

ATORVASTATIN INFLUENCE ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

In type 2 diabetes mellitus (DM 2) clinical consequences of atherosclerosis represent the main cause of mortality. LDL cholesterol and atherosclerosis are related in both healthy and diabetic subjects but the predisposition for atheroma is higher for those with DM 2, although their LDL cholesterol levels are similar to those of healthy subjects. This is because LDL particles are altered under diabetic conditions and become more atherogenic.

In our study we evaluated the efficacy of atorvastatin and found that the treatment with oral antidiabetic agents in combination with atorvastatin contributes to an improvement of glycemic control, the combined therapy being more effective than oral antidiabetics alone.

Rezumat

În diabetul zaharat de tip 2 (DZ 2) cauza principală de mortalitate este reprezentată de consecințele clinice ale aterosclerozei. LDL-colesterolul și ateroscleroza sunt relaționate atât în cazul subiecților sănătoși cât și al celor cu diabet, numai că la cei cu DZ 2 predispoziția pentru ateromatoză este mai mare, deși nivelurile lor de LDL-colesterol sunt similare cu cele ale subiecților sănătoși. Aceasta se datorează faptului că particulele LDL sunt modificate în condițiile diabetului și devin mai aterogenice.

În studiul realizat am evaluat eficacitatea atorvastatinei și am constatat că administrarea antidiabeticelor orale în asociere cu atorvastatina contribuie la o îmbunătățire a controlului glicemic, asocierea fiind mai eficientă decât antidiabeticelor orale administrate în monoterapie.

Keywords: atorvastatin, type 2 diabetes mellitus, glycemia.

Introduction

Type 2 diabetes mellitus (DM 2) is a complex disease associated with an increased risk of coronary heart disease and premature death. DM 2 importance as a risk factor for cardiovascular disease (CVD) is clear and the

latest recommendations of the European Society of Cardiology (ESC) Guidelines, in which diabetes is listed as a separate risk factor, mention that cardiovascular risk is at least twice higher in diabetic subjects than in those without diabetes [1].

Scientific data proved that LDL lowering with statins, in a variety of populations at risk for CVD, reduced the relative risk for cardiovascular events [2-5].

According to a meta-analysis of 14 randomized trials, statin therapy reduces the risk of major coronary events in patients with diabetes but without vascular disease [2, 3]. After the meta-analysis of five primary prevention trials data, statins therapy reduces major coronary events risk in a similar way in both diabetic patients and patients without diabetes [4]. Statins improve endothelial dysfunction by stimulating nitric oxide (NO) production in endothelial cells, modulating the release and action of vasoconstrictors [6].

In our study we aimed to evaluate atorvastatin effectiveness in reducing cardiovascular risk, improvement of glycemic control, lipid metabolism and decrease of inflammatory biomarkers in patients with DM 2.

Materials and methods

Patients with DM 2 enrolled in this study were recruited from the Clinic of Diabetes, Nutrition and Metabolic Diseases, Center for Cardiology and Clinic of Neurology, Emergency County Hospital, Craiova following the informed consent signed by each patient. Distribution of patients in groups was made according to a study protocol approved by the Ethics Committees of UMF Craiova and Emergency County Hospital. 84 patients were divided into two groups, respectively group A- 43 patients without manifested cardiovascular disease (CVD) and group B – 41 patients with acute cardiovascular events (CVE). Each group had two subgroups: patients without lipid lowering treatment (A1=23 patients, B1=22 patients) and patients treated with atorvastatin (A2=20 patients, B2=19 patients). Exclusion criteria included the presence of associated pathology that may have a major influence on statin bioavailability and other pharmacokinetic parameters (liver failure, heart failure, chronic renal failure), presence of microalbuminuria, participation in weight loss programs, administration of nonsteroidal antiinflammatory drugs (NSAIDs), therapy with cytochrome P450 3A4 (CYP3A4) inhibitors (macrolides, cyclosporine, ketoconazole, tacrolimus, fibrates, grapefruit juice, etc.), therapy with CYP3A4 inducers (barbiturates, griseofulvin, rifampin, phenytoin, etc.), therapy with

amiodarone, verapamil (increase the myopathy risk), chronic alcohol consumption, smoking, glycated hemoglobin (HbA1c) over 8%, blood pressure (BP) $\geq 130/80$ mmHg with or without antihypertensive therapy.

Of the 84 patients enrolled, 7 patients were new cases of type 2 diabetes and therefore they did not receive antidiabetic therapy at the time of sampling. 51 patients received sulfonylureas (glimepiride, glibenclamide) and 26 patients were treated with biguanides (metformin).

Of the 77 patients that received antidiabetic therapy, 17 received atorvastatin in a dose of 10 mg/day and 22 patients in a dose of 20 mg/day (distributed in groups A2 and B2) in two dosing regimens: 8 patients from those treated with 10 mg/day and 10 patients treated with 20 mg/day had received the drug for a short period of time, between 4-8 weeks, and 9 patients from those treated with 10 mg/day and 12 patients treated with 20 mg/day for a long period, between 12-24 weeks.

