

STATIN THERAPY IN PATIENTS WITH DIABETES AND HEPATITIS C

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Abstract

The objective of this study was to determine the effects of statin therapy (atorvastatin) on serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with type 2 diabetes mellitus (T2DM) and chronic hepatitis C (CHC).

A number of 77 patients with T2DM and CHC were selected, treated with atorvastatin, 20 mg, for 6 months, who underwent anthropometric measurements and biochemical tests (including fasting serum glucose, lipid profile, liver profile, cytokines profile) at baseline, after 1 month (clinical and biochemical profile for safety) and after 6 months of treatment.

The patients' average age was 52.53±9.7 years. Plasma low-density lipoprotein cholesterol (LDL-C) (-32.4 mg/dL), triglycerides (-29.7 mg/dL), total cholesterol (-32.8 mg/dL) decreased ($p<0.05$), and high-density lipoprotein cholesterol (HDL-C) (+3.04 mg/dL) increased ($p<0.05$), after 6 months. Atorvastatin treatment was associated with decreases of AST, ALT, and also leptin and interleukin-6 (IL-6) levels (all $p<0.05$) but we did not find any effect on plasma tumor necrosis factor-alpha (TNF- α) ($p=0.119$).

Atorvastatin was an effective and well tolerated treatment for lowering total cholesterol, LDL-C, triglycerides in patients with CHC. Among patients with CHC there was no significant elevation of liver enzymes during statin treatment, and we even noticed an improvement of hepatic profile.

Rezumat

Obiectivul acestui studiu a fost de a evalua influența tratamentului cu statine (atorvastatină) asupra aspartataminotransferazei (AST) și alaninaminotransferazei (ALT) la pacienții cu diabet zaharat tip 2 (DZT2) și hepatită cronică C (CHC).

Au fost selectați 77 de pacienți cu diabet zaharat tip 2 și CHC, tratați cu atorvastatină, 20 mg, timp de șase luni, la care am analizat parametrii antropometrici și testele biochimice (glicemia *à jeun*, profilul lipidic, profilul hepatic, profilul citokinelor) la momentul inițial, la 1 lună (evaluare clinică și biochimică pentru evaluarea siguranței) și la 6 luni.

Vârsta medie a fost de 52,53±9,7 ani. Nivelul plasmatic al lipoproteinelor cu densitate mică (LDL-C) (-32,4 mg/dL), al trigliceridelor (-29,7 mg/dL) și colesterolului total (-32,8 mg/dL) a scăzut ($p<0,05$), iar lipoproteinele cu densitate înaltă au crescut

(HDL-C) (3,04 mg/dL) ($p < 0,05$), după 6 luni. Tratamentul cu atorvastatina a fost asociat cu scăderea AST, ALT, a leptinei și interleukinei-6 (IL-6) (toate $p < 0,05$), dar nu s-a observat niciun efect asupra factorului de necroză tumorală-alfa (TNF- α) ($p = 0,119$).

Atorvastatina a fost un tratament eficient și bine tolerat pentru scăderea colesterolului total, LDL-C și trigliceridelor la pacienții cu CHC. La pacienții cu CHC nu a existat nicio creștere semnificativă a enzimelor hepatice în timpul tratamentului cu statine, s-a observat chiar o îmbunătățire a profilului hepatic.

Keywords: atorvastatin, diabetes, hepatitis C

Introduction

In 2005, the prevalence of hepatitis C virus (HCV) infection worldwide was estimated at 2.8% and the prevalence of HCV in Europe was 1.5-3.5% [1].

Recently, there has been growing evidence to suggest an association between HCV infection and diabetes mellitus (DM). A high prevalence of DM has been reported among patients chronically infected with HCV in comparison with controls or patients with other liver diseases [2-7]. Statins are the most efficacious drugs for decreasing low-density lipoprotein cholesterol levels (LDL-C); they reduce both primary and secondary cardiovascular risk in general population.

In diabetic patients without cardiovascular diseases (CVD), the target goal for LDL-C is 100 mg/dL (2.6 mmol/L) and, in individuals with CVD, a lower LDL-C goal of 70 mg/dL (1.8 mmol/l), using a high dose of a statin, is an option [8].

However, less is known about the safety of statin use in patients with liver disease. Statins have activity against HCV [9, 10] and, in fact, some statins appear to have greater anti-HCV activity than others [10]. The objective of this study was to determine the effects of statin therapy (atorvastatin) on serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with type 2 diabetes (T2DM) and chronic hepatitis C (CHC).

