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Atorvastatin and Antioxidants for the Treatment of Nonalcoholic Fatty Liver Disease: The St Francis Heart Study Randomized Clinical Trial

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OBJECTIVES: **Nonalcoholic fatty liver disease (NAFLD) is defined as the spectrum of benign fatty liver to necroinflammation and fibrosis. Its prevalence has been found to be as high as 39%. It is estimated that up to 15% of those affected will go on to have progressive liver disease. Currently, there is no proven therapy for NAFLD. In this study, we aim to determine whether statin therapy may be an effective treatment for NAFLD and identify independent predictors of NAFLD.**

METHODS: **In all, 1,005 men and women, aged 50–70 years were randomized to receive either a daily combination of atorvastatin 20 mg, vitamin C 1 g, and vitamin E 1,000 IU vs. matching placebo, as part of the St Francis Heart Study randomized clinical trial. Liver to spleen (LS) ratios were calculated on 455 subjects with available computed tomography scans performed at baseline and follow-up to determine NAFLD prevalence. Baseline and final LS ratios were compared within treatment groups, and results were compared between the treatment and placebo groups using univariate and multivariate analyses. Mean duration of follow-up was 3.6 years.**

RESULTS: **There were 80 patients with NAFLD at baseline. We identified baseline triglyceride levels (odds ratio (OR) = 1.003, $P < 0.001$) and body mass index (OR = 0.10, $P < 0.001$) as independent correlates of NAFLD. Treatment with atorvastatin combined with vitamins E and C significantly reduced the odds of NAFLD at the end of follow-up, 70 vs. 34% (OR = 0.29, $P < 0.001$).**

CONCLUSIONS: **In conclusion, atorvastatin 20 mg combined with vitamins C and E is effective in reducing the odds of having hepatic steatosis by 71% in healthy individuals with NAFLD at baseline after 4 years of active therapy.**

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INTRODUCTION

As the rates of obesity continue to rise dramatically in the United States (1), so do the associated comorbidities. Nonalcoholic fatty liver disease (NAFLD) is defined as the spectrum of benign fatty liver infiltration, or simple hepatic steatosis, to necroinflammation and fibrosis. The prevalence of NAFLD in the United States has not been well described but has been found to range from 15 to 39% (2). The majority of these patients have a benign fatty infiltrate, which is considered to be nonprogressive. However, it is estimated that up to 10–25% of those with NAFLD (or 2–7% of the entire population) will have nonalcoholic steatohepatitis (NASH), a combination of necroinflammation and fibrosis, which can ultimately lead to cirrhosis (3,4).

NAFLD is widely accepted to be the hepatic manifestation of metabolic syndrome, a known cause of increased mortality (5). Metabolic syndrome is characterized by a group of metabolic risk factors, including central obesity, dyslipidemia, insulin resistance, a prothrombotic state (e.g., high fibrinogen), high blood pressure, and a pro inflammatory state (e.g., elevated C-reactive protein) (6). The exact prevalence of NAFLD in patients with metabolic syndrome is unknown, though a high proportion of those with metabolic syndrome have elevated aminotransferases (7). However, 36% of patients with NAFLD have 3 or more components of

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metabolic syndrome and this number increases to 67% in those who are obese (5). NAFLD is now also known to independently increase overall mortality, with malignancy and cardiovascular disease being the most common cause of death (8,9).

Presently, we have no proven effective therapy for NAFLD. A large majority of the studies looking at potential therapies have been open-label pilot studies with small sample sizes (10). Treatment with antioxidants, insulin sensitizers, and weight loss, either through diet or weight-loss surgery, has shown some promise, although most of these data are inconclusive (11–17). Approximately 70% of patients with NASH also have concurrent dyslipidemia (2) making treatment with a lipid-lowering medication appear to be a reasonable approach. A few small pilot studies have noted atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, to be effective. A study evaluating 31 patients treated with 24 months of atorvastatin showed improvement in their NAFLD activity score and transaminase levels (2). Another distinct study had similar findings in 10 patients with NAFLD and dyslipidemia treated with atorvastatin for a mean of 38 weeks (18).

