

Prospective Study

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome

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Abstract

AIM: To investigate the effect of rosuvastatin monotherapy on non-alcoholic steatohepatitis (NASH). At present there is no effective treatment for non-alcoholic fatty liver disease or its advanced form NASH.

METHODS: This prospective study included 20 biopsy proven patients with NASH, metabolic syndrome (MetS) and dyslipidaemia. Biochemical parameters of the blood of the patients and an ultrasonography of the liver were performed at baseline. Then patients received

lifestyle advice and were treated for a 12 mo period with rosuvastatin (10 mg/d) monotherapy. Patients were re-evaluated during the study at 3 mo intervals, during which biochemical parameters of the blood were measured including liver enzymes. A repeat biopsy and ultrasonography of the liver were performed at the end of the study in all 20 patients. Changes in liver enzymes, fasting plasma glucose, serum creatinine, serum uric acid (SUA), high sensitivity C reactive protein (hsCRP) and lipid profile were assessed every 3 mo. The primary endpoint was the resolution of NASH and the secondary endpoints were the changes in liver enzyme and lipid values.

RESULTS: The repeat liver biopsy and ultrasonography showed complete resolution of NASH in 19 patients, while the 20th, which had no improvement but no deterioration either, developed arterial hypertension and substantial rise in triglyceride levels during the study, probably due to changes in lifestyle including alcohol abuse. Serum alanine transaminase, aspartate transaminase, and γ -glutamyl transpeptidase were normalised by the 3rd treatment month (ANOVA $P < 0.001$), while alkaline phosphatase activities by the 6th treatment month (ANOVA, $P = 0.01$). Fasting plasma glucose and glycated haemoglobin were significantly reduced ($P < 0.001$). Lipid values were normalised by the 3rd treatment month. No patient had MetS by the 9th treatment month. Body mass index and waist circumference remained unchanged during the study. Thus, changes in liver pathology and function should be attributed solely to rosuvastatin treatment. A limitation of the study is the absence of a control group.

CONCLUSION: These findings suggest that rosuvastatin monotherapy could ameliorate biopsy proven NASH and resolve MetS within 12 mo. These effects and the reduction of fasting plasma glucose and SUA levels may reduce the risk of vascular and liver morbidity and mortality in NASH patients. These findings need confirmation in larger studies.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Metabolic syndrome; Dyslipidaemia; Rosuvastatin; Fasting blood glucose; Serum uric acid

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Core tip: We treated 20 patients with metabolic syndrome (MetS) and biopsy proven non-alcoholic steatohepatitis (NASH) with rosuvastatin monotherapy for one year. Repeat liver biopsy and ultrasonography showed complete resolution of NASH in 19 patients, and normalization of liver enzymes, lipid profile and blood glucose; no patient had MetS at the end of the study. These findings suggest that rosuvastatin monotherapy could ameliorate biopsy proven NASH and resolve MetS within 12 mo. These effects and the reduction of fasting plasma glucose and serum uric

acid levels, if confirmed by larger studies, may reduce the risk of vascular and liver morbidity and mortality in NASH patients.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a term describing a histological spectrum of the most common liver disease (affects approximately 15%-30% of the general population in Western Countries) characterized by accumulation of fat ($> 5\%$) in liver cells in the absence of excessive alcohol intake, chronic viral hepatitis or other liver disease^[1]. The histological manifestations of NAFLD range from simple steatosis, steatohepatitis (NASH), liver fibrosis, cirrhosis, and may progress to hepatocellular carcinoma^[2]. NASH is characterised by steatosis plus necro-inflammation, and fibrosis, which can be diagnosed by liver biopsy^[2]. Recent data suggest that NAFLD is linked to increased cardiovascular disease (CVD) risk, independently of the risk related to components of the metabolic syndrome (MetS); NAFLD is the hepatic manifestation of MetS^[3]. It has also been shown that patients with NASH are at higher CVD risk than those with simple steatosis, emphasizing the role of chronic liver inflammation in the pathogenesis of atherosclerotic CVD^[3].

Statin treatment is safe in patients with mild to moderate elevations of liver enzymes due to NAFLD/NASH^[4]. It has been established that statin regimens substantially reduce the risk of death or atherosclerotic CVD events in a wide range of individuals^[5]. We reported that atorvastatin treatment is safe, improves liver tests, and liver ultrasonography as well as reduces CVD events in patients with NAFLD^[6,7]. We have also shown, in a pilot study ($n = 6$) involving liver biopsy, that rosuvastatin can have a beneficial effect on NASH resolution^[8]. In the present paper we report results of rosuvastatin monotherapy (10 mg/d) on liver enzymes, ultrasonography and biopsy of 20 patients with NASH and MetS within 12 mo of treatment. The patients were followed for an additional (mean) 18-mo period to ensure sustainability of results.

MATERIALS AND METHODS

Methods were described in the pilot study paper ($n = 6$)^[8]. Here we report the results of rosuvastatin (10 mg/d) monotherapy in 20 patients (this includes

the 6 patients included in the preliminary report). In short, this is a prospective, randomized, open-label study that involved patients with MetS, without overt type 2 diabetes mellitus (T2DM), not taking any previous hypolipidaemic therapy. The study protocol was approved by the ethical committee of Aristotle University and written informed consent was obtained from all patients before inclusion in the study.