Materials and Methods

The DIADIPOHEP (Adipocitokynes, link between virus C hepatitis and type 2 diabetes mellitus) study reported was approved by the Romanian National Authority for Scientific Research. The study was approved by the Ethics Commission of the hospital. There were selected 77 patients (38 males, 39 females) with history of CVD with T2DM and CHC, treated with atorvastatin, 20 mg for 6 months, who underwent anthropometric measurements (weight, height, BMI (body mass index)), blood pressure measurement and biochemical tests (glucose, glycated hemoglobin), lipid

profile (cholesterol, triglycerides, HDL-cholesterol (HDL-C)), liver profile (aspartate aminotransferase (ALT), alanine aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase, bilirubin, albumin, total protein), blood count, adipocytokine profile (adiponectin, leptin, tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6)) at baseline, 1 month (clinical and biochemical safety profile) and 6 months after the statin therapy. Before inclusion in the study all patients signed an informed consent. Cardiovascular risk was evaluated using the UK Prospective Diabetes Study (UKPDS) prediction score.

BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Based on the World Health Organization classification, overweight was defined as BMI between 25 and 29.9 kg/m², and obesity was defined as BMI over 30 kg/m² [11]. We also measured waist circumference (in centimeters) in the middle between the 12th rib and iliac crest.

Arterial blood pressure was measured three times at the end of the physical examination with the subject in sitting position. Participants whose average blood pressure levels were greater or equal to 140/90 mmHg or using antihypertensive medication were classified as hypertensive subjects [12].

Hypercholesterolemia was defined as total serum cholesterol levels greater than 170 mg/dL or the use of lipid-lowering agents, hypertriglyceridemia as triglycerides levels over 150 mg/dL, hypoHDL-cholesterolemia as HDL-C below 40 mg/dL and DM as a blood sugar \geq 126 mg/dL or the use of antidiabetic medication. [13] LDL-C was estimated using the Friedewald formula: estimated LDL-C = [total cholesterol] - [total HDL] - [estimated very low density lipoproteins (VLDL)]. VLDL can be calculated by dividing total triglycerides by 5. Direct LDL-C measures were used when triglycerides exceeded 300 mg/dL [14].

Insulin resistance (IR) was determined using Homeostasis model assessment (HOMA-IR) (fasting insulin level (mUI/L) x fasting glucose level (mg/dL)/405 [15].

The liver fibrosis was non-invasively assessed using the Forns index; a value < 4.2 excludes liver fibrosis and a value > 6.9 is a predictor for significant fibrosis [16].

Forns fibrosis index is based on platelet count, GGT, age and cholesterol levels, according to the formula:

$$7.811 - 3.131 \times \ln(\text{platelet count}) + 0.781 \times \ln(\text{GGT}) + 3.467 \times \ln(\text{age}) - 0.014 \times (\text{cholesterol}).$$

The AST to platelet ratio index (APRI) is a formula using the levels of serum AST concentration and platelet count. Its value is determined by the formula $\text{AST}/(\text{upper limit of normal})/\text{platelet count } (10^9/\text{L}) \times 100$ [17]. APRI is simpler to use than most of the other indices with similar performance to that of the Fibrotest (FT) and the Forns index. APRI was accurate in estimating fibrosis in patients with HCV [AUROC 0.87–0.89, sensitivity 94–100%, specificity 95–100%] [18,19] although some studies have reported that it cannot replace liver biopsy in the accurate staging of fibrosis in patients with hepatitis C. APRI <0.5 excludes liver fibrosis and a value ≥ 1.5 is a predictor for significant fibrosis.

CHC infection was defined by the presence of anti-HCV for at least 6 months and a positive HCV-viremia.

Patients with other etiology of chronic liver disease, hepatitis B virus infection, autoimmune liver disease, hemochromatosis, HIV infection, patients with history of hepatotoxic or steatosis-inducing drug use, patients having an alcohol consumption of more than 20 g/day for women and 30 g/day for men, history of pancreatitis were excluded from the study.

Other exclusion criteria included the use of any drugs known to affect lipid levels (eg, systemic steroids), immunosuppressive agents, or drugs associated with rhabdomyolysis in combination with statins (eg, cyclosporine, erythromycin).

Patients with T2DM and CHC were treated with metformin; no patients were treated with insulin. All patients were included into an educational program consisting of diet and exercises. The educational program included a description of the risk factors and their primary prevention, a distinct diet (with decreased calories, lipid and sodium intake) and moderate intensity exercises (at least 3 days/week, for minimum 30 minutes).