Given the increased mortality rates in patients with NAFLD, the rising rates of obesity, diabetes, and metabolic syndrome in this population, finding an effective therapy is of utmost importance. In this study, our aim is to determine whether statin therapy may be an effective treatment for NAFLD based on radiographic evidence, as well as identify independent predictors of NAFLD in an otherwise healthy population.

METHODS

Demographics

This is a substudy of the St Francis Heart Study randomized clinical trial, which is a double-blind, placebo-controlled randomized clinical trial of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E 1,000 U daily (active therapy), vs. matching placebos in 1,005 apparently healthy men and women aged 50–70 years. Additionally, all patients received 81 mg of aspirin. This study, which recruited from July 1996 to March 1999, was originally designed to evaluate the effect of this treatment on the risk of developing a cardiovascular event in healthy individuals deemed high risk by coronary calcium scores (19). The methods have been previously described (20). Briefly adults aged 50–70 years were screened and included if they did not have a history of coronary artery disease, insulin-dependent diabetes, a bleeding diathesis, severe anemia, cancer within the past 5 years, any condition likely to lead to death within 5 years, use of anticoagulants and cyclosporine, low-density lipoprotein >174 or <90, systolic blood pressure >180, diastolic blood pressure >100, and elevated transaminases >1.5 times the upper limit of normal. Additionally for this substudy, those persons without both a visible liver and spleen (necessary to accurately quantify liver fat) on the baseline computed tomography (CT) and at least one follow-up CT scan were excluded, leaving 455 individuals (45% of the original sample).

Radiographic methods

Abdominal CT imaging has been shown to be fairly accurate in identifying patients with moderate-to-severe steatosis (>30%) (21). Hepatic steatosis has been defined on CT using the absolute attenuation in Hounsfield units, a difference in the liver attenuation and spleen attenuation of less than –10 Hounsfield units, and a ratio of liver and spleen attenuation <1 (22,23). These modes of measurement have been shown to be equally effective in diagnosing hepatic steatosis ≥30% with areas under the receiver operating characteristic curve of 0.995, 0.991, and 0.991, respectively (24).

The patients underwent three noncontrast electron beam CT scans (Imatron C-150XP, Imatron, South San Francisco, CA), performed at baseline, followed by a 2-, then 4-year evaluation, with reconstruction to a 26-cm field of view. A total of 40 contiguous 3-mm slices were scanned during a single breath hold, beginning at the carina. The scan time was 100 ms per slice, synchronized to 80% of the RR interval (late diastole). We measured the attenuation of the liver and spleen in all participants in whom sufficient tissue was available on the existing heart scans already obtained.

The minimum and maximum attenuation values in Hounsfield unit were obtained from a 2-cm round region of interest in the left and right lobe of the liver as well as the spleen. If sufficient tissue was not available for a 2-cm measure, a 1-cm measurement was obtained. If <1 cm of tissue was available for measurement on the cardiac scan, the scan was excluded.

A mean value was then calculated for the liver and spleen and used to calculate a liver–spleen (LS) ratio. NAFLD was defined as an LS ratio <1. Readers should note that for the rest of the article when we refer to NAFLD we are referring to radiographically defined NAFLD, which is >30% hepatic steatosis. Baseline and final LS ratios were compared, and results were compared between the treatment and placebo groups.

Statistical methods

Results of summary outcome measures were reported as mean±s.d. Differences between groups were tested using χ^2 analyses for categorical data and two-sample Student's *t*-test for continuous variables. Univariate and multivariate analysis was used to determine what if any factors predicted fatty liver. We used general estimating equation model to analyze the multivariate predictors of fatty liver disease and the treatment response. This approach is optimal for population-based estimates for longitudinal, nested, and repeated measures designs. A 95% confidence interval (CI) was used and a two-tailed $P < 0.05$ was considered significant.

