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Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: A histopathological follow-up study

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***Background/Aims*: The effect of statins on hepatic histology in non-alcoholic fatty liver disease (NAFLD) is not known. This study explores hepatic histology in NAFLD patients before and after initiation of statin therapy and compares histological outcome with NAFLD patients who had not been prescribed statins.**

***Methods*: Sixty-eight NAFLD patients were re-evaluated. Follow-up ranged from 10.3 to 16.3 years. Subjects were clinically investigated and a repeat liver biopsy was obtained. No patient was taking statins at baseline while 17 patients were treated with statins at follow-up.**

***Results*: At baseline, patients that later were prescribed statins had significantly higher BMI and more pronounced hepatic steatosis. At follow-up patients on medication with statins continued to have significantly higher BMI. Diabetes was significantly more common among patients on medication with statins and they had significantly more pronounced insulin resistance. However, they exhibited a significant reduction of liver steatosis at follow-up as opposed to patients not taking statins. Despite exhibiting a high risk profile for progression of liver fibrosis, only four patients on statin treatment progressed in fibrosis stage.**

***Conclusions*: Statins can be prescribed in patients with elevated liver enzymes because of NAFLD.**

***Keywords*: Non-alcoholic fatty liver disease; Histology; Statin; Metabolic syndrome**

1. Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (''statins'') are among the most widely prescribed drugs in the developed countries [1] and their benefit in primary and secondary prevention of cardiovascular disease is undisputable [2]. With the publication of the new National Cholesterol Education Program III guidelines [3] the number of patients meeting criteria for treatment with statins has significantly increased [1].

Non-alcoholic fatty liver disease (NAFLD), which is most commonly associated with components of the metabolic syndrome [4], is now recognised as one of the most common causes of chronic liver disease worldwide. NAFLD represents a spectrum of disorders, including fatty liver alone and non-alcoholic steatohepatitis (NASH), which may slowly and often silently progress to cirrhosis [5,6]. Many, if not most, patients with hyperlipidemia and type 2 diabetes, which are the primary targets for treatment with statins, have co-existing NAFLD [7,8] and although liver-related morbidity and mortality is increased in NAFLD patients, the primary

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cause of death is cardiovascular disease [9]. Prevention of cardiovascular morbidity and mortality should therefore be of the utmost concern to every clinician when caring for NAFLD patients.

Patients with NAFLD are often identified by asymptomatic elevations of liver enzymes. Non-alcoholic hypertransaminasemia, in which viral or other causes of liver disease are excluded, has been used as a surrogate marker for NAFLD [10,11]. The current labelling states that statins should not be used in patients with active liver disease or unexplained persistent aminotransferase elevation. In clinical practice, gastroenterologists and hepatologists are often consulted to advise referring physicians about the safety of prescribing statins in patients with elevated serum transaminases, of whom the majority will not have a clinical history or serum markers that would explain abnormal liver biochemistry. Among these subjects NAFLD is the underlying cause of elevated liver enzymes in up to 90% [12]. Moreover, statins are now available without prescription in some parts of the world (United Kingdom) and thus a large number of individuals with undiagnosed NAFLD may consume these drugs.

There is a lack of more substantial literature on the effect of statins in NAFLD. Recently it was shown that hyperlipidemic patients with elevated baseline liver enzymes are not at higher risk for hepatotoxicity than hyperlipidemic patients with normal transaminases [13]. However, follow-up was limited to a 6-month period and hepatic histology was not examined. Reports, where liver histology in NAFLD patients was assessed before and after the initiation of statin treatment included few patients, lacked control groups, and are available only in abstract [14] or as a letter to the editor [15].

To gain further insights into the safety of statins in NAFLD, this retrospective study evaluates hepatic histology in NAFLD patients with elevated liver enzymes before and after initiation of statin therapy and compares histological outcome with NAFLD patients who had not been exposed to statins during follow-up.