Statistics

Results for continuous normally distributed data were expressed as mean \pm standard deviations (SD). The two Test of Normality used were Kolmogorov-Smirnov with a Lilliefors significance correction and Shapiro-Wilk statistic. The comparison of mean value at baseline, 1 month and 6 months was performed with paired *t*-test for continuous data normally distributed. Rank based non-parametric tests were used when the data did not conform to the normally distributed ones. We used this test for AST, ALT, GGT because the data were clearly skewed and the outliers have an important effect. P-value less than 0.05 was considered significant. All statistical analyses were performed using SPSS 19 (Statistical Package for Social Software).

Evaluation of efficacy

The primary analysis of efficacy was the change in LDL-C from baseline to 6 months, and the proportion of patients who achieved the target LDL-C level of 70 mg/dL after 6 months of treatment. Secondary efficacy measures were changes in HDL-C, total cholesterol, total cholesterol/HDL-C ratio, triglycerides after 6 months of treatment.

Evaluation of safety

Adverse events were defined as any unfavorable and unintended sign (including any abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not related to the product. Evaluation of safety was made at 1 month and 6 months. No unifying criterion defines the incidence of drug-related liver test abnormalities and their clinical relevance. A post-marketing drug-induced hepatotoxicity white paper defined drug-induced liver injury by the presence of increases in ALT level of more than 2 to 3 times the upper limit of normal or in conjugated bilirubin level of more than 2 times the upper limit of normal. However, it has been proposed that increases in ALT level of more than 10 times the upper limit of normal should be used to differentiate true hepatotoxicity from transaminitis [20].

Results and Discussion

The average age of the patients was 52.53±9.7 years (min 35, max 70). Obesity was present in 33.8% (n=26) of patients at baseline and in 23.4% (n=18) after 6 months. We observed an average weight loss of 3.66 kg (95%CI 2.891-4.43) of the initial weight. Baseline and after 6 months characteristics of the 77 subjects included in the study are summarized in table I.

Table I
Characteristics of patients at baseline and after 6 months of treatment

Parameters	Baseline	after 6 months	p-value
BMI (kg/m ²)	29.5±4.74	27.7±4.17	0.012
WHR	0.96±0.1	0.94±0.09	0.001
Total cholesterol (mg/dL)	195.29±44.92	165.44±27.7	0.002
Triglycerides (mg/dL)	152.21±61.7	122.4±35.3	0.001
HDL-C (mg/dL)	39.6±9	42.6±7.7	0.0001
LDL-C (mg/dL)	130.9±47	98.4±28.2	0.001
TC/HDL-C ratio	5.34±2.23	3.98±1.16	0.0022
FPG (mg/dL)	121.79 ± 58.5	105±37.9	0.001
BP systolic (mm Hg)	145.47±31.2	140.34±22.4	0.003
BP diastolic (mm Hg)	95.96±12.4	90.34±18.2	0.001
HOMA-IR	6.2±2.92	3.7±1.81	0.02
Adiponectin (ug/mL)	5.67±2.5	7.32±3.11	0.002
Leptin (ug/mL)	20.1±10.44	17.01±10.4	0.046
TNF-α (pg/mL)	13.99±6.9	11.1±4.29	0.119
IL-6 (pg/mL)	13.78±1.66	11.39±4.18	0.001

Values are means±SD

Abbreviations: BMI, body mass index; WHR, waist to hip ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; FPG, fasting plasma glucose; BP systolic, systolic blood pressure; BP diastolic, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; TNF- α , tumor necrosis factor-alpha; IL-6, interleukin-6.

Liver steatosis measured by echography and analyzed by the same gastroenterologist did not change significantly after treatment; steatosis was present in 44 patients (57.1%).

At baseline hypercholesterolemia was present in 74% (n=57) patients, hypertriglyceridemia in 50.6% (n=39) and hypoHDL-cholesterolemia in 55.8% (n=43); all patients had LDL-C over 100 mg/dL. After 6 months 46 patients (59.7%) achieved the LDL-C target value, 34 patients (44.2%) achieved the HDL-C target, 48 patients (62.3%) achieved total cholesterol target, 61 patients (79.2%) achieved the triglycerides target.

Plasma LDL-C (-32.4 mg/dL) (Figure 1), triglycerides (-29.7 mg/dL), total cholesterol (-32.8 mg/dL) decreased ($p < 0.05$) and HDL-C (+3.04 mg/dL) increased ($p < 0.05$) significantly, after 6 months.