Twenty MetS patients with increased serum liver enzyme activity and ultrasonographic image compatible with NAFLD were included. The presence of NASH was validated by liver biopsy. The age range was 18–70 years. Patients with overt CVD, congestive heart failure (CHF), stage 3 or higher of chronic kidney disease (CKD), rheumatic diseases, chronic viral hepatitis, congenital disorders of the liver, autoimmune hepatitis or excessive alcohol intake (21 and 14 u/wk for men and women, respectively) were excluded.

The study was designed to include 40 patients; 20 on rosuvastatin monotherapy and 20 on rosuvastatin-fenofibrate combination. All participants had MetS^[9] and dyslipidaemia [total cholesterol > 200 mg/dL, high density lipoprotein cholesterol (HDL-C) < 40 for men and < 50 mg/dL for women, triglycerides (TGs) > 150 mg/dL or combinations]^[10]. Participants received lifestyle advice with suggestions to adopt a hypocaloric and hypolipidaemic diet^[10] and regular exercise (at least 1 h of walking every day, if possible, or equivalent physical activity). For safety reasons we started treatment with 5 mg/d of rosuvastatin and if there were no side effects we titrated this dose to 10 mg/d at the end of the 1st treatment month (safety and titration visit).

The primary endpoint was the degree of resolution of NASH in the repeat biopsy compared with the baseline biopsy. Secondary endpoints were safety of treatment and degree of normalization of liver enzymes, lipid profile and liver ultrasonography. At every visit safety parameters [alanine transaminase (ALT), aspartate transaminase (AST), and creatine kinase (CK)] were assessed as well as gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP). The lipid profile (total cholesterol, TGs, LDL-C, HDL-C), fasting plasma glucose, serum creatinine, blood urea nitrogen (BUN) and serum uric acid (SUA) were assessed by standard methods. Body mass index (BMI), waist circumference, blood pressure (BP) and smoking habits were recorded at each visit.

Statistical analysis

All measured parameters had normal distribution and are reported as mean values and standard deviations. Paired *t*-tests and ANOVA for repeat measurements were used. A 2-tailed *P* < 0.05 was considered significant. All analyses were carried out using the SPSS 21.0 software (SPSS Inc., Chicago, IL).

RESULTS

We report the results of 20 patients on rosuvastatin monotherapy (10 mg/d). Patients on rosuvastatin-fenofibrate combination had identical (serum enzyme, ultrasonography, and liver biopsy) results (only TGs were lower but in both groups were within normal range) with those on rosuvastatin monotherapy. The rosuvastatin-fenofibrate combination was discontinued, because patients did not have MetS any longer and it was considered futile to insist on an unnecessary remedy^[11]. Patients on the rosuvastatin-fenofibrate combination continued with rosuvastatin monotherapy, but their results are not included in the present analysis, because for some period of time they were on combination therapy and this could have affected the results. We recruited 5 rosuvastatin-fenofibrate patients in the initial phase of this project, but there was no difference in results between those and the rosuvastatin monotherapy patients and thus these were put on rosuvastatin monotherapy. It was difficult to continue with the statin-fibrate combination (only 3 patients had a repeat biopsy), because most patients expressed the wish to discontinue the fibrate. This was due to the fear of their attending physicians (4 years ago physicians were reluctant to prescribe statin-fibrate combinations) due to liver or muscle side-effects of this combination. The results of these 5 patients are not included in the present study and the results of the 3 that made it to biopsy are not included either in the pilot or in the present study, because the number was too low to allow statistical analysis. In the rosuvastatin monotherapy group (*n* = 20) liver biopsy at baseline showed steatosis (fat content of the liver > 30%), hepatocyte ballooning degeneration, diffuse lobular mixed acute and chronic inflammation, and perivenular as well as perisinusoidal collagen disposition. Repeat liver biopsies in all 20 patients showed that all patients but one had a complete resolution of NASH (Figure 1 shows 3 pairs of biopsies at baseline and 12 mo later). At baseline, 2 pathologists, blinded to the decision of each other, graded the histology in the liver biopsies. Disease activity was assessed using a score that included NAFLD activity (scale: 0 to 3), lobular inflammation (scale: 0 to 3) and hepatocellular ballooning (scale: 0 to 2); higher scores indicate NASH severity^[12]. The study only included patients with a histology score of 8, to make certain that NASH was present at baseline^[12]. According to this classification^[12,13], the comparison of liver biopsies at one year after rosuvastatin treatment with those at baseline showed that in 19 patients there was a NAFLD activity score (based on the standardized grading system of measuring steatosis mentioned above^[12]) reduction from 3 to 0 (*P* < 0.001), while in one patient this fell from 3 to 1; lobular inflammation

