

Atorvastatin in the Treatment of Dyslipidemic Patients with Very High Cardiovascular Risk and Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic fat accumulation after ruling out other causes of hepatic steatosis. The aim of the study is to identify the role of statin therapy in dyslipidemic patients with very high cardiovascular risk and NAFLD in achieving low density lipoprotein (LDL) cholesterol targets while also evaluating the changes in liver enzymes levels. This prospective study included 140 patients with NAFLD, hyperlipidemia and elevated cardiovascular risk. Serum lipids were assessed and liver function tests were performed at baseline and at 6 months follow up in 10 mg/ 20 mg daily atorvastatin treatment schedule. The results showed that total cholesterol, LDL cholesterol and triglycerides were significantly reduced at 6 months follow-up, while high density lipoprotein (HDL) cholesterol has not undergone important changes. Statin treatment significantly improved alanine aminotransferase serum levels, whereas aspartate aminotransferase levels were not significantly reduced between baseline and follow-up. Although statin therapy appears to be safe and effective for use in patients with NAFLD, an insufficient treatment is commonly observed in clinical practice, in order to avoid liver damage. NAFLD is not only a major cause of liver related morbidity and mortality, but also an independent cardiovascular risk factor, with cardiovascular mortality being the most important cause of death. Therefore, detecting and modifying risk factors without impairing liver function is desirable.

Keywords: nonalcoholic fatty liver disease, cardiovascular risk, atorvastatin, dyslipidemia.

Nonalcoholic fatty liver disease (NAFLD) is defined as storage of triglycerides and free fatty acids in the liver after ruling out other causes of macrovesicular or microvesicular steatosis. NAFLD is the most common liver disease in developed countries, and its prevalence is increasing [1].

NAFLD is the first pathology on a histological spectrum of progressive liver diseases ranging from steatosis to steatohepatitis, liver fibrosis, cirrhosis and in some cases hepatocellular carcinoma. In one out of four patients NAFLD may progress to steatohepatitis [2].

Global prevalence of NAFLD varies depending on multiple factors. European prevalence in the general population is 20–30%. For males the prevalence of NAFLD is 2 times higher than for women [3].

Heart and liver function are closely associated, with heart diseases affecting the liver and liver diseases affecting the heart. There are also conditions affecting both organs simultaneously, which are caused by the same etiological factors [4].

NAFLD is not only associated with increased liver-related morbidity, but also with cardiovascular mortality, the most common cause of death in these patients being cardiovascular disease (CVD). A bidirectional association between NAFLD and the components of metabolic syndrome, such as abdominal obesity, insulin resistance, dyslipidemia, impaired fasting glucose or type 2 diabetes mellitus, has been established. The relationship between NAFLD and CVD involves risk factors other than traditional ones like atherogenic dyslipidemia or hepatic and peripheral insulin resistance. Independently, several proinflammatory and procoagulant liver synthesized factors, increased oxidative stress, altered adipokine

profile, endothelial dysfunction as well as genetic factors are involved in accelerated atherogenesis [5].

The gold standard for diagnosing NAFLD is liver biopsy. However, performing liver biopsy is not feasible in studies involving the general population, therefore the prevalence of NAFLD is estimated by indirect methods, such as abdominal ultrasonography [6].

The presence of an abnormal cardiometabolic phenotype with increased cardiovascular risk associated with the diagnosis of NAFLD may justify initiating statin treatment in this group of patients.

The association between statin therapy and an increased risk of elevated transaminases is common knowledge, but the risk is small and progression to liver failure is exceptionally rare. Stopping treatment or lowering the dose leads to normalization of liver enzyme levels [7]. Surprisingly, atorvastatin has been found to improve liver enzymes in patients with NAFLD [8].

Experimental part

Material and Methods

A total of 161 patients admitted to the Cardiology Clinic of Saint Spiridon Emergency Hospital in Iasi, Romania between January 2017 and December 2018 were initially enrolled in the study. Patients were evaluated at baseline using echocardiography, abdominal ultrasound, liver enzyme levels and lipid profile. All patients have also undergone a complete physical examination. The inclusion criteria in the study were: patients with NAFLD confirmed by ultrasound study, no lipid lowering drugs, low density lipoprotein (LDL) cholesterol higher than 70mg/dl, under

