Digestive and Liver Disease 46 (2014) 720–725

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Statin therapy is associated with a reduced risk of non-alcoholic fatty liver in overweight individuals

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ARTICLE INFO

Article history:
Received 11 February 2014
Accepted 7 April 2014
Available online 6 May 2014

Keywords:
Body mass index
HMG-CoA-reductase inhibitors
Metabolic syndrome
Steatosis

ABSTRACT

Background: Non-alcoholic fatty liver or hepatic steatosis is considered the hepatic manifestation of the metabolic syndrome. Statins are often used by patients with metabolic syndrome, but their effect in steatosis is not well established.
Aims: To study the association between statins and the presence of steatosis.
Methods: In the population-based Rotterdam Study, 2578 subjects underwent liver ultrasonography and had prescription data available. In a cross-sectional design, we investigated the effect of current, past, and duration of statin use. Logistic regression analyses were adjusted for age, sex, and other known risk factors.
Results: The prevalence of steatosis was 35.3%. We identified 631 current and 359 past statin users. In multivariable analyses, current statin use >2 years was associated with a significantly lower steatosis prevalence [OR 0.43, 95% CI 0.19–0.96]. Stratification by mean body mass index showed that this association was stronger in patients with body mass index ≥27.5 [OR 0.30, 95% CI 0.11–0.81 for current use >2 years], while in patients with body mass index <27.5 the association was non-significant.
Conclusion: Within the Rotterdam study, in patients with body mass index ≥27.5 current use of statins for >2 years was associated with a lower prevalence of steatosis.

1. Introduction

Non-alcoholic fatty liver (NAFLD) is the most common cause of serum alanine aminotransferase (ALT) elevation and of chronic liver disease in Western countries. The term NAFLD encompasses a spectrum of disease activity, ranging from simple hepatic steatosis or non-alcoholic fatty liver (NAFL), to non-alcoholic steatohepatitis (NASH) and NASH cirrhosis, which may lead to a decreased liver function, hepatocellular carcinoma, and liver failure [1–3]. NAFLD is considered as the hepatic manifestation of the metabolic syndrome. It is frequently associated with dyslipidemia, with elevated serum triglycerides and low-density lipoprotein (LDL) cholesterol, and a decrease in serum high-density lipoprotein (HDL) cholesterol [1–5]. Furthermore, NAFLD has been associated with the risk of incident cardiovascular disease (CVD), independently of the components of the metabolic syndrome, and the major cause of death in NAFLD is CVD [2,5–10].

Statins interfere with cholesterol metabolism in the liver by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the cholesterol synthesis pathway. This leads to up-regulation of LDL receptors in the liver, increased uptake of circulating LDL cholesterol, and subsequently to a decrease in LDL cholesterol concentration. Besides this reduction in LDL cholesterol, statins are effective in lowering of the triglyceride concentration and modestly effective in raising the HDL cholesterol concentration [11–16]. Statins are beneficial in the prevention of CVD with an approximately 20% relative risk reduction on mortality and major cardiovascular events in persons free of CVD [17,18]. In general, statins are well-tolerated and safe drugs [19].

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http://dx.doi.org/10.1016/j.dld.2014.04.002
1590-8658/

Statins are frequently used for several indications such as dyslipidemia, type 2 diabetes mellitus, and in patients at high risk of CVD [20]. There is some discussion as to whether statins are safe and effective in NAFLD, and whether they worsen hepatic steatosis, despite improvement of serum lipid concentration [21–25]. Clarification of this topic is important, since due to the co-existence of dyslipidemia and NAFLD, and a higher risk of CVD mortality in NAFLD patients, these patients will often be treated with statins for the primary and secondary prevention of CVD.

In the present study, the objective was to investigate whether statin therapy is associated with the presence of NAFL, considering both current and past use of statin therapy, and duration of statin therapy, in a large prospective cohort study in community-dwelling elderly. In an extended analysis, we investigated whether the association between the use of statin therapy and NAFL was modified by body mass index (BMI) because obesity is a strong and independent risk factor for NAFL.

2. Materials and methods

2.1. Setting

The Rotterdam Study is a prospective population-based cohort study of chronic diseases in the elderly population. From 1990 to 1993, 7983 inhabitants of the suburb Ommoord in Rotterdam, The Netherlands, aged 55 years or older, participated in the Rotterdam Study (RS-I) and gave written informed consent. Ethical approval was obtained from the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. Baseline examinations took place from March 1990 through July 1993. Follow-up examinations were conducted periodically, every 4–5 years. In 2000, an extended cohort was enrolled, the Rotterdam Study II (RS-II). Three-thousand-eleven inhabitants entered the study and have been continuously followed since then. Furthermore, in 2006, a younger cohort was enrolled, the Rotterdam Study III (RS-III), containing 3932 inhabitants aged 45 years or older. Abdominal ultrasonography was added to the core protocol at the fifth survey of the Rotterdam Study (February 2009–February 2012), which constitutes the baseline survey for the present study.