Biochemical evaluation

We collected venous blood samples *à jeun*, processed them to obtain plasma in order to assess fasting plasma glucose, plasma lipids and lipoproteins (total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol) and glycated hemoglobin (HbA1c). Fasting plasma glucose and plasma lipids were assessed by enzymatic methods adapted for automatic devices using commercial kits (Abbott Diagnostics). HbA1c was evaluated using a latex enhanced turbidimetric immunoassay (Dialab). LDL-cholesterol was calculated using Friedewald's formula.

Statistical analysis

All results are expressed as mean $\pm$ standard deviation (SD). Clinical characteristics of patients were compared among groups using one-way analysis of variance (ANOVA). Pearson correlation coefficients were calculated to evaluate the relationship between metabolic parameters. For all comparisons, p values <0.05 were considered as statistically significant.

Results and discussion

The average age for the group of patients without manifested CVD (group A) was 53.61 ± 6.68 years and the distribution by sex showed a predominance of women (61.9% vs. 38.1%); in the group of patients with acute CVE (group B), the average age was 69.88 ± 9.56 years, with a predominance of men, 72.22% vs. 27.78%. We observed that acute CVE events had a higher incidence in men than in women, mainly in those aged between 60-80 years. In group A, the average time from diabetes onset was

42.61 $\pm$ 57.86 months and in group B, 29.05 $\pm$ 49.49 months, which suggests, surprisingly and contrary to literature data [7], that the time from DM 2 onset did not influence acute CVE incidence. In diabetic patients, acute myocardial infarction or stroke may occur irrespective of the time interval since DM 2 onset, but dependent on the existence of metabolic imbalance.

Parameters characterizing carbohydrate metabolism, glycemia and glycated hemoglobin, had increased significantly ($p < 0.05$) in patients with acute CVE without lipid-lowering treatment, 165.5 $\pm$ 12.87 mg/dL, respectively 7.4 $\pm$ 0.39 %, compared with those without manifest CVD untreated with lipid-lowering drugs, 147.23 $\pm$ 22.39 mg/dL, 6.54 $\pm$ 0.41% respectively, which highlights the importance of maintaining glycemic control to prevent acute CVE in diabetic patients.

There are no studies devoted exclusively to demonstrate the effect of lipid-lowering treatment on morbidity and mortality in diabetic patients with acute CVE, but studies which evaluated the effectiveness of lipid-lowering medication in people with cardiovascular risk included subjects with diabetes in different proportions. The analysis of their results showed a significant decrease in the number of cardiovascular events in people with diabetes who received atorvastatin [5, 9].

In our study, plasma glucose and glycated hemoglobin levels were significantly higher ($p < 0.05$) in patients untreated with lipid-lowering drugs (subgroups A1 and B1) than those who received treatment with atorvastatin (subgroups A2 and B2) (Fig.1), were independent of dose, but were significantly lower in patients who had a long period of therapy (12-24 weeks vs. 4-8 weeks).

Therefore, we suggest that atorvastatin influences glycemic control to reduce glycemia and HbA1c levels, the dose of 10 mg/day or 20 mg/day of atorvastatin proved to be insignificant in this regard, observation reported also by other researchers in various recent publications [8,9], although the subject remains controversial.

The analysis of blood glucose levels and glycated hemoglobin (HbA1c) didn't reveal significant changes between patients treated with metformin and atorvastatin compared with those treated with glimepiride or glibenclamide and atorvastatin, suggesting that both classes of oral agents have similar action and efficacy on the carbohydrate metabolism (Table I). A significant decrease ($p < 0.05$) was observed in patients given oral antidiabetics and atorvastatin compared with patients not treated with atorvastatin, which proves that atorvastatin helped to improve the glycemic control (Table I).

