The Long Road from Obesity to Atherosclerosis via the Liver

ABSTRACT 1

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Fatty Liver is an Independent Predictor of Early Carotid Atherosclerosis

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Background & aims: Whether steatosis is incidentally or causally associated with carotid atherosclerosis is debated, and long-term follow-up data are missing. This study aims to examine the impact of steatosis on the presence and progression of carotid intima-media thickness (C-IMT) and carotid plaques (CP) in a large cohort with longitudinal follow-up.

Methods: A retrospective single-center study between 1995 and 2012. Transversal cohort: patients with ≥ 2 cardiovascular risk factors without previous cardiovascular events. Longitudinal cohort: patients with two consecutive C-IMT measurements more than 2 years apart. Steatosis was defined by a surrogate marker, the fatty liver index (FLI). CP and C-IMT were assessed by carotid ultrasound.

Results: In the transversal cohort ($n = 5671$) both C-IMT and the Framingham risk score (FRS) increased across FLI quartiles (0.58 ± 0.12 , 0.61 ± 0.14 , 0.63 ± 0.14 , 0.64 ± 0.14 mm, and $5 \pm 5\%$, $9 \pm 7\%$, $12 \pm 8\%$, $15 \pm 9\%$, $P < 0.001$ for both). Steatosis predicted C-IMT better than diabetes or dyslipidemia. Steatosis independently predicted C-IMT ($P = 0.002$) and FRS ($P < 0.001$) after adjustment for metabolic syndrome and cardiovascular risk factors. In the longitudinal cohort ($n = 1872$, mean follow-up 8 ± 4 years), steatosis occurred in 12% and CP in 23% of patients. C-IMT increased in patients with steatosis occurrence (from 0.60 ± 0.13 mm to 0.66 ± 0.14 mm, $P = 0.001$) whereas it did not change in those that stayed free of steatosis. Steatosis at baseline predicted CP

occurrence (OR = 1.63, 95% CI 1.10–2.41, $P = 0.014$), independent of age, sex, type-2 diabetes, tobacco use, hsCRP, hypertension and C-IMT.

Conclusions: In patients with metabolic syndrome at risk for cardiovascular events, steatosis contributes to early atherosclerosis and progression thereof, independent of traditional cardiovascular risk factors.

ABSTRACT 2

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Overweight in Late Adolescence Predicts Development of Severe Liver Disease Later in Life: A 39 Years Follow-Up Study

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Background & aims: The increased prevalence of overweight has been suggested to contribute to the worldwide increase in liver diseases. We investigated if body mass index (BMI) in late adolescence predicts development of severe liver disease later in life.

Methods: We performed a cohort study using data from 44,248 men (18–20 years) conscribed to military service in Sweden between 1969 and 1970. Outcome data were collected from national registers to identify any diagnosis of severe liver disease (i.e., diagnosis of decompensated liver disease, cirrhosis or death in liver disease) until the end of 2009. A Cox regression model was applied using BMI as independent variable. The model was adjusted for use of alcohol, use of narcotics, smoking, high blood pressure and cognitive ability at time of conscription.

Results: During a follow-up period of a mean of 37.8 years, 393 men were diagnosed with severe liver disease (mean time to diagnosis 24.7 years). BMI (Hazard ratio [HR] = 1.05 for each unit increase in BMI, 95% confidence interval [CI]: 1.01–1.09, $P = 0.008$) and overweight (HR = 1.64 for BMI 25–30 compared to BMI 18.5–22.5, 95% CI: 1.16–2.32, $P = 0.006$) were associated with an increased risk of development of severe liver disease.

Conclusions: Being overweight in late adolescence is a significant predictor of severe liver disease later in life in men.

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COMMENTARY

It is well known now that nonalcoholic fatty liver disease (NAFLD) occurs in the setting of obesity, insulin resistance, hypertension and dyslipidemia.¹ Equally well known is that patients with NAFLD have higher risk of cardiovascular disease (CVD) and CVD may in fact be responsible for more deaths than liver failure or hepatocellular carcinoma (HCC).² However, most of this knowledge comes from cross-sectional studies. The complex interplay and confounding effects of various metabolic risk factors make analysing the direct contribution of obesity on steatosis and of steatosis on atherosclerosis difficult on a cross-sectional study design. It is not clear how long it takes for metabolic risk factors to translate into clinically significant liver disease. Also, is the high risk of CVD in NAFLD simply a manifestation of the underlying metabolic dysfunction or does NAFLD play an active role in atherogenesis? These questions are important not only from a therapeutics development point of view but also from a public health perspective. Given the global epidemic of obesity³ and NAFLD⁴ it is imperative to understand the natural history of CVD vis-à-vis these conditions to put in place screening and primary prevention programs. Randomized controlled trials answering these questions are unfeasible due to ethical reasons as well as loss to follow-up due to the time frame involved in the pathogenesis of these conditions. Hence, cohort studies with long follow-up periods are probably our best bet to understand the effects of obesity on the liver and the role of liver steatosis in CVD.

