COMPARISON OF ROSUVASTATIN AND ATORVASTATIN FOR LIPID LOWERING AND SAFETY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract: Introdution. Dyslipidemia is associated condition of type 2 diabetes. Statins are first line therapy for dyslipidemia. They can cause elevations in liver biochemistries and there is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity. The aim of the study was to compare rosuvastatin with atorvastatin in reducing of lipids and their effect on hepatic enzymes.
Material and methods. Prospective study on internal department in Clinical Hospital, Shtip, R of North Macedonia was performed. All patients with type 2 diabetes and dyslipidemia, who had been consecutive exanimated from January to April, 2019 year, without previously treatment with statins, were enrolled in the study. The choice of drug (rosuvastatin or atorvastatin) was random. The dose of statins were chosen depending of atherosclerotic cardiovascular disease (ASCVD) score. Fasting lipids, hepatic transaminases, creatinin phosphokinase, fasting glycaemia, and glycosylated hemoglobin (HbA1c), at baseline and after 2 months treatment with rosuvastatin or atorvastatin, were measured. Data were analyzed by SPSS statistical software using t-test for dependent samples.
Results. Twelve (20%) man and 48 (60%) women, with mean age of 66 years, and mean body mass index=27kg/m2 finalised the study. Forty two patients (70%) received rosuvavstain, and 18 (30%) received atorvastatin. The two groups were well matched according the age and BMI. The average used doses of rosuvastatin and atorvastatin were 15.35 ± 4.98, and 22.0 ± 12.24mg, respectively. Both statins significantly reduced total cholesterol, LDL-C, and triglicerides. HDL-C level was increased, but without statistical significance. Rosuvastatin reduced total cholesterol and LDL-C levels more than atorvastatin. Atorvastatin reduced triglyceride levels more than rosuvastatin. Both of the statins didn't changed hepatic transaminase and creatinin phosphokinase levels during treatment. The mean values of hepatic transaminases were even lower after treatment. Fasting glycaemia and HbA1c decreased without statistical significance after treatment. Both treatments were similarly well tolerated with no unexpected safety concerns.
Conclusion. Statins are potent and safe drugs for dyslipidemia in patients with diabetes, and they have no adverse effect on liver function. According to our results rosuvastatin should be preferred statin when LDL-C is with higher values, and atorvastatin should be preferred when in addition to LDL-C, triglyceride should also be reduced.
Keywords: atorvastatin, dyslipidemia, rosuvastatin

1. INTRODUCTION

Dyslipidemia is common in diabetes and there is strong evidence that cholesterol lowering improves cardiovascular outcomes. There is an association between atherosclerotic cardiovascular disease and serum cholesterol and triglyceride levels in diabetic patients. There is strong and convincing evidence that cholesterol lowering therapy significantly reduces cardiovascular disease in patients with diabetes (Colhoun et al, 2004; Kearney et al, 2008).
Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors) are the mainstay of therapy for dyslipidemia, esspecially in lowering LDL-C (Perk et al, 2012). They are the most prescribed class of medications. Several statins are available, differing in their absorption, bioavailability, plasma-protein binding, excretion, and solubility profiles. Statins are used in primary and secondary prevention of cardiovascular diseases. Despite their proven efficacy, statins can provoke muscle and liver injury. Statins can cause elevations in liver biochemistries and there is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity (Gazzerro et al, 2012). All statins are cleared by the liver and their clearance depends on hydrophobicity. The more hydrophilic compounds, exhibit more pronounced active renal excretion, while the lipophilic compounds are mainly excreted by the liver (Pastoria et al, 2015).
So, statin use could cause a mild rise in serum liver enzymes, which may rarely become severe and require treatment discontinuation. The exact mechanism by which statins cause ALT elevations is uncertain and liver damage is extremely rare (Colivicchi, Sternhufvud & Gandhi, 2015).
The objective of this study was to compare the atorvastatin and rosuvastatin in efficacy and safety in patients with diabetes.

2. MATERIAL AND METHODS

Sixty patients with diabetes and dyslipidaemia were enrolled in the study. In all patients statins were prescribed for the first time. The choice of drug was random. The dose of statins were chosen depending of ASCVD score. Before and after 2-2.5 months of the statin therapy, fasting glyacaemia, HbA1c, total cholesterol, LDL-C, HDL-C, triglyceride, alanine aminotransferase (AST), aspartate aminotransferase (ALT), and creatinin phosphokinase (CK) were measured.

The study did not include patients with hepatic or renal insufficiency, serum creatinine kinase (CK) levels >3 × the upper limit of normal (ULN), and known hypersensitivity to statins.

Data were analyzed by SPSS statistical software using t-test for dependent samples. Results are presented as averages and percentages. Less than 0.05 is considered statistically significant.

3. RESULTS

Sixty patients, 12 (20%) man and 48 (60%) women, in mean age 66,1 ± 7,07 years with mean BMI=27 kg/m2 were analyzed. Forty two patients (70%) received rosuvavstain, and eighteen (30%) received atorvastatin. The two groups were well matched according the age. The average used doses of rosuvastatin and atorvastatin were 15.35 ± 4.98, and 22.0 ± 12.24mg, respectively. After mean period of 2.1 months the analyzed variables were again collected. The average values of lipids before and after tretamen with atorvastatin and rosuvastatin are shown in table 1.