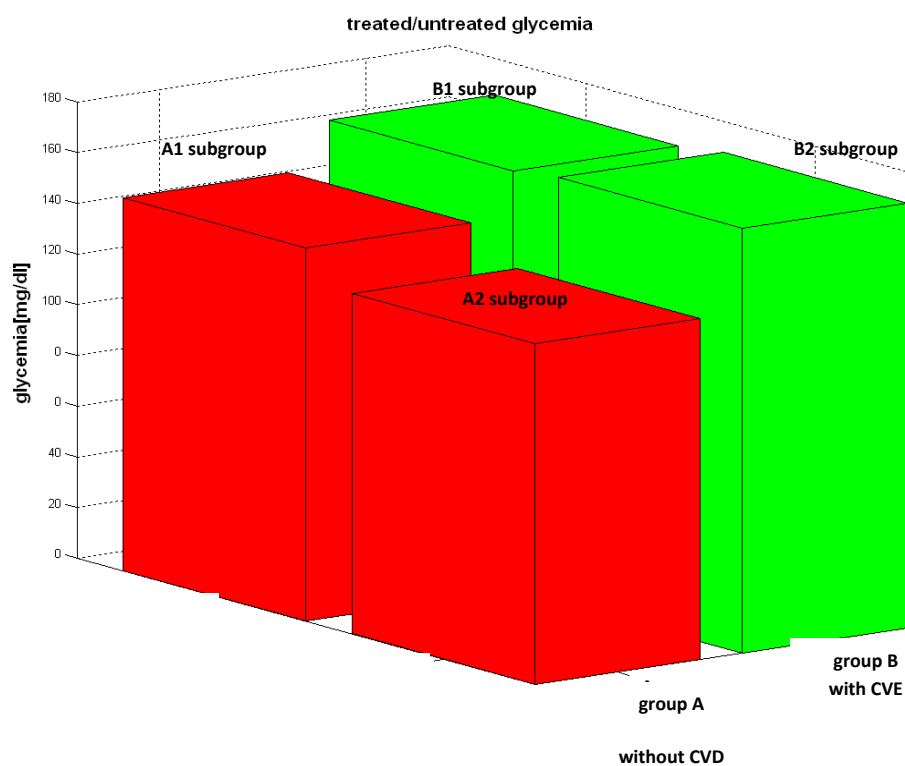


Figure 1

Graphic representation of plasma glucose levels in patients without cardiovascular disease (CVD, group A) and in patients with cardiovascular events (CVE, group B), untreated with lipid-lowering (A1, B1 subgroups) and treated with atorvastatin (A2, B2 subgroups)

Table I

Values of carbohydrate metabolism parameters (mean $\pm$ SD) in patients with type 2 diabetes, according to the oral type of antidiabetic administered

Parameter	Biguanides and atorvastatin	Sulfonylureas and atorvastatin	Biguanides	Sulfonylureas
Glycemia[mg/dl]*	147.21 $\pm$ 1.41	148.03 $\pm$ 2.16	156.16 $\pm$ 2.22	161.12 $\pm$ 3.12
HbA1c [%]**	6.84 $\pm$ 0.18	6.88 $\pm$ 0.15	7.08 $\pm$ 0.62	7.19 $\pm$ 0.44

Note: Statistical significance: *p = 0.035, **p = 0.025

Note: There were compared the following groups of patients:

- biguanides and atorvastatin vs. biguanides
- sulfonylureas and atorvastatin vs. sulfonylureas

Horvath et al. (2008) reported that atorvastatin can directly affect cholesterol status in a non-hepatic cell line (the reduction of cholesterol synthesis resulting in a concomitant decline in plasma membrane (PM) cholesterol which translates to an improved cellular response to insulin, as evidenced by an amplified insulin-regulated GLUT4/glucose transport response [8]. They predicted that this statin-induced PM effect also occurs in skeletal muscle, a tissue responsible for approximately 80% of post-prandial glucose disposal and is regarded as a major peripheral site of insulin resistance in diabetes [8].

Recent studies call into question that lipophilic statins can reduce insulin sensitivity, but their effects are controversial in humans. Some researchers have found that simvastatin and atorvastatin improve insulin sensitivity in some patients with diabetes, while others showed that simvastatin didn't change nor worsened insulin sensitivity in diabetic patients, significantly increased levels of insulin and leptin and decreased levels of adiponectin and insulin sensitivity [9, 10]. In contrast, pravastatin increased adiponectin levels and insulin sensitivity and didn't modify insulin and leptin levels [10].

These new data add important perspectives of clinical significance.

Although there were demonstrated comparable effects on lipoproteins and endothelium-dependent dilation, simvastatin and pravastatin have differential metabolic effects in patients with hypercholesterolemia, effects that could have therapeutic implications for patients with insulin resistance [10].

Other studies reported that atorvastatin attenuates glucose transporter GLUT4 expression in adipocytes by altering glucose tolerance [11].

Due to the controversy raised, the mechanisms by which statins have different effects on insulin sensitivity are not clearly elucidated and require further evaluation.

Conclusions

Statins have beneficial pleiotropic effects on vascular wall cells. The treatment with statins was one of the most significant advances in the prevention and treatment of atherosclerosis. The benefits of statin therapy in reducing cardiovascular risk extend beyond their effects on serum lipids.

Diabetic patients who used oral antidiabetic agents in combination with atorvastatin had lower glucose levels than those who received only oral antidiabetic therapy.

Atorvastatin therapy in type 2 diabetes mellitus patients regardless of LDL-cholesterol levels helps to maintain the optimal metabolic balance which results in a reduction of the risk of micro and macrovascular complications (particularly acute myocardial infarction), a decrease of expenditure for hospitalization and an improved quality of life in these patients.

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