Medication dispensing data were obtained from the fully computerized pharmacies in the Ommoord suburb. Information on all filled prescriptions from January 1st 1991 until December 1st 2011 was available and included information on the product name of the drug, the Anatomical Therapeutical Chemical code, the amount dispensed, the prescribed dosage regimen and the date of dispensing [26].

Detailed information on design, objectives and methods of the Rotterdam Study has been described before [27,28].

2.2. Study population

The study population consisted of all participants with complete data on the extensive interview and clinical examination at the fifth survey of the Rotterdam Study (February 2009–February 2012). The clinical examination included a fasting blood sample, abdominal ultrasonography, and anthropometric assessment. Medication prescription data on the use of statin therapy was available until December 1st, 2011. Therefore, all participants with an interview and clinical examination date after December 1st, 2011 were excluded.

2.3. Exposure to statins

For every prescription of a statin, the duration was calculated by dividing the number of dispensed tablets by the prescribed daily number. Repeated prescriptions which were filled within seven days after ending a previous one, were considered as one single episode of continuous use. At the date of ultrasonography, every cohort participant was classified into the following mutually exclusive categories: 'current use' if the ultrasonography was performed within a prescription episode; 'past use' if the patient had been treated with statins in the past but did not use statins on the day of ultrasonography; 'non-use' meant that the participant had not used statins at all during the study period. The prescribed daily dose of statin therapy was expressed in standardized defined daily doses (DDD), according to the World Health Organization [26].

2.4. Outcome

The outcome of interest was the presence of non-alcoholic fatty liver (NAFL), assessed by abdominal ultrasonography in all study participants. Abdominal ultrasonography was performed by certified and experienced technicians on a Hitachi HI VISION 900. Images were stored digitally and re-evaluated by a hepatologist with more than ten years experience in ultrasonography. The diagnosis and grading of fatty liver was determined according to the protocol by Hamaguchi et al. [29]. Severity of fatty liver was classified as 'no fatty liver' (score 0–1), 'mild fatty liver' (score 2–3), or 'moderate to severe fatty liver' (score 4–6). Individuals with any of the following possible secondary causes of fatty liver were excluded from the analyses: (1) current excessive alcohol consumption or a history of excessive alcohol consumption, (2) positive HBsAg or anti-HCV, and (3) use of pharmacological agents historically associated with fatty liver (i.e. amiodarone, corticosteroids, methotrexate, and tamoxifen).

2.5. Co-variables

To control for confounding, we adjusted the analyses for age, sex, prescribed dose of statin therapy, serum total cholesterol level, number of ethanol consumptions weekly, presence of type 2 diabetes mellitus, the individual components of the metabolic syndrome, presence of CVD in history, and use of fibrates or other cholesterol-lowering medication. CVD in history was defined as a myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), heart failure, carotid desobstruction, cerebrovascular accident (CVA), or a transient ischemic attack (TIA) in the history [30–32]. Information on co-variables was obtained by an interview at home, laboratory measurements, and anthropometric assessments at the research center. The interview was designed to obtain data concerning demographics, medical history, co-morbid conditions, smoking behaviour, physical activity, and alcohol consumption.

Fasting blood samples were collected on the morning of ultrasound examination. Blood lipids, serum glucose, ALT, aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and total bilirubin were measured using automatic enzymatic procedures (Roche Diagnostics GmbH, Mannheim, DE). HbsAg and anti-HCV antibodies were measured by automatic immunoassay (Roche Diagnostics GmbH, Mannheim, DE).

Anthropometric measurements were performed by well trained nurses. Waist and hip circumference were measured in centimeters. BMI was calculated as the weight (in kg) divided by height (in m^2). The average of two blood pressure measurements, obtained at a single visit in sitting position after a minimum of 5 min rest, was used for analysis. Presence of type 2 diabetes mellitus was defined as the use of glucose-lowering drugs, a non-fasting glucose level of more than 11.0 mmol/L, or a fasting glucose level of more than 6.9 mmol/L. The metabolic syndrome was defined according to the following criteria: (1) abdominal obesity, defined as a waist circumference in men >102 cm (40 in.) and in women >88 cm (35 in.), (2) serum triglycerides $\geq$150 mg/dL (1.7 mmol/L), (3) serum