Atorvastatin and antioxidants: The remedy for non-alcoholic fatty liver disease?

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SUMMARY

This paper reports a sub-study of the St Francis Heart Study which was a double-blind, placebo-controlled, randomized clinical trial designed to test the effectiveness of active therapy with atorvastatin 20 mg daily, vitamin C 1 g daily and vitamin E 1000 i.u. daily versus matched placebo in reducing the risk of adverse cardiac events in healthy people who were at increased risk as determined by coronary calcium scores. The study participants were healthy adults aged 50–70 years, without a history of coronary artery disease, type 1 diabetes mellitus, bleeding disorder, severe anaemia, cancer within the past 5 years, any condition likely to cause death in the subsequent 5 years, patient on anticoagulants or on cyclosporin, low-density lipoprotein (LDL) >174 mg/dl or <90 mg/dl, systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg, and elevated transaminase >1.5-times the upper limit of normal.

The objective of this sub-study was (i) to assess whether the statin and antioxidant therapy was effective in the treatment of non-alcoholic fatty liver disease (NAFLD), and (ii) to identify the predictors of NAFLD in an otherwise healthy population. NAFLD was defined radiographically as liver-to-spleen (LS) ratio of <1, which is >50% hepatic steatosis. This was calculated by dividing the mean liver attenuation score by the mean spleen score, on abdominal CT. For this sub-study, along with the above-mentioned criteria, participants without a visible liver and spleen on a baseline CT were excluded. There were 455 participants in this sub-study: 229 in the treatment arm and 226 in the placebo arm. The mean (SD) length of follow-up was 3.6 (1.1) years, with 85% compliance rate for medication in both arms. Both arms did not differ significantly on baseline characteristics. In univariate analysis, hypertension, higher triglyceride (TG), lower high-density lipoprotein (HDL) level, and higher body mass index (BMI) were significantly associated with severe-to-moderate hepatic steatosis. On multi-variate analysis (after adjusting for age, sex, baseline LDL, HDL, TG, systolic blood pressure, diastolic blood pressure, BMI and diabetes), TG levels (Odds ratio [OR] 1.003, p<0.001, 95% CI 1.002–1.006) and BMI (OR 1.1, p<0.001, 95% CI 1.05–1.14) remained significant.

At baseline, 80 patients were diagnosed with NAFLD, 44 in the treatment group and 36 in the placebo group. After 2 years, the number reduced to 62 patients, 35 in the treatment and 27 in the placebo group; after 4 years, the number was 59 patients, 32 in the treatment and 27 in the placebo group. Both total cholesterol and LDL were lower in the treatment group (169 [38.6] and 90.3 [37.9], respectively) compared to the placebo group (210.6 [31.6] and 123.3 [39.9], respectively) at follow-up; this was statistically significant (p<0.001).

The average LS score increased in the treatment group significantly compared to that in the placebo group even after controlling for HDL, LDL and TG levels (OR 0.28, 95% CI 0.14–0.57, p<0.001). To see whether the reduction in NAFLD prevalence was due to the effect of dyslipidaemia, subgroup analysis was done on those patients whose baseline cholesterol was <200 mg/dl (n=21, OR 0.12, 95% CI 0.02–0.90, p<0.04), and TG<150 mg/dl (n=34, OR 0.17, 95% CI 0.06–0.51, p<0.002). Systolic blood pressure (OR 0.95, 95% CI 0.93–0.99, p=0.007) and TGs (OR 1.004, 95% CI 1.004–1.0074, p=0.02) were significant predictors of NAFLD at the end of the treatment.

In the 375 persons who were not diagnosed as having NAFLD at baseline, a greater proportion of those on placebo (17.6%) developed NAFLD than on active therapy (12.1%). However, these results were not statistically significant. Three participants had transaminase levels which were greater than twice the normal limit at second year of follow-up. At the end of the study, it came back to normal levels.

The authors concluded that atorvastatin 20 mg with vitamin C and E is effective in reducing the progression of NAFLD.