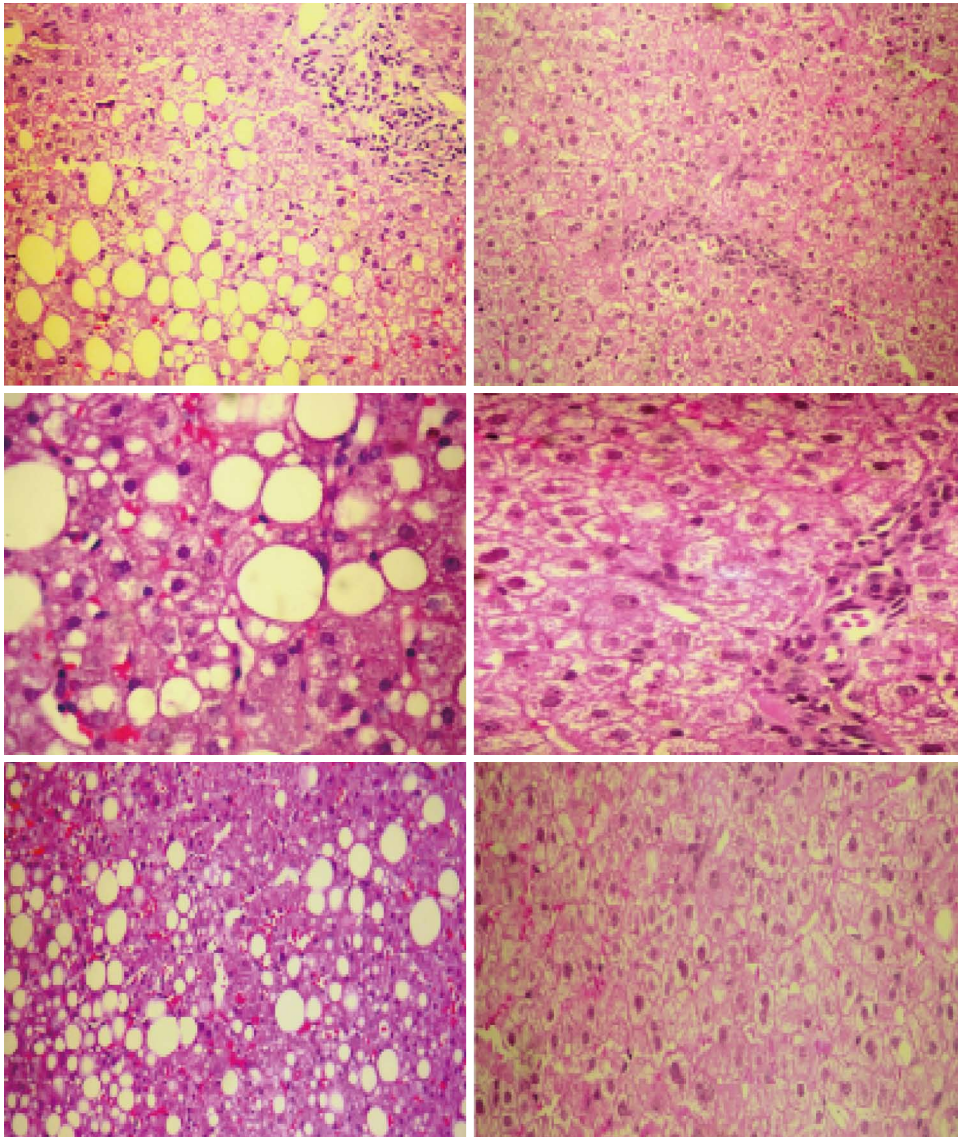


Figure 1 Presentation of the baseline and repeat liver biopsies in 3 metabolic syndrome patients with non-alcoholic steatohepatitis on rosuvastatin (10 mg/d) monotherapy for 12 mo. On the left panel liver biopsies of patients with non-alcoholic steatohepatitis presenting steatosis (fat content of the liver > 30%), hepatocyte ballooning degeneration, diffuse lobular mixed acute and chronic inflammation, and perivenular, perisinusoidal collagen disposition. On the right panel liver biopsies of the same 3 patients after one year monotherapy with 10 mg/d of rosuvastatin presenting total normal liver tissue.

was reduced from 3 to 0 in 19 patients ($P < 0.001$), while in the same patient mentioned above it changed from 3 to 2; hepatocellular ballooning changed from 2 to 0 ($P < 0.001$), while in the same patient mentioned above it changed from 2 to 1. Even in the one patient (without full histological improvement) the total histological NASH score was 4 (*i.e.*, < 5 that indicates definite or possible NASH)^[12,13]. There were no significant differences between the evaluations of the 2 pathologists in grading NASH activity in all 20 patients.

The patient, as also reported in the pilot study, which did not show either any improvement or deterioration of NASH in the second biopsy, was the one that had arterial hypertension and high TG levels, attributed to a change in life-style habits, including excess alcohol consumption. We advised him to adopt a healthier lifestyle but we were not successful. This

patient was not submitted to a third biopsy later, but he had normalization of the liver enzymes and the ultrasonographic image of the liver by the end of second year of the study while on rosuvastatin and adopting a healthier lifestyle for at least a year.

The changes in measured parameters during the 12 mo of the duration of the study, between the two biopsies, are reported in Table 1 and Figure 2.

There were no statin-related safety problems-side effects from the liver or the muscles. In contrast, liver enzymes were normalized by the 6th treatment month and remained normal thereafter. Even the one patient that had no improvement in the repeat liver biopsy had normal liver enzyme levels.

The lipid profile was completely normalized by the 3rd treatment month (Table 1), while all 20 patients did not have MetS any more from the 9th treatment month

