210, 0.65 (4.80-7.00)
Differences, $p \leq 0.05$ Wilcoxon test	p=0.152	p=0.296			
A) HbA1c %, mean±SE, SD (min-max)	7.259±0.201, 1.01 (5.70-9.80)	7.162±0.282, 1.41 (5.00-10.80)	p=0.449	-	-
B) HbA1c %, mean±SE, SD (min-max)	7.882±0.388, 1.94 (5.85-11.80)	6.725±0.21, 1.05 (5.02-9.10)	p=0.039*	-	-
Differences, $p \leq 0.05$ Wilcoxon test	p=0.484	p=0.242			

A) Values of FG or HbA1c measured before the introduction of therapy or immediately (within 3 months) after the introduction of therapy. B) Values of FG or HbA1c measured at the patient's last follow-up examination (after at least 3 months on statin therapy), FG: Fasting glucose, HbA1c: Hemoglobin A1c

TABLE 3. Correlation between duration of statin therapy in CVD patients and analyzed parameters (FG and HbA1c) at the last follow-up examination (after at least 3 months on statin therapy)

Duration of atorvastatin therapy in months		Duration of rosuvastatin therapy in months	
FG	HbA1c	FG	HbA1c
rho=0.501 p=0.001*	rho=0.437 p=0.033*	rho=0.275 p=0.067	rho=0.593 p=0.001*

Spearman rho, $p \leq 0.05$*, CVD: Cardiovascular diseases, FG: Fasting glucose, HbA1c: Hemoglobin A1c, DM: Diabetes mellitus

TABLE 4. Correlation between duration of statin therapy in CVD patients with DM and analyzed parameters (FG and HbA1c) at the last follow-up examination (after at least 3 months on statin therapy)

Duration of atorvastatin therapy in months		Duration of rosuvastatin therapy in month	
FG	HbA1c	FG	HbA1c
rho=0.547 p=0.001*	rho=0.439 p=0.028*	rho=0.365 p=0.031*	rho=0.632 p=0.001*

Spearman rho, $p \leq 0.05$*, CVD: Cardiovascular diseases, FG: Fasting glucose, HbA1c: Hemoglobin A1c, DM: Diabetes mellitus

high-potency statins (atorvastatin and rosuvastatin) has higher risk of diabetes than with low-potency statins (simvastatin, pravastatin, and lovastatin) (17,26). In addition, a recent study, examining the mechanisms of the effects of statins on glucose metabolism, found that atorvastatin and rosuvastatin activate hepatic gluconeogensis through affecting the expression of gluconeogenic enzymes and hepatic autophagy, leading to dysglycemia in mice (5).

In this study, we examined whether the use of high-potency statins may have effect on FG and HbA1c levels. Thus, the obtained results have shown a significant increase of FG in CVD patients on long-term statin therapy in relation to control group (CVD patients not treated with statins) (p = 0.034), while no significant change in HbA1c between statin-treated patients and control was found (Table 1). Comparing the diabetogenic effects of atrovastatin and rosuvastatin, we found that the HbA1c in CVD patients on atorvastatin therapy was significantly higher comparing to HbA1c in CVD patients on rosuvastatain therapy (p = 0.028) (Table 1). Furthermore, we have found that the FG levels were significantly increased (p = 0.027) after atrovastatin therapy in CVD patients (Table 1). Similar results were obtained in the group of CVD patients with DM Type 2. The value of HbA1c in diabetogenic CVD patients on atorvastatin therapy was significantly higher comparing to HbA1c in those on rosuvastatain therapy (p = 0.039) (Table 2). A strong statistically significant correlation between the increase of FG and HbA1c with the duration of the statin therapy in patients with CVD was also found (Tables 3 and 4). It is especially important to point out that the correlations of FG and HbA1c with the length of therapy were also highly significant in the subgroup of patients with DM Type 2 (Table 3), although they were on oral antidiabetic therapy and it would be reasonable to expect that FG and HbA1c levels do not increase due to antidiabetic therapy. This result suggests significant effects of statin therapy on FG and HbA1c levels, regardless of antidiabetic therapy.