RESULTS

Demographics

A total of 455 subjects were analyzed: 226 in the placebo group and 229 in the treatment group. Roughly 93% of the population was non-Hispanic white, with a mean age of 59 (s.d.±6.0) years. Medication compliance from the original cohort was assessed every 3 months and was defined as consumption of at least 85% of the study medication. The subjects averaged 85% compliance for the active therapy and its matching placebo. The average length of follow-up was 3.6±1.1 years. Baseline characteristics were similar between groups and are listed in **Table 1**.

Table 1. Baseline demographics

Variable	Placebo (*N*=226)		Treatment (*N*=229)		*P* value
	Number (%)	Mean (s.d.)	Number (%)	Mean (s.d.)	
Age (years)		59.3 (5.9)		59.2 (6.0)	0.89
Male	159 (70.3)	—	164 (71.6)	—	0.77
Race					
White	209 (92.5)	—	214 (93.5)	—	0.69
Black	4 (1.8)	—	6 (2.6)	—	0.54
Hispanic	7 (3.1)	—	3 (1.3)	—	0.19
Asian	6 (2.7)	—	4 (1.8)	—	0.51
Other	0 (0.0)	—	2 (0.9)	—	0.16
Hypertension	76 (33.6)	—	72 (31.4)	—	0.62
Diabetes	20 (8.9)	—	14 (6.1)	—	0.27
Family history of CAD	123 (54.4)	—	121 (52.8)	—	0.74
Smoke history	129 (66.8)	—	139 (67.8)	—	0.45
Cholesterol	—	229.7 (34.4)	—	224.3 (36.3)	0.10
LDL	—	148.9 (30.4)	—	147.7 (31.6)	0.68
HDL	—	50.7 (14.3)	—	48.4 (11.9)	0.06
TG	—	155.0 (113.2)	—	141.7 (87.2)	0.16
BMI	—	29.4 (5.0)	—	30.4 (4.9)	0.055
SBP (*r*)	—	137.3 (19.6)	—	134.5 (18.9)	0.12
DBP (*r*)	—	79.3 (9.1)	—	78.2 (9.3)	0.19
NAFLD (LS<1)	36 (15.9)	—	44 (19.2)	—	0.36

BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, liver–spleen ratio; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TG, triglyceride.

Univariate predictors of severe to moderate hepatic steatosis at baseline scan include the presence of hypertension ($P=0.004$), lower high-density lipoprotein (HDL) levels ($P=0.0005$), higher triglyceride (TG) levels (<0.0001), and higher body mass index (BMI) (<0.0001) (**Table 2**). We performed multivariate analysis controlling for age, sex, baseline low-density lipoprotein cholesterol, HDL cholesterol and TG levels, systolic and diastolic blood pressures, diabetes, and BMI. Baseline TG levels (odds ratio (OR) = 1.003, $P<0.001$, 95% CI = 1.002, 1.006) and BMI (OR = 1.10, $P<0.001$, 95% CI = 1.05, 1.14) remained the significant predictors of baseline NAFLD.

NAFLD response to active therapy

There were a total of 80 patients with LS ratios <1 on CT: 36 in the placebo group and 44 in the treatment group. By year 2, this population was reduced to 62: 27 in the placebo group and 35 in the treatment group. At year 4, the total population was 59: 27 in the placebo group and 32 in the treatment group. Baseline characteristics were similar between groups, with the exception of the presence of more subjects with a family history of cardiovascular disease in the placebo group in comparison with the treatment group ($P=0.05$) (**Table 3**).

Among the 80 patients with NAFLD, total cholesterol and low-density lipoprotein cholesterol levels were significantly reduced by treatment: 210.6±31.6 (control) vs. 169.9±38.6 (treatment, $P<0.001$) and 123.3±39.9 (control) vs. 90.3±37.9 (treatment, $P<0.001$), respectively. The follow-up mean HDL values; 46.8±16.9 (placebo) vs. 43.5±8.3 (treatment, $P=0.25$), and mean TG levels; 195.4±131.6 (placebo) vs. 169.4±123.4 (treatment, $P=0.37$), did not differ significantly between treatment and control groups.