Table 1 Changes in measured parameters during the study

Parameter	Baseline	1 st mo	3 rd mo	6 th mo	9 th mo	12 th mo	P value (ANOVA)
Age (yr)	40.5 ± 5.6	-	-	-	-	-	-
Gender (male)	16	-	-	-	-	-	-
Cigarette smoking	13	13	13	12	12	11	NS
BMI (kg/m ²)	31.5 ± 1.1	31.3 ± 1.0	31.4 ± 1.0	31.6 ± 1.1	31.6 ± 1.2	31.5 ± 1.2	NS
Waist circumference (cm)	110.5 ± 6.2	110.4 ± 6.0	109.9 ± 6.1	110.6 ± 6.3	110.7 ± 6.2	110.4 ± 6.2	NS
Total cholesterol (mg/dL)	251 ± 22	226 ± 17	192 ± 16	185 ± 12	181 ± 8	179 ± 9	< 0.001
Triglycerides (mg/dL)	187 ± 19	161 ± 20	143 ± 26	123 ± 11	121 ± 22	117 ± 18	< 0.001
HDL-cholesterol (mg/dL)	38 ± 5	40 ± 5	42 ± 7	42 ± 4	43 ± 3	44 ± 5	< 0.001
LDL-cholesterol (mg/dL)	180 ± 23	152 ± 15	121 ± 17	118 ± 14	114 ± 9	110 ± 11	< 0.001
Serum creatinine (mg/dL)	0.93 ± 0.2	0.92 ± 0.2	0.94 ± 0.2	0.92 ± 0.2	0.91 ± 0.2	0.90 ± 0.2	NS
hsCRP (mg/L)	4.2 ± 1.3	-	-	2.7 ± 0.8	-	1.6 ± 0.5	< 0.001
BUN (mg/dL)	34 ± 8	34 ± 8	35 ± 8	34 ± 7	33 ± 6	31 ± 6	NS
SUA (mg/dL)	5.5 ± 1.1	5.4 ± 1.0	5.2 ± 0.9	5.0 ± 0.7	4.9 ± 0.8	4.8 ± 0.9	0.016
Plasma glucose (mg/dL)	102 ± 8	101 ± 8	96 ± 6	93 ± 7	89 ± 5	87 ± 5	< 0.001
HbA _{1c} (%)	5.3 ± 0.4	-	5.1 ± 0.4	5.0 ± 0.5	4.9 ± 0.3	4.8 ± 0.3	< 0.001
Metabolic Syndrome, <i>n</i>	20	20	18	9	0	0	< 0.001

Data are presented as mean ± SD. BMI: Body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein; NS: Not significant; BUN: Blood urea nitrogen; SUA: Serum uric acid; HbA_{1c}: Glycosylated haemoglobin.

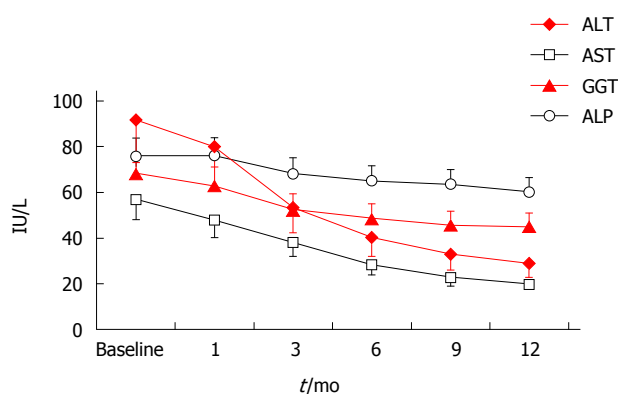


Figure 2 Liver enzyme changes in 20 patients with non-alcoholic steatohepatitis during the 12 mo of rosuvastatin (10 mg/d) monotherapy. The reduction in serum alanine transaminase (ALT), aspartate transaminase (AST) and γ -glutamyl transpeptidase (GGT) levels became statistical significant by the 3rd month of treatment (ANOVA for the 12 mo period $P < 0.001$) and for alkaline phosphatase (ALP) by the 6th mo of treatment (ANOVA for the 12 mo period $P = 0.01$).

(Table 1). It should be noted that these happened in the absence of any change in waist circumference (and BMI), the only MetS component that persisted after 9th month of treatment. Mean SUA levels were significantly reduced (Table 1)

Fasting plasma glucose levels and HbA_{1c} were significantly reduced by rosuvastatin in all patients, by the 6th treatment month, even in the patient with no

improvement in the repeat liver biopsy (Table 1).

DISCUSSION

The main findings of this prospective study, which included 20 MetS patients with biopsy proven NASH, were that monotherapy with 10 mg/d of rosuvastatin was linked to resolution of NASH (as established by a second liver biopsy, measurement of serum liver enzymes and liver ultrasonography), complete regression of MetS, reduction in SUA levels, and a large reduction in plasma glucose levels. These happened within 12 mo of treatment, although some changes were evident within the first treatment months. The lipid profile was totally normalized by rosuvastatin early during follow-up. Follow-up of patients for a mean period of 18 mo after the second biopsy did not show any indication of NASH or MetS relapse.

Five years ago we have shown in a post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study ($n = 1600$; 437 patients had moderately abnormal liver tests at baseline)^[6] that atorvastatin therapy was safe in patients with coronary heart disease (CHD) and mild to moderate elevations of serum transaminases, probably due to NAFLD as indicated by liver ultrasonography after exclusion of other liver diseases. Not only atorvastatin did not increase liver enzymes but it normalised liver

tests and liver ultrasonography within the duration of the study^[6]. Moreover, atorvastatin treatment induced substantial reductions in CVD events (68% vs usual care) during the 3-year follow-up period compared with the participants with CHD and normal liver enzymes (39% vs usual care); $P = 0.007$ ^[6]. These findings were confirmed one year later by the Assessing The Treatment Effect in Metabolic Syndrome Without Perceptible diabeTes (ATTEMPT) study in patients with MetS but without overt CVD or T2DM ($n = 1123$; 326 had modestly elevated liver enzymes and ultrasonographic evidence of NAFLD)^[7]. In 2013 the post hoc analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering [IDEAL] trial ($n = 8863$) showed that high dose atorvastatin treatment (80 mg) in 1,081 (12.2%) patients, who had an ALT \geq ULN, normalised ALT values and substantially reduced 5-year CVD event rates compared with simvastatin [11.5% for simvastatin and 6.5% for atorvastatin, hazard ratio (HR) 0.556; 95% confidence interval (CI) 0.367-0.842; $P = 0.0056$ vs 20-40 mg simvastatin treatment], confirming our findings^[14].