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treatment hypertension and very high cardiovascular risk (using SCORE system recommended by European Guidelines or classified in this group using ESC/EAS Guidelines for the management of dyslipidemias) [9]. LDL cholesterol was used as the primary lipid analysis. Exclusion criteria were chronic alcohol consumption, other causes of liver steatosis, chronic liver disease and decompensated heart failure. Additionally, the prevalence of uncontrolled hypertension was also evaluated. Left ventricular ejection fraction was calculated using Simpson's method. 20 patients were excluded from the study due to therapeutic non-compliance or loss of follow-up. 1 patient was excluded due to AST concentrations >3 times the upper limit at the 1 month follow-up evaluation. Ultimately, 140 patients were left in the study, 67 women and 73 men, aged between 48 and 88, with an average of 65.15 ± 11.19 years old. All 140 patients had high LDL cholesterol levels at baseline, and 70 patients (50%) also presented high triglyceride (levels >150mg/dL). From the first evaluation, all patients received treatment with atorvastatin 10 mg (n=99) and 20 mg (n=41) according to basal serum cholesterol levels. The patients also received dietary and lifestyle advice as part of NAFLD treatment. Subsequently, patients were evaluated at the 1 month and the 6 months follow-up. The Informed Consent Form was signed by all participants in the study.

The study aims to prospectively evaluate the role of statin therapy in dyslipidemic patients with NAFLD and very high cardiovascular risk in achieving LDL cholesterol targets while also watching for changes in liver enzymes.

Statistical analysis

Results are presented as the medians and ranges for quantitative data or as numbers and percentages for qualitative data. The biological parameters obtained have been analyzed using One Sample T Test and Paired Samples T Test. Data was processed using SPSS and Microsoft Excel. $P < 0.05$ was retained for statistical significance.

Results and discussions

Hypolipemiant treatment was associated with the improvement of lipid profile in all patients with dyslipidemia and NAFLD. Regarding the lipid profile, total cholesterol (214.15 ± 34.63 mg/dL versus 161.80 ± 34.28 mg/dL, $p < 0.0001$), LDL cholesterol (143.76 ± 36.35 mg/dL versus 100.21 ± 36.26 mg/dL, $p < 0.0001$) and triglycerides (163.00 ± 87.77 mg/dL versus 120.60 ± 72.42 mg/dL, $p < 0.0001$) were significantly reduced at the 6 months follow-up, while high-density lipoprotein (HDL) cholesterol (44.63 ± 20.50 mg/dL versus 45.61 ± 20.36 mg/dL, $p = 0.52$) was not significantly altered at the second evaluation (fig. 1).

Statin treatment significantly improved alanine aminotransferase (ALT) whereas aspartate aminotransferase (AST) was not significantly reduced between baseline and follow-up (fig. 2).

26 patients (17.8%) achieved LDL-c target, having a <70 mg/dL after 6 months of atorvastatin treatment (fig. b3).

105 patients presented normal triglycerides values after 6 months treatment. Improvement in serum triglycerides was observed in 35 of patients (25%).

29 patients (19.4%) presented uncontrolled blood pressure in spite of receiving antihypertensive treatment. Mean blood pressure was $126.00 \pm 20.70/77.71 \pm 12.20$ mmHg. The mean ejection fraction was 47%.

The prevalence of type 2 diabetes and metabolic syndrome in the studied population was 74% and 83%, respectively.

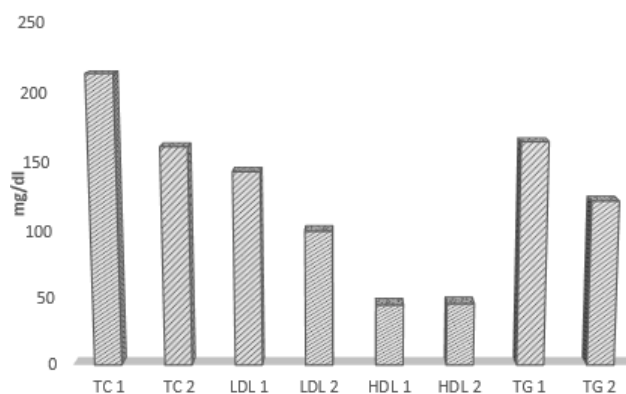


Fig. 1. Total cholesterol (TC1), low-density lipoprotein cholesterol (LDL1), triglycerides (TG1) and high-density lipoprotein cholesterol (HDL1) before statin treatment and at the 6 months follow-up (TC2, LDL2, TG2, HDL2). TC1, LDL1 and TG1 were significantly reduced during treatment ($p < 0.0001$)