There was a higher percentage of patients with NAFLD at the time of the second CT scan (2.1±1.0 years) in the placebo group (77.8%) when compared with the treatment group (37.1%, $P=0.001$). At the end of follow-up (3.6±1.1 years) this difference remained significant; 70.4% (placebo) vs. 34.4% (treatment; OR = 0.29, 95% CI = 0.15–0.57, $P<0.001$) (**Figure 1**). The average LS ratio increased from 0.71±0.40 to 1.106±0.52 in subjects assigned to treatment with atorvastatin (**Figure 2**). This difference was still significant after controlling for baseline HDL, low-density lipoprotein, and TGs (OR = 0.28, 95% CI = 0.14–0.57, $P<001$). In subgroup analyses of those with a total cholesterol <200 ($n=21$, OR = 0.12, 95% CI = 0.02–0.90, $P=0.04$) and TG level <150 ($n=34$ OR = 0.17, 95% CI = 0.06–0.51, $P=0.002$), there was still an improvement in NAFLD seen in those on active therapy. When we controlled for

Table 2. Correlates of baseline NAFLD

Variable	Fatty liver (*N*=80)	Normal liver (*N*=375)	*P* value
Age (years)	58.3 (5.9)	59.4 (6.0)	0.10
Gender	—	—	0.16
Male	62 (77.5)	261 (69.6)	—
Female	18 (22.5)	114 (30.4)	—
Hypertension			
Yes	37 (46.3)	111 (29.6)	0.004*
No	43 (53.8)	264 (70.4)	—
DM			
Yes	7 (8.8)	27 (7.2)	0.63
No	73 (91.3)	348 (92.8)	—
Family history of CAD			
Yes	37 (46.3)	207 (55.2)	0.15
No	43 (53.8)	168 (44.18)	—
Smoking history			
Yes	44 (61.1)	224 (64.4)	0.60
No	28 (38.9)	124 (35.6)	—
Cholesterol	226.5 (38.4)	227.0 (34.8)	0.90
LDL	143.6 (32.4)	149.3 (30.6)	0.14
HDL	45.0 (10.9)	50.3 (13.4)	0.0005*
TG	196.8 (144.7)	138.0 (85.8)	0.0000*
BMI	32.9 (4.6)	29.3 (4.8)	0.0000*
SBP (*r*)	140.1 (18.6)	135.0 (19.3)	0.04*
DBP (*r*)	81.4 (9.2)	78.1 (9.1)	0.05*
White	76 (95.0)	347 (92.5)	0.43
Black	0	10 (2.7)	0.14
Hispanic	3 (3.8)	7 (1.9)	0.30
Asian	0	10 (2.7)	0.14
Other	1 (1.3)	1 (0.27)	0.23

BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TG, triglyceride.
*$P<0.05$.

age, sex, baseline BMI, race, baseline systolic and diastolic blood pressure, baseline diabetes, and follow-up lipid values, there was still a significant reduction in the prevalence of fatty liver in the treatment group (OR=0.36, 95% CI=0.16–0.83, $P=0.017$). Follow-up TG levels were a significant predictor of NALFD at the end of treatment (OR=1.004, 95% CI=1.004–1.0074, $P=0.02$), as well as systolic blood pressure (OR=0.95, 95% CI=0.93–0.99, $P=0.007$) in this model.

Atorvastatin, vitamins E and C, and NAFLD development

In those without NAFLD at baseline ($n=375$), we found that 17.6% of the placebo group developed NAFLD compared to 12.1% of the treatment group. This difference was not statistically different ($P=0.23$).

Hepatic toxicity

There were three subjects in our study with transaminase elevations greater than twice the upper laboratory limit of normal by year 2 of follow-up. These elevations were all resolved by year 4 of follow-up (**Table 4**).