A previous study with rosuvastatin showed a suboptimal clinical, laboratory and biopsy proven benefit in 9 patients with NASH and dyslipidaemia^[15]. This may be attributed to the very low dose of rosuvastatin administered (2.5 mg/d)^[15]. A study with pitavastatin included 20 patients with biopsy-proven NASH with dyslipidaemia^[16]. After treatment for 12 mo with pitavastatin 2 mg/d NASH-related metabolic parameters improved, including histology in some patients, however, 3 of 13 patients had progression of fibrosis during treatment^[17]. Studies with simvastatin^[17] or pravastatin^[18] in NASH patients showed that NASH alters the expression of hepatic uptake transporters which may increase the risk of statin-induced adverse drug reactions (myopathy). In a pilot study that included 16 patients with biopsy proven NASH (14 completed the study and 10 underwent 1-year repeat liver biopsy), simvastatin monotherapy did not seem to be an effective treatment for NASH^[19]. A recent study in rats showed that simvastatin delays the evolution of NASH-related fibrosis, improving its prognosis^[20]. Thus, clinical, laboratory, ultrasonography and liver biopsy benefits related to statin treatment may be compound specific and dose related.

The mechanisms involved in the biochemical, ultrasonographic, and histological improvement with some statins at specific doses is not clear^[21]. An animal study evaluated whether rosuvastatin changes the carbohydrate and lipid metabolism and the development of NAFLD in male C57Bl/6 mice (3-month-old) on a high-fat diet (60% lipids) compared with standard chow (10% lipids) for 15 wk^[22]. Rosuvastatin improved glucose intolerance, insulin sensitivity and NAFLD in this animal model of diet-induced obesity in a dose-dependent manner and changed the fat distribution from visceral to subcutaneous^[22].

Therefore, rosuvastatin therapy may help patients with MetS because of beneficial pleiotropic effects^[22].

Data on the mechanisms of improvement of NASH patients who are at a higher risk for liver- and vascular-related morbidity and mortality than those with simple steatosis^[23], are scarce^[23]. An open-label prospective study of atorvastatin (10 mg/d) for 24 mo included 31 patients with biopsy-proven NASH and hyperlipidaemia^[24]. Follow-up liver biopsy was performed in 17 patients. BMI and plasma glucose levels did not change during the treatment, while 23 patients (74.2%) presented normal transaminase levels. During the study adiponectin levels increased significantly and the levels of tumour necrosis factor- α (TNF- α) decreased significantly^[24]. Liver steatosis and NASH-related metabolic parameters improved with treatment, including fibrosis in some patients. However, 4 of 17 patients had progression of fibrosis over the 2-year period, with 3 of them progressing to stage 3^[24]. These results suggest that atorvastatin may have acted *via* a reduction in markers of systemic inflammation (*e.g.*, TNF- α), as well as increased adiponectin levels^[24]. It has been suggested that oxidative stress that promotes the pathogenesis of atherosclerosis might be one key link between NASH and CVD^[25]. Thus, atorvastatin may be effective in NASH treatment not only through reduction of inflammatory cytokine production, but also reactive oxygen species generation in the liver. These are also the two major pathophysiological mechanisms involved in the progression from NAFLD to NASH^[25]. Similar effects were shown with 20 mg of rosuvastatin^[26]. Moreover, it has been shown that atorvastatin treatment (10 mg/d for 12 mo) improved metabolic and histological parameters in 43 biopsy proven NASH patients with dyslipidaemia and that this effect was probably related to the reduction in serum levels of advanced glycosylated end products (AGEs) that might be useful as a marker for NASH presence^[27]. The above, as well as our findings, suggest that the effect of statins on NASH is dose dependent^[24-27].

Another important finding of the present study was the complete resolution of MetS by the 9th treatment month. This was mainly due to the substantial reduction in TG levels, a significant increase in HDL-C levels and (paradoxically) to the reduction in fasting plasma glucose levels. Rosuvastatin treatment has been reported to have a negative effect on plasma glucose homeostasis^[28] and has been linked to new onset diabetes (NOD)^[29]. However, it has been shown that the risk of NOD in statin-treated patients was related to female gender (16/20 of our patients were males), old age (the mean age of our patients was 40.5 years), and to intensity of the statin and its dose (in our study rosuvastatin, a potent statin, was prescribed at 10 mg/d; a relatively low dose)^[29]. These factors may explain the lack of NOD but not the great reduction of fasting plasma glucose levels. In a prospective randomized open-label study in non-diabetic patients with dyslipidaemia, rosuvastatin

(10 mg) exerted a favourable effect on glucose homeostasis, by improving insulin resistance index. This effect was not shown with atorvastatin (20 mg), although the effect of both statins on blood glucose and HbA_{1c} levels was neutral^[30,31]. There are data showing that NAFLD/NASH play a central role in the genesis of an insulin-resistant state in obese subjects, independent of the role of visceral fat, suggesting that the improvement of NASH might contribute to the reduction of insulin resistance^[32,33]. It has been shown in NAFLD patients that exercise-induced reduction in fetuin-A (a blood protein synthesized in the liver that may be associated with the pathogenesis of NAFLD and T2DM) levels is closely linked to exercise-induced improvement in glucose tolerance, due to the reduction of skeletal muscle insulin resistance^[34]. Thus, early resolution of NASH might have been involved in the reduction in fasting plasma glucose levels and HbA_{1c} in our patients.