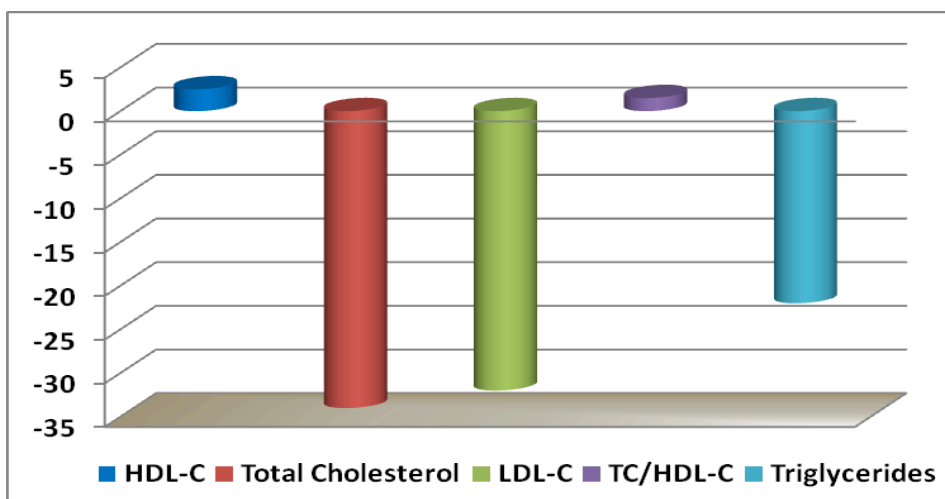


Figure 1
Median decrease in lipid parameters (mg/dL)

In table II there are presented the liver function tests at baseline, one and six months of treatment. AST and ALT decreased (the median decrease was 5 U/L for AST and 5 U/L for ALT) ($p = 0.062$ respectively $p = 0.033$). APRI decreased after 6 months ($p = 0.0001$). No side effects were reported in our study.

Table II
Liver function tests at baseline, one and six months of treatment

Parameters	Baseline	1 month	p-value (baseline-1 month)	6 months	p-value (baseline-6 months)
AST (UI/L)	53.55±30.9 (47)	52.05±31.8 (45)	0.175	48.37±30.32 (42)	0.062
ALT (UI/L)	61.5±32.4 (58)	59.42±32.2 (58)	0.005	56.5±31.5 (53)	0.033
GGT (UI/L)	65.78±41.5 (56)	63.5±40.4 (55)	0.01	63.3±39.4 (55)	0.035
Albumin (g/dL)	4.29±0.4	-	-	4.3±0.36	0.43
Bilirubin (mg/dL)	0.64±0.21	0.64±0.19	0.73	0.62±0.18	0.65
INR	1.05±0.19	-	-	1.02±0.17	0.43
AST/ALT ratio	0.94±0.4	0.92±0.33	0.209	0.93±0.33	0.684
APRI	0.29±0.04	-	-	0.26±0.02	0.0001
Forns index	2.5±3.2 (2.53)	-	-	2.5±2.8 (2.35)	0.736

Values are means±SD; for variables abnormal distributed we used median
Abbreviations: AST, aspartate-aminotransferase; ALT, alanine-aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; APRI, AST to platelet ratio index.

In patients with normal levels of AST (AST below 37 UI/L, n=37) there were no significant changes after 6 months ($p=0.67$). In patients with high levels of AST at baseline we observed a significant improvement under treatment with atorvastatin ($p=0.05$) - figure 2.

In patients with normal levels of ALT (ALT below 41 UI/L, n=23) at baseline we noticed improved values, without significance ($p=0.14$) - figure 2. Atorvastatin treatment decreased ALT levels in patients with high ALT levels at baseline ($p=0.002$).

In patients with normal or high GGT at baseline (GGT below 50 UI/L, n=42) we observed a significant decrease after 1 month and 6 months ($p=0.01$ respectively, $p=0.035$) - figure 2.

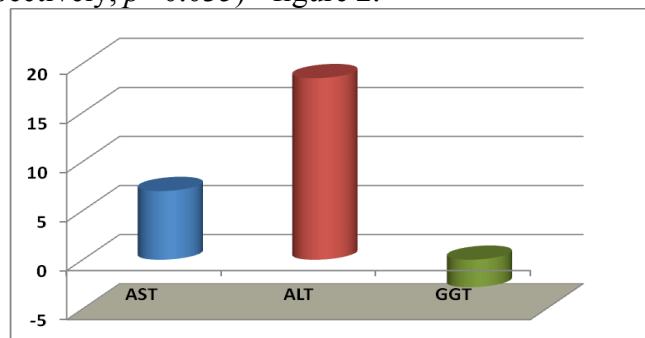


Figure 2

Median changes for the parameters of hepatic profile (UI/L)

Atorvastatin treatment was associated with reduced levels of leptin and IL-6 ($p=0.046$ respectively $p=0.001$) but we did not find any effect on plasma TNF- α ($p=0.119$). We observed a statistically significant increase of adiponectin level ($p=0.002$).