DISCUSSION

Summary

In this study, we evaluated the effects of 4 years of 20 mg daily atorvastatin treatment combined with daily vitamins E and C, in apparently healthy individuals with radiographically diagnosed NAFLD, i.e., hepatic steatosis >30%. There were a total of 455 subjects included in this study, 80 of whom had NAFLD at baseline. There was a 71% reduction in the risk of having moderate-to-severe hepatic steatosis at the end of the study in those on treatment. In order to evaluate whether the reduced prevalence of NAFLD at the end of the study was a direct effect of treating and improving dyslipidemia, we performed a subgroup analysis on NAFLD patients with baseline total cholesterol values <200 and/or TG levels <150. We found that the risk reduction remained significant, although this population was smaller and so further studies are necessary for definitive conclusions to be drawn. Follow-up TG levels were a significant predictor of fatty liver at the end of the study among those with NAFLD at baseline, with an OR of 1.004. This estimated odds ratio would imply that a 50 unit increase in triglyceride levels increases the odds of continuing to have NAFLD by 20%. Follow-up SBP was also a significant predictor of NAFLD at the end of the study, with an OR of 1.007 i.e. at 10 point increase in SBP increases the odds of NAFLD at follow-up by 7%.

We found that in patients without NAFLD at baseline, more people in the placebo group ($n=22$) developed fatty liver than those receiving active therapy ($n=14$). This difference was not statistically different ($P=0.23$), possibly because of the overall small numbers. Further studies must be carried out in order to draw any significant conclusions on the impact this combination of drugs has on preventing the development of NAFLD.

Similar to other studies, we found that hypertension, low HDL, and increased TG levels (all components of the metabolic syndrome) were significant correlates of baseline fatty liver in this population (6). Interestingly, we did not find a significant association with diabetes and baseline NAFLD. This is likely due to the overall low number of diabetics in this population ($n=7$).

Significance

This study showed a significant reduction in moderate-to-severe hepatic steatosis in a randomized population treated with a combination of atorvastatin, vitamins E and C. Our findings also confirm the evidence obtained from pilot data showing the efficacy of statin therapy on NAFLD (**Table 5**). Approximately 70% of patients with NASH also have been found to have concurrent dyslipidemia (2). Another distinct study found 60% of patients with mixed hyperlipidemia had evidence of hepatic steatosis (25), making atorvastatin an ideal treatment. We have shown atorvastatin to be beneficial in those with normal cholesterol (<200; OR=0.12, 95% CI=0.02–0.90) and TG (<150; OR=0.17, 95% CI=0.06–0.51)

Table 3. Baseline demographics of those with NAFLD at baseline

Variable	Placebo (*N*=36)		Treatment (*N*=44)		*P* value
	Number (%)	Mean (s.d.)	Number (%)	Mean (s.d.)	
Age (years)	—	57.9 (5.3)	—	58.6 (6.4)	0.60
Male	29 (80.6)	—	33 (75.0)	—	0.55
Race					
White	209 (92.5)	—	214 (93.5)	—	0.69
Black	0	—	0	—	N/A
Hispanic	1 (2.8)	—	2 (4.6)	—	0.68
Asian	0	—	0	—	N/A
Other	0 (0.0)	—	2 (0.9)	—	0.36
Hypertension	17 (47.2)	—	20 (45.5)	—	0.88
Diabetes	3 (8.3)	—	4 (9.1)	—	0.90
Family history of CAD	21 (58.3)	—	16 (36.4)	—	0.05*
Smoke history	21 (63.6)	—	23 (51.0)	—	0.69
Cholesterol	—	230.4 (33.3)	—	223.3 (42.2)	0.41
LDL	—	144.5 (31.5)	—	142.9 (33.5)	0.83
HDL	—	46.2 (13.3)	—	44.0 (8.4)	0.36
TG	—	216.4 (161.6)	—	180.7 (129.0)	0.27
BMI	—	32.7 (4.4)	—	33.1 (4.8)	0.76
SBP (*r*)	—	140.5 (21.2)	—	139.7 (16.4)	0.87
DBP (*r*)	—	81.5 (10.0)	—	81.3 (8.7)	0.92

BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TG, triglyceride.
*P=0.05.