From the other MetS components waist circumference (as well as body weight and BMI) was not reduced and BP showed a small but non-significant reduction. Thus, any improvement of NASH cannot be attributed to these MetS components.

SUA is considered by some as a MetS component^[35] possibly associated with CVD risk in MetS and NAFLD/NASH^[36]. Thus, SUA levels reduction by rosuvastatin in the present study might have contributed to a further reduction of CVD risk, beyond the improved lipid profile and amelioration of NASH. We have shown in the GREACE study that all CVD patients were independently (after backwards regression analysis) benefited (had fewer vascular events) by SUA level reduction^[37]. However, those with MetS benefited more from statin treatment than those without MetS^[38]. Furthermore, an atorvastatin-based multifactorial intervention in MetS patients without established CVD or T2DM reduced SUA levels, especially in stage 3 CKD patients; this might have contributed to the reduction in CVD events in these patients^[39].

This study did not include a control group and each patient acted as his/her control. This was because, based on our and other previous findings and lipid guidelines it was unethical to deprive statin treatment in NASH patients with MetS.

In conclusion, Rosuvastatin (10 mg/d) monotherapy for 12 mo was associated with resolution of NASH, regression of MetS and reduction in plasma glucose and SUA levels, without any change in body weight, BMI, or waist circumference, in patients with MetS and dyslipidaemia. These results will hopefully reduce the risk of NOD and vascular and liver morbidity and mortality related to MetS and its liver manifestation, NAFLD/NASH. There is a need to confirm these results in larger prospective studies, given that NAFLD might have already affected almost 1 billion people (the most common chronic hepatic disorder in Western countries, with a prevalence of 20%-30%^[40,41], increasing to 57%-74% among obese patients^[42], and 5%-18% in

Asia with a strong trend to increase over time^[40]). At present, three decades of research on pharmacological treatment have provided limited options^[1]; especially for NASH there is very little evidence supporting the efficacy of most regimens^[43].

COMMENTS

Background

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease worldwide. It may evolve to non-alcoholic steatohepatitis (NASH), cirrhosis and in a few patients to hepatoma. NAFLD is considered the hepatic manifestation of metabolic syndrome (MetS). NAFLD, but mainly NASH, are related to increased cardiovascular disease (CVD) risk and more patients die from vascular than liver disease.

Research frontiers

Currently there is no generally acceptable treatment for NASH.

Innovations and breakthroughs

Up until recently statins were not prescribed to patients with NAFLD/NASH and thus high CVD risk patients were deprived from an effective treatment. Data from *post hoc* analyses showed a benefit from statin treatment in these patients in reducing both the liver and the CVD risk without major adverse events. However, this had to be proven by liver biopsy.

Applications

The results of the study suggest that in patients with MetS and biopsy proven NASH rosuvastatin monotherapy resulted in complete resolution of both NASH and MetS after a year of treatment.

Terminology

Thus, NASH and MetS two major CVD risk factors were effectively treated with a statin that may not have been allowed in these patients some years ago.

Peer-review

A novel paper suggesting a possible treatment for a wide spread disease worldwide.

REFERENCES

- 1 **Baran B**, Akyüz F. Non-alcoholic fatty liver disease: what has changed in the treatment since the beginning? *World J Gastroenterol* 2014; **20**: 14219-14229 [PMID: 25339808 DOI: 10.3748/wjg.v20.i39.14219]
- 2 **Jiang CM**, Pu CW, Hou YH, Chen Z, Alanazy M, Hebbard L. Non alcoholic steatohepatitis a precursor for hepatocellular carcinoma development. *World J Gastroenterol* 2014; **20**: 16464-16473 [PMID: 25469014]
- 3 **Fargion S**, Porzio M, Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. *World J Gastroenterol* 2014; **20**: 13306-13324 [PMID: 25309067]
- 4 **Bader T**. Yes! Statins can be given to liver patients. *J Hepatol* 2012; **56**: 305-307 [PMID: 21963520 DOI: 10.1016/j.jhep.2011.08.016]
- 5 **Baigent C**, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376**: 1670-1681 [PMID: 21067804 DOI: 10.1016/S0140-6736(10)61350-5]
- 6 **Athyros VG**, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelas ED, Theocharidou E, Karagiannis A, Mikhailidis DP. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet* 2010; **376**: 1916-1922 [PMID: 21109302 DOI: 10.1016/S0140-6736(10)61272-X]
- 7 **Athyros VG**, Gioulema O, Ganotakis ES, Elisaf M, Tziomalos K, Vassiliadis T, Liberopoulos EN, Theocharidou E, Karagiannis A, Mikhailidis DP. Safety and impact on cardiovascular events of long-term multifactorial treatment in patients with metabolic

