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High prevalence of apolipoprotein B dyslipoproteinemias in non-alcoholic fatty liver disease: The lifelines cohort study

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ABSTRACT

Objective. Cardiovascular disease (CVD) is a major adverse consequence of non-alcoholic fatty liver disease (NAFLD). The association of NAFLD with various apolipoprotein B (apoB) dyslipoproteinemias is unclear. We determined the prevalence of specific apoB dyslipoproteinemias in subjects with suspected NAFLD.

Methods. This study was conducted among 22,865 fasting adults living in the northern part of the Netherlands (Lifelines Cohort Study). Six apoB dyslipoproteinemias were defined using an algorithm derived from apoB, total cholesterol and triglycerides. NAFLD was defined as Fatty Liver Index (FLI) ≥60. Advanced hepatic fibrosis was defined as NAFLD fibrosis score (NFS) ≥0.676.

Results. 4790 participants (20.9%) had an FLI ≥ 60. NAFLD subjects were older, more likely to be men, more obese and more often had diabetes and metabolic syndrome ($P < 0.001$ for each). Among NAFLD subjects, any apoB dyslipoproteinemia was present in 61.5% vs. 16.5% in subjects without NAFLD ($P < 0.001$). Elevated chylomicrons were not observed in NAFLD. In univariate analysis, NAFLD was associated with a higher prevalence of each apoB dyslipoproteinemia vs. subjects with an FLI < 60 ($P < 0.001$), except for low density lipoprotein (LDL) dyslipoproteinemia. Additionally, each apoB dyslipoproteinemia was independently associated with NAFLD in age- and sex-adjusted logistic regression analysis, including the apoB dyslipoproteinemias together ($P < 0.001$). The prevalence of apoB dyslipoproteinemias was not altered in subjects with NFS ≥0.676.

Conclusions. NAFLD rather than advanced hepatic fibrosis is independently associated with increased prevalence of chylomicrons + very low-density lipoproteins (VLDL) remnants, VLDL, LDL and VLDL + LDL dyslipoproteinemias. ApoB dyslipoproteinemias may contribute to increased CVD risk associated with NAFLD.

Abbreviations: ApoA-I, apolipoprotein A-I; apoB, apolipoprotein B; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular disease; chylo, chylomicrons; eGFR, estimated glomerular filtration rate; FLI, Fatty Liver Index; GGT, gamma-glutamyltransferase; HDL, high density lipoproteins; LDL, low density lipoproteins; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NFS, non-alcoholic fatty liver disease fibrosis score; T2DM, type 2 diabetes mellitus; TG, triglycerides; VLDL, very low-density lipoproteins.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease, which encompasses a wide spectrum of liver damage, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and hepatic fibrosis. NAFLD is gaining recognition as a major health issue [1–6]. Its increasing prevalence is most likely due to the global epidemic of obesity and type 2 diabetes mellitus (T2DM), conditions which are strongly associated with NAFLD [2,3]. NAFLD is considered to reflect the hepatic component of the metabolic syndrome (MetS), since there is a strong association with central obesity, dyslipidemia and hypertension [7–9]. In line, insulin resistance is considered to be important in the development of NAFLD and an independent association between NAFLD and insulin resistance has been repeatedly demonstrated [3,10].

It is well known that NAFLD is associated with plasma lipoprotein abnormalities, in particular elevated triglycerides and low HDL cholesterol, as well as with an increase in the ratio of total cholesterol to HDL cholesterol and apolipoprotein (apo) B to apoA-I [5,11–14], both of which being appropriate indices of the risk of atherosclerotic CVD [15,16]. Enhanced delivery of adipose tissue-derived fatty acids to the liver provides a central mechanism responsible for hepatic fat accumulation [17,18]. In turn, an increased liver fat content is regarded as the main driving force of enhanced production of very low-density lipoproteins (VLDL), resulting in an increased plasma concentration of large VLDL particles and hence in higher triglycerides [17,19,20]. Furthermore, several genetic abnormalities in pathways affecting hepatic VLDL production contribute to the pathogenesis of hepatic fat accumulation, which underscores the importance of intrahepatic pathways of lipoprotein synthesis for NAFLD development [21,22]. In addition, common apolipoprotein E polymorphisms may play a role in the pathogenesis of NAFLD [23,24].

Although many studies point to an association between NAFLD and dyslipoproteinemia, its phenotypic characterization is still incomplete. Recently, it has been proposed to focus on specific apoB dyslipoproteinemias in the expectation that this could contribute to better CVD risk prediction and targeted treatment [25]. De Graaf et al. have developed an algorithm, based on plasma apoB, the main apolipoprotein of triglyceride-rich lipoproteins (chylomicrons and VLDL), low density lipoproteins (LDL) and intermediate density lipoproteins, total cholesterol and triglycerides, which enables to characterize 6 distinct apoB dyslipoproteinemias, each with a characteristic pathophysiology [26].

Growing evidence suggests that CVD is a leading cause of death in patients with NAFLD, which may be even independent of traditional cardiovascular risk factors [3,27–32]. This provides a rationale to better delineate abnormalities in apoB-containing lipoproteins in NAFLD, and to assess whether the association of specific apoB dyslipoproteinemias with NAFLD is independent of T2DM and MetS.

The present study was carried out in the frame of the Lifelines Cohort Study, a large scale epidemiological project in the general population from the north of the Netherlands. Here, we determined the extent to which the prevalence of specific apoB dyslipoproteinemias is increased in Lifelines participants with suspected NAFLD.

2. Methods

2.1. Study Design

This cross-sectional study was conducted within the framework of the Lifelines Cohort Study. The Lifelines Cohort Study is a multi-disciplinary prospective population-based cohort study of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Participants were recruited via general practitioners. Furthermore, adults could also self-register to participate. All participants provided written informed consent [33–35].

2.2. Study Participants

All study participants were older than 18 years at time of enrolment. Participants were excluded if data were missing required to calculate the Fatty Liver Index (FLI) or NAFLD fibrosis score (NFS), to assess MetS components, total cholesterol, triglycerides, apoB, cardiovascular morbidities, and renal function. Subjects with missing data with respect to alcohol consumption, medication use, previous medical history, as well as subjects excessively using alcohol, previously diagnosed hepatitis or cirrhosis, participants who use lipid-lowering drugs or diabetic medication, and being non-fasting at the time of blood collection were also excluded. Fig. 1 provides a flow chart of the selection of participants for the present study.

2.3. Data Collection and Measurements

Data were collected in the Lifelines Cohort Study between 2006 and 2013. Participants visited the Lifelines research sites for a physical examination and extensive questionnaires were collected. A standardized protocol was used to obtain blood pressure and anthropometric measurements (height, weight, and waist circumference). Systolic and diastolic blood pressures were measured 10 times during a period of 10 min, using an automated Dynamap Monitor (GE, Healthcare, Freiburg, Germany). The size of the cuff was chosen according to the arm circumference. The average of the final three readings was used for both the systolic as the diastolic blood pressure. Anthropometric measurements were measured without shoes; weight was measured without heavy clothing. Body weight was measured to the nearest 0.5 kg. Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Height and waist circumference were measured to the nearest 0.5 cm. Waist circumference was measured in standing position with a tape measure all around the body at the level midway between the lower rib margin and the iliac crest [33,35]. Venous blood was collected after an overnight fast.