Pais et al.⁵ conducted a large retrospective review of patients from 1995 to 2012 assessing the effect of NAFLD on CVD. Fatty liver was diagnosed using the Fatty Liver Index (FLI), a score calculated from body mass index, waist circumference, serum triglycerides and gamma-glutamyl transferase. A cut-off of more than 60 was used to diagnose NAFLD. CVD risk was assessed by carotid intima media thickness (C-IMT)⁶ (an ultrasound marker of atherosclerosis and predictor of stroke and myocardial infarction) and Framingham risk score (FRS)⁷ (a mathematical computation of the future risk of CVD events calculated using traditional cardiovascular risk factors such as age, sex, cholesterol, hypertension, diabetes and smoking). In the cross-sectional portion of the study, they analysed data from 5671 individuals with at least 2 cardiovascular risk factors attending a primary CVD prevention clinic in Paris, France. They found that C-IMT and FRS increased with FLI and FLI was better predictor of C-IMT better than diabetes or dyslipidemia. The effect of FLI on C-IMT and FRS was independent of metabolic syndrome and cardiovascular risk factors. More importantly they also performed a longitudinal analysis involving 1872 individuals who had a follow-up carotid ultrasound at least 2 years after the first scan with a mean interval of 8 ± 4 years. Along with an increase in prevalence of obesity,

weight gain and diabetes, the prevalence of hepatic steatosis increased significantly from 24% at baseline to 30% at follow-up. Incident steatosis occurred in 12% and regression of steatosis occurred in 6% patients. In parallel there was increase in C-IMT and prevalence of carotid plaques (CP). Steatosis at baseline predicted development of new CP on follow-up independent of age, sex, type-2 diabetes, high blood pressure, tobacco use, hsCRP, baseline C-IMT even after adjusting for lipid, cardiovascular and diabetes therapies. Patients with incident steatosis had higher C-IMT on follow-up than those free of steatosis although their baseline C-IMT was similar.

This study is limited by its retrospective nature and the fact that only about 1/3rd of the participants had repeat measurements for inclusion in the longitudinal portion of the study. Also, NAFLD was diagnosed based on FLI, which while specific is not very sensitive to diagnose NAFLD.⁸ Since clinical events of CVD take many years to appear, measures of atherosclerosis which are surrogate validated markers of CVD were used in this study. These data suggest that hepatic steatosis is an independent risk factor for CVD and it is clear that patients with NAFLD should be screened for CVD and its traditional risk factors. However, the results of this study raise some pertinent questions for further research. Will scoring systems incorporating NAFLD parameters result in better CVD risk prediction compared to existing scores? Is presence of NAFLD an indication to initiate primary prevention strategies for CVD? More tantalisingly will treatment of NAFLD serve as a therapeutic tool for CVD?

Continuing with the theme of large scale longitudinal studies to understand NAFLD, the study by Hagström et al.⁹ sought to determine the long-term effects of obesity at a young age on development of liver disease in the future. They conducted a retrospective population based cohort study including 44,248 males aged between 18 and 20 years who joined the military in Sweden between 1969 and 1970 with a mean follow-up of 38 years till 2009. Since military service was mandatory, this cohort included almost all Swedish males aged 18–20 years during that time except those with severe disabilities or disease. Outcome of interest was development of severe liver disease defined by the authors as a diagnosis of cirrhosis, decompensated liver disease, or death from liver disease. Outcomes were based on well maintained national registries with more than 99% coverage. During follow-up period, loss to follow-up was only 0.96% due to emigration. Severe liver disease occurred in 393 (0.9%) men with a mean time to first diagnosis of 24.7 years (range 3–39 years). 174 cases were first diagnosed with decompensated liver disease, 165 cases were first diagnosed with liver failure or cirrhosis and an additional 54 men died with liver disease as a cause of death. A total of 213 of the 393 cases died during follow-up. Body mass index (BMI) at baseline was an independent predictor of severe liver disease in the future with an adjusted hazards

ratio (HR) of 1.05 per each unit increase in BMI (95% CI 1.01–1.09, $P = 0.008$) in the multivariate model after adjusting for competing factors like alcohol consumption, smoking, use of narcotics, blood pressure, cardiovascular fitness, cognitive ability and self-rated health. A BMI of 25–30 kg/m² was associated with an adjusted HR of developing severe liver disease of 1.64 (95% CI 1.16–2.32, $P = 0.006$) compared to individuals with normal BMI.

This study is impressive for its large sample size, selection of a relatively healthy homogenous population at baseline and long follow-up to hard clinical endpoints with minimal attrition. However, the study did not have data on evolution of risk factors at follow-up such as changes in BMI, alcohol consumption or acquisition of chronic viral hepatitis which may have a bearing on the risk of future liver disease. Also, individuals with compensated asymptomatic cirrhosis who are at risk of developing HCC and decompensation in the near future would not be picked up by the registries which are dependent on hospital coding. Hence, there may be an underestimation of liver disease by this study. Nonetheless this study puts forth an important public health message that obesity in late adolescence has a 64% higher risk of severe liver disease in the future than the non-obese. The prevalence of overweight (5.8%) and obesity (0.8%) in 1969–1970 was much lower than what is seen in today's youth. Pooled prevalence of overweight and obesity among children and adolescents in India is 19.3%.¹⁰ With approximately 30–40% of Indian population belonging to this age group the magnitude of severe liver disease in the future due to obesity in India is likely to be enormous. This is a worrying statistic.

These 2 cohort studies highlight the complex interplay between obesity, NAFLD and CVD and the potential epidemic of obesity related liver and cardiovascular disease that is in front of us. With a mean time of almost 25 years between diagnosis of obesity and development of severe liver disease, there are plenty of opportunities for us to alter its course. Are we ready to face this challenge?

CONFLICTS OF INTEREST

The author has none to declare.

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