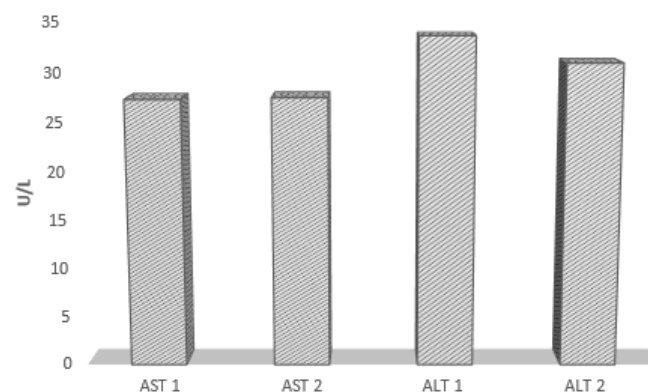


Fig. 2. Aspartate Aminotransferase (AST) was not significantly modified between baseline AST1 27.33 ± 18.28 U/L and follow-up AST2 27.46 ± 17.26 U/L, $p = 0.85$. Alanine Aminotransferase (ALT), was significantly reduced at the 6 months follow-up ALT1 33.58 ± 32.04 U/L versus ALT2 30.89 ± 19.99 U/L ($p = 0.038$).

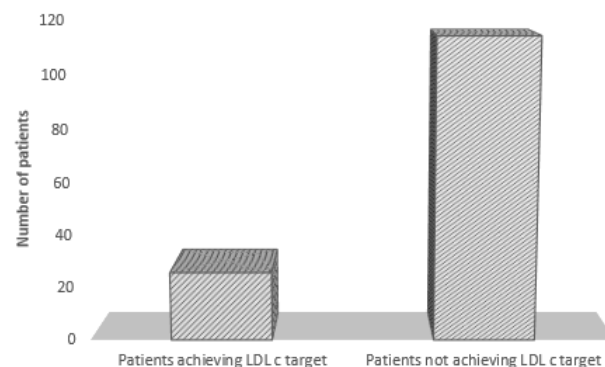


Fig. 3. Number of patients achieving or not achieving low-density lipoprotein cholesterol (LDL c) target of <70mg/dL according ESC Guidelines for very high cardiovascular risk

No correlation was found between lipid profile components and blood pressure or the ejection fraction.

In this study, short-term atorvastatin therapy appears to be a safe and effective treatment tool for patients with NAFLD. Therefore, avoiding treatment in order to prevent liver damage is not justified. Patients with NAFLD do not present a higher risk for serious liver injury caused by statins, so they can be used to treat dyslipidemia in patients with NAFLD [6]. A recent review that included 12 trials regarding statin therapy in patients with NAFLD has shown that no study reported elevated liver enzymes caused by

statin treatment, with some of them showing improved transaminase levels [10].

Lowering cholesterol level in dyslipidemic patients with very high cardiovascular risk reduces the incidence of both cardiovascular morbidity and mortality. Beside the hypolipemiant effect, statins have beneficial effects on endothelial function, enhance the stability of atherosclerotic plaques and play an anti-inflammatory and anti-proliferative role [11].

This prospective study found that a low percentage (17.8%) of patients reach LDL cholesterol targets. Achieving a LDL cholesterol level of <70mg/dL, according to ESC/EAS Guidelines for management of dyslipidemias, is difficult and requires a longer treatment period [9]. More aggressive treatment of dyslipidemia is needed in very high risk patients by titrating to higher doses. Independent of other metabolic comorbidities, *cardiovascular mortality* seems to be the most important cause of death in patients with NAFLD. Therefore, aggressive reduction of CVD risk factors should be taken into account in all patients. Studies report a higher portion of patients achieving LDL cholesterol goals in low and moderate risk groups, while a much lower portion reach the target in high and very high risk groups [12-14]. Another study also showed improvement of liver enzymes in NAFLD patients with hyperlipidemia treated with statins, particularly atorvastatin [15].

Association between ultrasound-based grading of the severity of NAFLD and abnormal cardiometabolic profile has been found. The Framingham Risk Score is correlated with the ultrasound based severity of NAFLD. Using sonography to identify patients with NAFLD may help prevent cardiovascular events, allowing patients to benefit from appropriate therapies earlier [16].

Lifestyle changes improve aminotransferases serum levels and lower the risk of CVD, while hypolipemiant treatment is indicated for patients with dyslipidemia who did not respond adequately to diet and exercise therapy. In patients with very high cardiovascular risk statin treatment is indicated in association with lifestyle changes, for achieving LDL cholesterol targets but also for its pleiotropic effects.

It is important to understand the clinical relevance of NAFLD in patients with or without high cardiovascular risk, to use all diagnostic tools and administer treatment according to the most recent guidelines in order to prevent hepatic and extra-hepatic complications [17,18]. A recent review highlights that since patients with elevated cardiovascular risk require statin treatment, it would be advisable to select a specific statin that provides liver as well as cardiovascular risk reduction [19]. Other studies suggest that proprotein convertase subtilisin kexin type-9 inhibitors ameliorates NAFLD, while the association of antioxidant vitamins C and E with statin therapy in men does not bring any additional benefits [20,21].