COMMENT

There is evidence from three pilot studies that statins are beneficial in the treatment of NAFLD. These three studies showed an improvement in aminotransferase levels when patients with NAFLD were treated with statins. One study showed a concomitant improvement in ultrasonography as well. This randomized controlled trial provides further support for the usefulness of statins in the management of NAFLD.

However, a few methodological issues deserve attention. As it is a sub-study of a larger study, issues of sample size estimation have not been described. As CT was used to diagnose NAFLD, persons with fat <30% would not have been identified as NAFLD. Hence, the results of this study would apply to only those persons who already have fat >30%. At baseline, other liver disorders were excluded based on a single parameter of elevated transaminase levels, twice the normal values. From this study, it would be difficult to ascertain the relative importance of atorvastatin, vitamin C and vitamin E in the treatment regimen.

Studies on the prevalence of NAFLD in India show that it may soon require concerted public health intervention. A hospital-based study done in Allahabad reported a prevalence of 32.2%. A community-based study on residents of a railway colony reported a prevalence of 16.6%. Both studies used sonography for the diagnosis of NAFLD. In both studies, obesity was significantly associated with NAFLD. A community-based study from a rural administrative unit of West Bengal reported a NAFLD prevalence of 8.7%. This study used ultrasoundography and CT for the diagnosis of NAFLD. A survey of 1230 autopsies carried out in a tertiary care hospital in Mumbai reported a 15.8% prevalence of fatty liver with diabetes and hypertension as risk factors in 10% of the cases. A meta-analysis of cohort studies, with overweight and obesity as exposure, and hepatic cancer as outcome, reported that, compared with persons of normal weight, the summary relative risks of liver cancer were 1.17 (95% CI 1.02–1.34) for those who were overweight, and 1.89 (95% CI 1.51–2.36) for those who were obese. The authors opined that the risk was mediated through the development of NAFLD. Studies done in tertiary care hospitals in India on the incidence of hepatocellular carcinoma showed that a high proportion of cases
(30% and 21%) were due to non-infective and non-alcoholic causes, respectively.10,11

Further, there is evidence of increased prevalence of dyslipidaemia and deficiency of plasma antioxidants in the Indian population. A study in an urban population in Jaipur reported a high prevalence of dyslipidaemia. The most common in both men and women was low HDL cholesterol (men 54.9%, women 54.2%). High total cholesterol, high LDL cholesterol and high levels of TGs were also reported in a substantial number of patients.12 A study from western India reported subnormal plasma levels of ascorbic acid and retinol in both men and women, who were apparently healthy.13

The prevalence of NAFLD in people with diabetes is high. A hospital-based study from Mumbai reported the prevalence of NAFLD to be as high as 87% among people with diabetes with fatty infiltrates on ultrasonography; NAFLD being diagnosed by histopathology.14 A study on subjects of Chennai Urban Rural Epidemiology Study reported the prevalence of NAFLD to be 32%; a higher prevalence was reported among people with diabetes.15 WHO has projected that, by the year 2030, India will have nearly 70 million people with diabetes mellitus.16 Simultaneously, obesity and overweight are emerging as new threats due to changes in lifestyle and dietary habits, more so among children and adolescents.17 The prevalence of overweight/obesity in adult Indian men has been reported to be 9.2%.18 Since the risk factors for NAFLD are common with those of cardiovascular disease, patients with NAFLD are at increased risk for adverse cardiovascular events.19 Some studies have pointed out that NAFLD may be common even in non-obese and those who do not have diabetes.20 Thus, NAFLD is emerging as a public health problem in India, which needs to be tackled.

Primary preventive strategies for the control of NAFLD would be the same as those for many other non-communicable diseases—dietary modification, exercise, lifestyle changes. However, it is equally imperative to provide relief to those who have developed NAFLD. For such patients, one needs to identify effective treatment modalities to supplement behaviour change communication. Secondary prevention would necessitate use of drugs to control NAFLD per se, as well as concomitant conditions, such as diabetes. Based on the available literature, a combination of atorvastatin with vitamins C and E appears to be an effective treatment of non-alcoholic fatty liver disease with dyslipidaemia. Indian J Gastroenterol 2004;23:131–4.8


REFERENCES