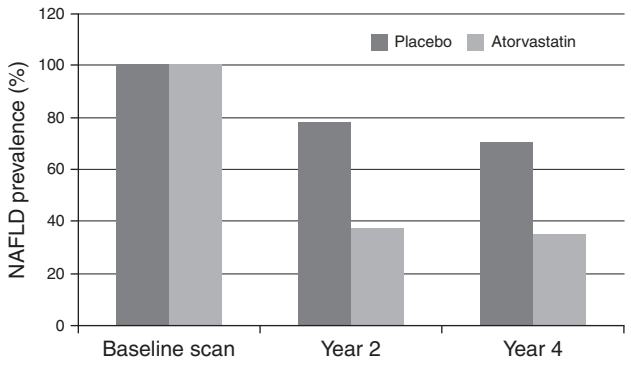

Figure 1. Bar graph showing the prevalence of nonalcoholic fatty liver disease (NAFLD) at baseline at and the 2nd and final computed tomography (CT) scans.

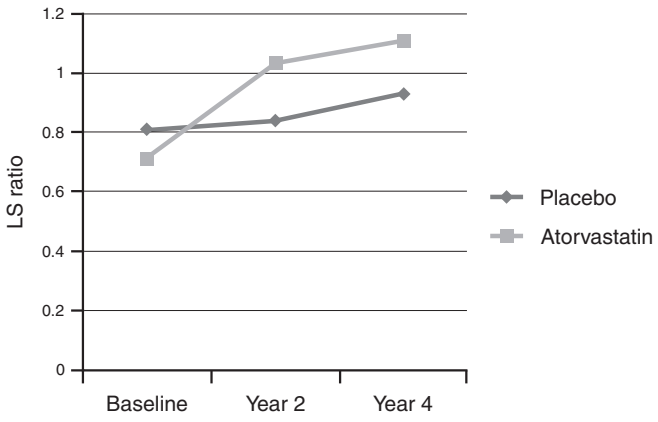

Figure 2. Line graph showing the change in liver–spleen (LS) ratio at baseline and at the second and final computed tomography (CT) scans in the different treatment groups.

levels, making it a potential therapy in those NAFLD patients without dyslipidemia. The evidence on the efficacy of vitamin E has been more equivocal; although some studies have shown vitamins E and C to be a promising treatment of NAFLD (15,26), others have shown them to be ineffective (16,27). However, recent unpublished data from the PIVENS (pioglitazone versus vitamin E for the treatment of non-diabetic patients with non-alcoholic steatohepatitis) trial (28) did show a significant improvement in NASH in those taking vitamin E when compared with pioglitazone and placebo. This has been the largest randomized trial to date to show the efficacy of vitamin E, making it a viable treatment option.

Hepatic toxicity

The potential for hepatic toxicity from statins, ranging from transaminase elevations to the rare occurrence of acute liver

Table 4. Patients with transaminase elevations

	Baseline fatty liver	Baseline		Year 2 follow-up		Year 4 follow-up	
		AST	ALT	AST	ALT	AST	ALT
Patient 1	Yes	34	39	19	118	49	37
Patient 2	No	20	19	59	106	—	—
Patient 3	No	22	49	50	234	11	13

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 5. Summary of studies using statin therapy for NAFLD

References	*N*	Study design	Diagnosis	Therapy	Dose	Duration (months)	Aminotransferase improvement	Histological improvement	Imaging
Horlander *et al.* (32)	7	Open label	NASH	Atorvastatin	Varied	12	Improved	Improved IN, S, and F	N/A
Kiyici *et al.* (14)	27	Open label	NASH	Atorvastatin	10 mg	6	Improved	N/A	CT improved
Rallidis *et al.* (33)	5	Open label	NASH	Pravastatin	20 mg	6	Improved	Improved IN, S, and F, no change in F	N/A
Hatzitolios *et al.* (34)	28	Open label	NAFLD	Atorvastatin	20 mg	6	Improved	N/A	US: improved
Gomez-Dominguez *et al.* (35)	22	Open label	NAFLD	Atorvastatin	Varied	12	Improved	N/A	US: no change
Antonopoulos *et al.* (36)	23	Open label	NAFLD	Rosuvastatin	10 mg	8	Improved	N/A	N/A