Table 1. The average values of lipids before and after statin therapy

	Aatorvastatin		P-value	Rosuvastatin		P-value
Total cholesterol (mmol/L)	6.0 ± 0.55	4.02 ± 0.88	<0.05	5.9± 1.45	3.62 ± 1.19	<0.001
LDL-C (mmol/L)	3.36±0.4	2.37±0.3	<0.001	3.15±0.6	2.04±0.3	<0.001
HDL-C (mmol/L)	1.25±0.4	1.28±0.4	NS	1.32±0.3	1.37±0.2	NS
Triglicerides (mmol/L)	2,21±0,9	1,28 ± 0,67	<0.05	2,23±0,9	1,35 ± 0,48	<0.05

NS-non significant

Both treatments were well tolerated. There were no cases of myopathy. There were no clinically relevant changes in AST or ALT (>3 × ULN), they even reduced after teratment. There were no clinically important elevations in CK in either group throughout the study (table 2).

Glycemic parameters were improved before treatment with statins. The difference before and after treatment remained no-significant (table 2).

Table 2. The average values of hepatic enzymes and glycemic parameters before and after treatment

	Before statin treatment	After statin treatment	P value
AST (IU/L)	23.68 ± 12.5	23.0± 7.9	NS
ALT (IU/L)	21.93 ±14.1	20.06± 6.13	NS
CK (IU/L)	71.37±23	188.3±87	NS
fasting glycaemia (mmol/L)	8.7± 4.0	6.8 ± 1.9	NS
HbA1c (%)	8.45 ± 2.8	7.32± 2.1	NS

NS-non significant

4. DISCUSSION

Patients with type 2 diabetes most commonly have elevated LDL-C, elevated triglyceride and low HDL-C, which is associated with a high risk of cardiovascular disease. We made a comparison of the effects of rosuvastatin and atorvastatin on lipids and hepatic enzymes in type 2 diabetic patients.

Both statins significantly reduced total cholesterol, LDL-C, and triglyceride after 2 months of treatment. There were difference in mea dose between the two statins. In the atorvastatin group, the mean dose was lower than the dose of rosuvasatatin (22.0 ± 12.24, and 15.35 ± 4.98mg, respectively). The most of the patients achieved LDL-C goals after 2 months period of treatment. But, there were still a number of patients which did not achieved triglyceride goals. Probably they need longer treatment.

According to the results, rosuvastatin was superior in lowering the total cholesterol and LDL-C in diabetic patients, but the dosage of rosuvastatin was higher. Otherwise, atorvastatin showed superiority in lowering of triglyceride.

Patients with type 2 diabetes who have dyslipidemia should be treated with statins. Our results suggest that atorvastatin should be used in patients with higher triglyceride. Of course, if triglyceride values are significantly increased, then the first choice is fibrates.

Previously published studies have shown rosuvastatin was more effective than atorvastatin in reducing a range of total cholesterol, non-HDL-C, LDL-C/HDL-C ratio, non-HDL-C/HDL-C ratio, and total cholesterol/HDL-C ratio (De Backer et al, 2003; Berne & Siewert-Delle, 2005). Also, both statins produces increases in HDL-C (8). Zhao et Peng showed non-inferiority of rosuvastatin 5 mg and superiority of rosuvastatin 10 mg compare to atorvastatin 10 mg for lowering LDL-C in high-risk Chinese patients with dyslipidemia (Zhao & Peng, 2018). In our study the doses of HDL-C wasn't changed significantly. They were lower after 2 months treatment but without significant importance. Maybe longer treatment of larger number of patients will showed statistical significance.

Type 2 diabetes is associated with hepatic steatosis. Hepatic adverse effects are one of the most commonly known adverse effects reported with statins. Statin use need not be avoided in patients with preexisting liver dysfunction such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and compensated chronic liver disease if its use is clearly indicated (Jose, 2016). In this study atorvastatin and rosuvastatin didn't influence significantly on hepatic enzymes, so they are save for use in patients with type 2 diabetes. But we must mention that almost all patients have normal transaminases before starting with statin therapy.

Kalantari & Naghipour (2014) found no relationship between different doses of atorvastatin prescribed and ALT/AST changes in the patients. But their levels were higher after statin treatment compare with its baseline values. Two retrospective studies examining 7473 patients with mildly elevated transaminase levels found fewer severe increases in transaminase levels in patients using statins than in patients not using them over a 12-month period (Chalasani et al, 2004; Vuppalanchi, Teal & Chalasani, 2005). A small study of 68 patients with biopsy-proven nonalcoholic fatty liver disease showed no change in liver enzymes but a statistically significant 46 percent reduction in the quantitative steatosis on repeat biopsy in the 17 patients taking statins at follow-up (Ekstedt et al, 2007). Two small studies evaluating patients with nonalcoholic steatohepatitis showed no change (seven patients)15 or a reduction (five patients)12 in liver enzymes among those taking statins, both studies also demonstrated some degree of improvement in liver pathology (Hortander, Kwo, Cummings & Koukoulis, 2001; Rallidis, Drakoulis & Parasi, 2004).

Fasting glycaemia and HbA1c improved after 2 months treatment probably because of intervention in patient's hypoglycemic therapy.

There are only few studies in our country which compare these two kinds of statins in their potency, and no studies in analyzing their safety on hepatic function in diabetic patients. On the other hand, the study wasn't double blind randomized study, and includes small number of patients, especially small number of patients treated with atorvastatin. Future larger study on our population should be done.

5. CONCLUSION

Statins are potent and safe drugs for dyslipidemia in patients with diabetes, and they have no adverse effect on liver function.

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