Although both atorvastatin and rosuvastatin are high-potency statins with similar activity profile (16), they differ in hydrophilicity (14,15). Atrovastatin is lipophilic statin, and they passively diffuse through the hepatocellular membrane and similarly, they are also able to diffuse in extrahepatic tissues, thus showing reduced hepatoselectivity. On the other hand, rosuvastatin is hydrophilic statin, and it targets the liver more efficiently because their uptake is carrier-mediated (14,15). Despite this, numerous data indicate that both statins affect the glucose metabolism. Atorvastatin is associated with a significant increase in FG (4), it also had a particularly marked effect on HbA1c (17,19), which we also showed in this study. Rosuvastatin has a significant effect on the increase of FG in non-diabetic patients (4), as well as HbA1c (2,17).

Several other studies have examined the effects of atorvastatin and rosuvastatin in diabetic and non-diabetic patients, and the results are inconsistent. The results of the meta-analysis on statins and glycemic control (18) and the results of a few other studies in patients with diabetes suggest that statin therapy is associated with a modest increase in HbA1c (17,27,28), which we also showed for atorvastatin. The effects of atorvastatin and rosuvastatin in non-diabetic patients are inconsistent. Although a few studies have reported a significant increase in HbA1c in non-diabetic atorvastatin and rosuvastatin users (17,29), a randomized trial of these two statins in non-diabetic patients reported that HbA1c levels were similar to baseline after 3 months of treatment (23). We have not tested the differences in the diabetogenic effects of these statins in non-diabetic patients because we had insufficient number of non-diabetic patients for statistical analysis and this is the main limitation of this study. Pre-existing diabetes, due to various factors, worsens over time regardless of statin therapy; therefore, it would be significant to examine and compare the impact of long-term statin therapy in both diabetic and non-diabetic patients, especially considering the study that showed that neither of high-potency statins investigated (atorvastatin and rosuvastatin) had significant effect on HbA1c in non-diabetic patients (23). However, we still showed that the effects of atorvastatin on HbA1c are significant in the total sample, which includes both diabetics and non-diabetic patients (Table 1). Furthermore, one of the limitations of this study is the fact that statin users were not on statin therapy of equal duration. We overcame that limitation by the correlation of the duration of the therapy and levels of FG and HbA1c which was strongly significant. Thus, as the CVD patients included in this study were under statin therapy in the intervals from 5 to 216 months for patients on atorvastatin, and 5-174 months for rosuvastatin, the correlation between duration of statin therapy and monitored parameters (FG and HbA1c) was tested (Table 3). Obtained results have shown a strong significant correlation between FG and HbA1c with the duration of statin therapy in total sample (Table 3), and in diabetogenic CVD patients (Table 4), suggesting that long-term therapy with both, atorvastatin or rosuvastatin, may have significant diabetogenic effects, but the atorvastatin therapy has more significant effects, especially on HbA1c, which is consistent to previous findings. In addition, these results could be explained by the fact that atorvastain is lipophilic statin which is able to diffuse in extrahepatic tissues (14,15). One of the proposed explanations is that the higher diffusion rate of lipophilic statins to the intracellular space can interfere with cellular processes, leading to decreased intracellular insulin secretion in response to glucose (29), consequently upregulating the gluconeogenesis. Considering recent findings that showed atorvastatin is inducing hepatic gluconeogenesis (5), the increase of FG level and HbA1c may be consequence of atorvastatin-induced hepatic gluconeogenesis.

CONCLUSION

Long-term therapy with high-potency statins, atorvastatin, and rosuvastatin may increase levels of FG and HbA1c in patients with CVDs, where atorvastatin still shows more significant effects on glucose metabolism compared to rosuvastatin. Considering that statin therapy is very important in the prevention and treatment of CVDs, it is necessary to find the way to increase the benefits of these drugs and reduce their diabetogenic effects.

AVAILABILITY OF DATA

The dataset used and/or analyzed during the present study are available from corresponding author on reasonable request.

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DECLARATION OF INTEREST

Authors declare no conflict of interest.

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