2. Patients and methods

2.1. Patients

Between 1988 and 1993 all consecutive asymptomatic patients ($n = 212$) referred for evaluation of chronically (>6 months) elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), >41 U/L (0.70 μkat/L), and/or elevated serum alkaline phosphatase, >106 U/L (1.80 μkat/L), to the Department of Gastroenterology and Hepatology, University Hospital in Linköping and to the Department of Internal Medicine, Oskarshamn County Hospital, were studied. A diagnostic work-up was performed including physical examination, laboratory investigations and liver biopsy [16].

A total of 137 patients were at baseline diagnosed with NAFLD. These patients had biopsy-proven hepatic steatosis without any other concomitant liver disease, or medication associated with fatty infiltration of the liver. Moreover, their reported average weekly alcohol consumption was less than 140 g when answering a questionnaire. The clinical course of this cohort has been described in a previous report [9]. None of these patients were on medication with statins when diagnosis of NAFLD was made.

2.2. Data collection

Each NAFLD patient was currently identified by linking his or her unique personal identification number to the National Registry of Population. All medical records from primary care health centers and hospitals were reviewed. All living subjects of the study cohort were asked to participate in a follow-up study. Those who accepted were offered clinical and biochemical investigation, ultrasonography of the liver, and liver biopsy. A detailed questionnaire was used to evaluate current and previous alcohol consumption.

Subjects had blood drawn for analysis of complete blood counts, prothrombin, transferrin, iron, transferrin saturation, ferritin, AST, ALT, ALP, γ glutamyl transferase, bilirubin, C reactive protein, fasting total cholesterol, LDL, HDL, triglycerides, fasting plasma glucose, fasting serum insulin, glycosylated hemoglobin (HbA1c), and plasma protein electrophoresis. In addition blood was obtained for detection of HBsAg, anti-HCV antibodies, HBV-DNA, HCV-RNA, transglutaminase antibodies, antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and mitochondrial antibodies (AMA).

Subjects under dietary or drug treatment for diabetes mellitus were regarded as having diabetes mellitus. The remaining subjects performed a 75 g oral glucose tolerance test after an overnight fast.

2.3. Histopathological evaluation

At follow-up an ultrasound guided percutaneous liver biopsy was performed by the same physician on an outpatient basis using a 1.6 mm Biopince needle. All biopsies at baseline and at follow-up were read by the same experienced liver pathologist, who was blinded to patient details. Liver fibrosis was assessed semiquantitatively on a scale of 0–4 as previously described [17].

Five variables associated with hepatic necroinflammatory activity were assessed: portal and periportal tract inflammation were graded as none, mild, moderate, and severe (0–3); lobular inflammation was graded 0-3 based on inflammatory foci per 20× (0 is absent; 1 is 1 to 2/20×; 2 is up to 4/20×; 3 is >4/20×); hepatocellular ballooning was graded as none, mild, and marked (0–2); Mallory's hyaline was graded as absent, occasional, and several (0–2) [17].

Moreover, quantitative steatosis was measured as percentage of liver biopsy area containing fat [18]. NASH was defined as the presence of steatosis plus any stage of fibrosis or steatosis plus lobular inflammation plus ballooning degeneration [19].

2.4. Statistical analysis

Categoric variables are presented as number and percentage, and continuous as mean and standard deviation or median and range. Statistical analyses were performed using SPSS software (version 14.0 for Windows). Differences between two groups were evaluated using t tests for normally distributed continuous variables and Mann–Whitney U-test or Wilcoxon signed rank test when the assumption of normality was not met. Dichotomous variables were tested using Fisher's exact test. A multivariate linear regression analysis using backward elimination was performed to evaluate clinical and biochemical variables associated with change of quantitative steatosis between baseline and follow-up biopsies. At each step, the variable with the largest probability of F value was eliminated, provided the P value exceeded 0.10. Sex and pharmacological treatments were coded as indicator variables. A P value of <0.05 was considered statistically significant.

2.5. Ethical considerations

Written informed consent was obtained from all participating subjects. The study design was approved by the Ethics Committee at the University Hospital in Linköping.