- syndrome and abnormal liver function tests: a post hoc analysis of the randomised ATTEMPT study. *Arch Med Sci* 2011; **7**: 796-805 [PMID: 22291824 DOI: 10.5114/aoms.2011.25554]
- 8 **Kargiotis K**, Katsiki N, Athyros VG, Gioulema O, Patsiaoura K, Katsiki E, Mikhailidis DP, Karagiannis A. Effect of rosuvastatin on non-alcoholic steatohepatitis in patients with metabolic syndrome and hypercholesterolaemia: a preliminary report. *Curr Vasc Pharmacol* 2014; **12**: 505-511 [PMID: 24805248]
 - 9 **Grundy SM**, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735-2752 [PMID: 16157765 DOI: 10.1161/CIRCULATIONAHA.105.169404]
 - 10 **Grundy SM**, Cleeman JI, Merz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227-239 [PMID: 15249516 DOI: 10.1161/01.CIR.0000133317.49796.0E]
 - 11 **Tenenbaum A**, Fisman EZ. "If it ain't broke, don't fix it": a commentary on the positive-negative results of the ACCORD Lipid study. *Cardiovasc Diabetol* 2010; **9**: 24 [PMID: 20550659 DOI: 10.1186/1475-2840-9-24]
 - 12 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461 DOI: 10.1002/hep.20701]
 - 13 **Sanyal AJ**, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; **362**: 1675-1685 [PMID: 20427778 DOI: 10.1056/NEJMoa0907929]
 - 14 **Tikkanen MJ**, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, Kastelein JJ, Holme I, Pedersen TR. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol* 2013; **168**: 3846-3852 [PMID: 24001698 DOI: 10.1016/j.ijcard.2013.06.024]
 - 15 **Nakahara T**, Hyogo H, Kimura Y, Ishitobi T, Arihiro K, Aikata H, Takahashi S, Chayama K. Efficacy of rosuvastatin for the treatment of non-alcoholic steatohepatitis with dyslipidemia: An open-label, pilot study. *Hepatol Res* 2012; **42**: 1065-1072 [PMID: 22583925 DOI: 10.1111/j.1872-034X.2012.01034.x]
 - 16 **Hyogo H**, Ikegami T, Tokushige K, Hashimoto E, Inui K, Matsuzaki Y, Tokumo H, Hino F, Tazuma S. Efficacy of pitavastatin for the treatment of non-alcoholic steatohepatitis with dyslipidemia: An open-label, pilot study. *Hepatol Res* 2011; **41**: 1057-1065 [PMID: 21951922 DOI: 10.1111/j.1872-034X.2011.00849.x]
 - 17 **Clarke JD**, Hardwick RN, Lake AD, Canet MJ, Cherrington NJ. Experimental nonalcoholic steatohepatitis increases exposure to simvastatin hydroxy acid by decreasing hepatic organic anion transporting polypeptide expression. *J Pharmacol Exp Ther* 2014; **348**: 452-458 [PMID: 24403518 DOI: 10.1124/jpet.113.211284]
 - 18 **Clarke JD**, Hardwick RN, Lake AD, Lickteig AJ, Goedken MJ, Klaassen CD, Cherrington NJ. Synergistic interaction between genetics and disease on pravastatin disposition. *J Hepatol* 2014; **61**: 139-147 [PMID: 24613363 DOI: 10.1016/j.jhep.2014.02.021]
 - 19 **Nelson A**, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. *J Clin Gastroenterol* 2009; **43**: 990-994 [PMID: 19448566 DOI: 10.1097/MCG.0b013e31819c392e]
 - 20 **Wang W**, Zhao C, Zhou J, Zhen Z, Wang Y, Shen C. Simvastatin ameliorates liver fibrosis via mediating nitric oxide synthase in rats with non-alcoholic steatohepatitis-related liver fibrosis. *PLoS One* 2013; **8**: e76538 [PMID: 24098525 DOI: 10.1371/journal.pone.0076538]
 - 21 **Riche DM**, Fleming JW, Malinowski SS, Black CA, Miller KH, Wofford MR. Resistant nonalcoholic fatty liver disease amelioration with rosuvastatin and pioglitazone combination therapy in a patient with metabolic syndrome. *Ann Pharmacother* 2014; **48**: 137-141 [PMID: 24259612 DOI: 10.1177/1060028013507239]
 - 22 **Neto-Ferreira R**, Rocha VN, Souza-Mello V, Mandarim-de-Lacerda CA, de Carvalho JJ. Pleiotropic effects of rosuvastatin on the glucose metabolism and the subcutaneous and visceral adipose tissue behavior in C57Bl/6 mice. *Diabetol Metab Syndr* 2013; **5**: 32 [PMID: 23816341 DOI: 10.1186/1758-5996-5-32]
 - 23 **Schreuder TC**, Verwer BJ, van Nieuwkerk CM, Mulder CJ. Nonalcoholic fatty liver disease: an overview of current insights in pathogenesis, diagnosis and treatment. *World J Gastroenterol* 2008; **14**: 2474-2486 [PMID: 18442193 DOI: 10.3748/wjg.14.2474]
 - 24 **Hyogo H**, Tazuma S, Arihiro K, Iwamoto K, Nabeshima Y, Inoue M, Ishitobi T, Nonaka M, Chayama K. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. *Metabolism* 2008; **57**: 1711-1718 [PMID: 19013295 DOI: 10.1016/j.metabol.2008.07.030]
 - 25 **Angelico F**, Del Ben M, Pignatelli P, Violi F. Comment on "atorvastatin improves disease activity of nonalcoholic steatohepatitis partly through its tumour necrosis factor- α -lowering property". *Dig Liver Dis* 2013; **45**: 81-82 [PMID: 22917635 DOI: 10.1016/j.dld.2012.07.009]
 - 26 **Pignatelli P**, Carnevale R, Di Santo S, Bartimoccia S, Nocella C, Vicario T, Loffredo L, Angelico F, Violi F. Rosuvastatin reduces platelet recruitment by inhibiting NADPH oxidase activation. *Biochem Pharmacol* 2012; **84**: 1635-1642 [PMID: 23022230 DOI: 10.1016/j.bcp.2012.09.011]
 - 27 **Kimura Y**, Hyogo H, Yamagishi S, Takeuchi M, Ishitobi T, Nabeshima Y, Arihiro K, Chayama K. Atorvastatin decreases serum levels of advanced glycation endproducts (AGEs) in nonalcoholic steatohepatitis (NASH) patients with dyslipidemia: clinical usefulness of AGEs as a biomarker for the attenuation of NASH. *J Gastroenterol* 2010; **45**: 750-757 [PMID: 20112031 DOI: 10.1007/s00535-010-0203-y]
 - 28 **Kei A**, Liberopoulos E, Elisaf M. Effect of hypolipidemic treatment on glycemic profile in patients with mixed dyslipidemia. *World J Diabetes* 2013; **4**: 365-371 [PMID: 24379928 DOI: 10.4239/wjd.v4.i6.365]
 - 29 **Chen CW**, Chen TC, Huang KY, Chou P, Chen PF, Lee CC. Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an asian country. *PLoS One* 2013; **8**: e71817 [PMID: 23951249 DOI: 10.1371/journal.pone.0071817]
 - 30 **Anagnostis P**, Selamatzidou D, Polyzos SA, Panagiotou A, Slavakis A, Panagiotidou A, Athyros VG, Karagiannis A, Mikhailidis DP, Kita M. Comparative effects of rosuvastatin and atorvastatin on glucose metabolism and adipokine levels in non-diabetic patients with dyslipidaemia: a prospective randomised open-label study. *Int J Clin Pract* 2011; **65**: 679-683 [PMID: 21564441 DOI: 10.1111/j.1742-1241.2011.02655.x]
 - 31 **Anagnostis P**, Adamidou F, Slavakis A, Polyzos SA, Selamatzidou D, Panagiotou A, Athyros VG, Karagiannis A, Kita M. Comparative Effect of Atorvastatin and Rosuvastatin on 25-hydroxy-Vitamin D Levels in Non-diabetic Patients with Dyslipidaemia: A Prospective Randomized Open-label Pilot Study. *Open Cardiovasc Med J* 2014; **8**: 55-60 [PMID: 25110531 DOI: 10.2174/1874192401408010055]
 - 32 **D'Adamo E**, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, Caprio S. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. *Diabetes Care* 2010; **33**: 1817-1822 [PMID: 20668154 DOI: 10.2337/dc10-0284]
 - 33 **Firneisz G**. Non-alcoholic fatty liver disease and type 2 diabetes mellitus: the liver disease of our age? *World J Gastroenterol* 2014; **20**: 9072-9089 [PMID: 25083080 DOI: 10.3748/wjg.v20.i27.9072]
 - 34 **Malin SK**, Mulya A, Fealy CE, Haus JM, Pagadala MR, Scelsi AR, Huang H, Flask CA, McCullough AJ, Kirwan JP. Fetuin-A is linked to improved glucose tolerance after short-term exercise