F, fibrosis; CT, computed tomography; IN, inflammation; N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RCT, randomized control trial; S, steatosis; US, ultrasound.

disease, remain a concern for many practitioners. Systematic reviews have yielded variable results; although some have found no difference in the incidence of transaminase elevations in patients receiving moderately dosed statins (29), other studies have found a positive relationship between statin dose and transaminase levels (30). At this time, however, the implications of transaminase elevations caused by statin therapy are not well known and have not been well correlated to the degree of histological injury (31). In our study, there were only three patients who developed transaminase elevations greater than two times the upper laboratory normal value in year 2. Of the two patients with four year follow-up transaminases available, patient 3's values had completely normalized and patient 1's values had significantly decreased.

Limitations

This study does have a few limitations. First, our active treatment is a cocktail of atorvastatin, vitamins C and E. It is difficult to determine the extent each of the treatment components contributed to the treatment results or if the results were due to synergy. Given the high prevalence of dyslipidemia in patients with NAFLD and the low cost of vitamins E and C, a regimen of the combination therapy would seem to be the best approach. Second, our measurement of hepatic steatosis, although objective, is not the gold standard. Currently, we do not have noninvasive means to determine which patients with fatty liver infiltrate have NASH. We are also limited in our ability to predict which patients with fatty liver will go on to develop NASH. This is challenging for a number of reasons: we cannot perform invasive liver biopsies on every patient with fatty liver infiltrate, yet an estimated 7–17% of those patients with NASH are thought to go on to develop cirrhosis (4,6). CT scans are not able to accurately characterize the amount of hepatic fat when the total content is <30%. Hepatic steatosis >30%, however, is diagnosed fairly accurately with CT using the LS ratio, with the area under the receiver operating characteristic curve of 0.991 (24). Therefore, we were able to identify those with moderate-to-severe hepatic steatosis and hope that this is an adequate surrogate for those who also have NASH. Third, although patients with transaminase levels >1.5 times the upper limit of normal were excluded, specific cases of chronic liver disease were not identified for exclusion. With the relatively low prevalence of these diseases in the general population, the impact on this trial is likely low and any possible confounding should have affected the treatment and placebo groups equally. Finally, we excluded all those without both a liver and spleen on their CT scan. It is unclear, though it would seem unlikely that these scans were incomplete due to patient level characteristics, these data were likely missing at random and was treated as such.

In conclusion, atorvastatin 20 mg in combination with vitamins C and E lowered the risk of having moderate-to-severe hepatic steatosis by 70% in a healthy population of 80 patients with NAFLD at baseline after 4 years of therapy. We also have convincing evidence that it is equally efficacious in patients without dyslipidemia, although further studies with a larger population need to be conducted.

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CONFLICT OF INTEREST

Guarantor of the article: Temitope Foster, MD, MSCR.

Specific author contributions: Drafting of the paper, statistical analysis, and approval of the final draft submitted: Temitope Foster; study concept and design, critical revision of the paper for important intellectual content, and approval of the final draft submitted: Matthew Budoff; critical revision of the paper for important intellectual content, and approval of the final draft submitted: Sammy Saab; drafting of the paper, and approval of the final draft submitted: Naser Ahmadi; acquisition of data, data management, and approval of the final draft submitted: Craig Gordon; acquisition of data, critical revision of the paper for important intellectual content, and approval of the final draft submitted: Alan D. Guerci.

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Potential competing interests: Dr Matthew Budoff is on the speaker's bureau for General Electric and Pfizer. The remaining authors declare no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Nonalcoholic fatty liver disease (NAFLD) is a common disease with a prevalence that continues to grow.
- ✓ NAFLD is an independent cause of increased mortality.
- ✓ There is no proven effective therapy for NAFLD.

WHAT IS NEW HERE

- ✓ Atorvastatin along with vitamins E and C appears to be an effective treatment for NAFLD.
- ✓ Patients with NAFLD without dyslipidemia also appear to benefit from treatment with this regimen.
- ✓ Atorvastatin can be used safely in patients with NAFLD.

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