Conclusions

In our study liver function was not negatively affected by low statin doses; on the contrary, improvement of ALT serum levels has been observed. Adding small doses of statins seems safe, but reaching LDL targets for patients with very high cardiovascular risk requires long treatment periods.

This study's limitations include the small sample size and the fact that NAFLD was assessed by ultrasonography and not by magnetic resonance spectroscopy or histologically by liver biopsy. Controlled trials are needed to further investigate the impact of NAFLD on outcomes of liver disease and CVD.

References

1. PERUMPAIL, B.J., KHAN, M.A., YOO, E.R., CHOLANKERIL, G., KIM, D., AHMED, A., *World. J. Gastroenterol*, 23, no. 47, 2017, p. 8263-8276.
2. DIEHL, A.M., DAY, C., *N Engl J Med*, no. 377, 2017, p. 2063-2072.
3. BEDOGNI, G., MIGLIOLI, L., MASUTTI, F., TIRIBELLI, C., MARCHESINI, G., BELLENTANI, S., *Hepatology*, no. 42, 2005, p. 44-52.
4. MOLLER, S., BERNARDI, M., *Eur Heart J*, 34, no. 36, 2013, p. 2804-2811
5. PAIS, R., GIRAL, P., KHAN, J.F., ROSENBAUM, D., HOUSSET, C., POYNARD, T., RATZIU, V., *J Hepatol*, no. 65, 2016, p. 95-102.
6. CHALASANI, N., YOUNOSSE, Z., LAVINE, J. E., CHARLTON, M., CUSI, K., *Hepatology*, no. 67, 2018, p. 328-357.
7. KASHANI, A., PHILLIPS, C.O., FOODY, J.M., WANG, Y., MANGALMURTI, S., KO, D.T., KRUMHOLZ, H.M., *Circulation*, no. 114, 2006, p. 2788-97.
8. EGAN, M., PRASAD, S., *J. Fam. Pract.* 60, no. 9, 2011, p. 536-8.
9. CATAPANO, A.L., GRAHAM, I., DE BACKER, G., WIKLUND, O., CHAPMAN, M.J., *Eur. Heart J.*, 37, no. 39, 2016, p. 2999-3058.
10. SIGLER, M.A., CONGDON, L., EDWARDS, K.L., *Clin. Med. Insights: Gastroenterol*, no. 11, 2018, p. 1-9.
11. KAVAILPATI, N., SHAH, J., RAMAKRISHAN, A., VASNAWALA, H., *Indian J. Endocrinol. Metab.*, 19, no. 5, 2015, p. 554-62.
12. NICHOLS, G.A., AMBEGAONKAR, B.M., VASILISA-SAZONOV, V., BROWN, J.B., *Am. J. Cardiol.*, 104, no. 12, 2009, p. 1689 - 1694.
13. MARONI, L., GUAISTI, L., CASTIGLIONI, L., MARINO, F., CONTINI, S., MACCHI, V., DE LEO, A., *AJMS*. 342, no. 5, 2011, p. 383-387.
14. ALLEN, A.M., THERNEAU, T.M., LARSON, J.J., COWARD, A., SOMERS, V., KAMATH, P.S., *Hepatology*, no. 57, 2018, p. 1726-1736.
15. HIDEYUKI, H., TAZUMA, S., ARIHIRO, K., IWAMOTO, K., NABESHIMA, INOUE, M., ISHITOBI, T., NONAKA, M., CHAYAMA, K., *Metabolism.*, 57, no. 12, 2008, p. 1711 - 1718.
16. CUENZA, L.R., RAZON, T.L.J., DAYRIT, J.C., *J. Cardiovasc. Thorac. Res.* 9, no. 2, 2017, p. 85-89.
17. MULLISH, B.H., FORLANO, R., MANOUSOU, P., MIKHAILIDIS, D.P., *Expert Rev. Gastroenterol. Hepatol.*, 12, no. 12, 2018, p. 1175-1177.
18. RINELLA, M.E., *JAMA*, 313, no. 22, 2015, p.2263-2273.
19. DOUMAS, M., IMPRIALOS, K., DIMAKOPOULOU, A., STAVROPOULOS, K., BINAS, A., ATHYROS, V.G., *Curr. Pharma. Des.*, no. 24, 2019, p. 4587.
20. THEOCHARIDOU, E., PAPADEMETRIOU, M., REKLOU, A., SACHINDIS, A., BOUTARI, C., GIOULEME, O., *Curr. Pharma. Des.*, no. 24, 2018, p. 3654.
21. HADZI-PETRUSHEV, N., DIMOVSKA, K., JANKULOVSKI, K., MITROV, D., MLADENOV, M., *Adv. Pharmacol. Sci*, 2018, 4673061.

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