- training in nonalcoholic fatty liver disease. *J Appl Physiol* (1985) 2013; **115**: 988-994 [PMID: 23928114 DOI: 10.1152/jappphysiol.00237.2013]
- 35 **Tsouli SG**, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS. Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? *Metabolism* 2006; **55**: 1293-1301 [PMID: 16979398 DOI: 10.1016/j.metabol.2006.05.013]
 - 36 **Katsiki N**, Athyros VG, Karagiannis A, Mikhailidis DP. Hyperuricaemia and non-alcoholic fatty liver disease (NAFLD): a relationship with implications for vascular risk? *Curr Vasc Pharmacol* 2011; **9**: 698-705 [PMID: 21388346 DOI: 10.2174/157016111797484152]
 - 37 **Athyros VG**, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Milionis HJ, Mikhailidis DP. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Am J Kidney Dis* 2004; **43**: 589-599 [PMID: 15042535]
 - 38 **Athyros VG**, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, Tziomalos K, Ganotakis ES, Elisaf M. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. *Nephrol Dial Transplant* 2007; **22**: 118-127 [PMID: 16998214 DOI: 10.1093/ndt/gfl538]
 - 39 **Athyros VG**, Karagiannis A, Ganotakis ES, Paletas K, Nicolaou V, Bacharoudis G, Tziomalos K, Alexandrides T, Liberopoulos EN, Mikhailidis DP. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the ATTEMPT study. *Curr Med Res Opin* 2011; **27**: 1659-1668 [PMID: 21714711 DOI: 10.1185/03007995.2011.595782]
 - 40 **Yoon HJ**, Cha BS. Pathogenesis and therapeutic approaches for non-alcoholic fatty liver disease. *World J Hepatol* 2014; **6**: 800-811 [PMID: 25429318 DOI: 10.4254/wjh.v6.i11.800]
 - 41 **Milić S**, Stimac D. Nonalcoholic fatty liver disease/steatohepatitis: epidemiology, pathogenesis, clinical presentation and treatment. *Dig Dis* 2012; **30**: 158-162 [PMID: 22722431 DOI: 10.1159/000336669]
 - 42 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMra011775]
 - 43 **Younossi ZM**, Reyes MJ, Mishra A, Mehta R, Henry L. Systematic review with meta-analysis: non-alcoholic steatohepatitis - a case for personalised treatment based on pathogenic targets. *Aliment Pharmacol Ther* 2014; **39**: 3-14 [PMID: 24206433 DOI: 10.1111/apt.12543]

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