Atorvastatin, 20 mg/day, was an effective and well tolerated treatment for lowering total cholesterol, LDL-C and triglycerides in patients with chronic hepatitis C, without elevation of liver enzymes during treatment. In this study we observed an improvement of both lipid profile and liver enzymes (AST, ALT, GGT). Our results are in accordance with a recent paper published by Henderson *et al.* showing that, among HCV-infected patients, AST and ALT levels for the prescribed statins decreased over a 6 to 12-month follow-up period compared to patients not taking statins [21].

In our patients, after 6 months 59.7% achieved LDL-C target, 44.2% achieved HDL-C target, 62.3% achieved total cholesterol target and 79.2% achieved triglycerides target.

Current recommendations from the National Cholesterol Education Program Adult Treatment Panel III advise liver chemistry monitoring on initiation of statin treatment, 12 weeks after initiation, and then yearly or even before, if indicated (eg, when changing dose) [22]. No consensus exists about the best time to recheck liver biochemistry values. Because in our study patients presented viral liver diseases, for safety reasons, we monitored aminotransferases at 1 month. Other authors suggest repeating the analysis in patients with elevated aminotransferase levels after 3-6 weeks [23-25].

Normalization of the values of aminotransferases was observed not only in patients with chronic hepatitis C; in the Heart Protection Study trial, the liver profile was rechecked after 3 weeks with normalization in more than 70% of the cases [24]. Statin treatment is a promising option for the management of patients with steatohepatitis and dyslipidemia [26]. In patients who have increased aminotransferases, indicating lower doses of atorvastatin was effective in treating dyslipidemia associated with nonalcoholic steatohepatitis, as well as improving both biochemical and histopathological parameters (necroinflammatory component and steatosis) [27]. In another study in patients with nonalcoholic fatty liver disease and hyperlipidemia the use of atorvastatin was found to be both effective and safe and therefore, aminotransferases normalized in 56% [28].

Statin use was associated with an improved sustained virological response among both diabetics and non-diabetics receiving combination antiviral therapy [29].

Statins should continue to be avoided in advanced end-stage liver disease, as there is a lack of safety data in these patients and drug metabolism would be severely compromised.

Treatment with statins can be used in those with chronic, stable hepatitis C with elevated cardiac risk or a previous cardiac event [30].

These findings suggest that there is not a higher risk of alterations in liver biochemistry values in patients with chronic HCV infection.

In our study we observed an average weight loss of 3.66 kg (95%CI 2.891-4.43) of the initial weight. Modest weight loss alone is associated with normalization of aminotransferases [31] and weight loss reduced hepatic steatosis and fibrosis in patients with chronic HCV [32].

In this study, FPG and HOMA-IR index improved. Although treatment for diabetes was not modified, lifestyle changes and monitoring at shorter intervals of time have contributed to this improvement. In another study, Kon et al. showed that atorvastatin treatment increased fasting plasma insulin and glycated hemoglobin levels in patients with or without diabetes [33]. The data from Azzam Si et al. indicate that the use of atorvastatin did not have a significant effect on an insulin resistance measure [34]. Ionică FE et al. proved that atorvastatin helped to improve the glycemic control in diabetic patients [35].

Patients with diabetes, with obesity have an altered cytokine profile [36,37]. The effects of statins on serum leptin and adiponectin levels are controversial. Similar to the results of other studies treatment with atorvastatin was associated with increased adiponectin [38,39] and decreased leptin levels [39,40]. In other studies treatment with atorvastatin reduced the level of IL-6 [41].

National Lipid Association Statin Safety Task Force Liver Expert Panel [42] shown that asymptomatic elevations of aminotransferases is a class effect of statins and they do not indicate liver dysfunction, and chronic liver diseases or cirrhosis Child A should not be considered contraindications for use of statins. Liver failure which requires hospitalization or cause death or liver transplantation is rarely caused by statins [42].

Conclusions

Atorvastatin was an effective and well tolerated treatment for lowering total cholesterol, LDL-C and triglycerides in patients with hepatitis C. Among patients with chronic hepatitis C there was no significant elevation of liver enzymes during statin therapy; we even observed an improvement of liver profile. This practice is supported by increasing evidence that attests not only the safety but also the additional benefits of

statin therapy for these population groups. Statin therapy should not be stopped or contraindicated in this patient population; however, more prospective randomized placebo-controlled studies are needed to confirm the safety and efficacy of the studied therapeutic approach.

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