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The effect of obesity on the association between liver fat and carotid atherosclerosis in a multi-ethnic cohort

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ABSTRACT

Objective: Non-alcoholic fatty liver disease is the most common liver disorder in Western society, increasing in parallel with obesity and the metabolic syndrome. Evidence suggests that there is an independent relationship between liver fat (LF) and atherosclerosis, however it is unknown if this applies to low risk populations. The purpose of this study was to evaluate the association between LF and measures of sub-clinical carotid atherosclerosis in men and women of Aboriginal, Chinese, European, and South Asian origin.

Methods and results: Healthy men and women were assessed for LF (computed tomography scan) and atherosclerosis (carotid ultrasound) in addition to cardiovascular risk factors, demographics, and body composition. Liver Hounsfield units (HU) values were negatively correlated with age, BMI, waist circumference (WC), percent body fat, carotid intima media thickness total plaque area, and total area. LF was significantly associated with carotid IMT and total area after adjustment for sex, age, ethnicity, education, income and smoking status. However after adjusting for BMI and WC, LF was no longer significantly associated with atherosclerosis.

Conclusion: Increased LF may be associated with atherosclerosis, however, after adjustment for body composition, LF was not significantly associated with sub-clinical atherosclerosis. BMI and WC are useful anthropometric measures for the evaluation of CVD risk independent of LF.

1. Introduction

Obesity is an escalating global health problem with rates continuing to increase in both developed and developing countries [1]. This is a concern as obesity is associated with increased cardiometabolic risk, type 2 diabetes, and cardiovascular disease (CVD). Elevated body fat is associated with increased deposition of triglycerides in the liver which increases dyslipidemia and insulin resistance [2]. Excess liver fat (LF) can lead to non-alcoholic fatty liver disease (NAFLD), which is a spectrum of disorders defined by an abnormal accumulation of triglycerides in the liver in the absence of significant alcohol intake; it ranges from a simple fatty liver (steatosis), to a fatty liver along with inflammation, known as non-alcoholic steatohepatitis [3]. NAFLD is progressively becoming the most recognized liver disorder in Western countries with its prevalence paralleling the rise in obesity and type 2 diabetes [4]. The prevalence of NAFLD in the general population is 15%–20% with rates as high as 70%–90% in obese and type 2 diabetic populations [4].

People with NAFLD are at an increased risk of developing cardiovascular disease (CVD) as it is associated with a number of CVD risk factors including insulin resistance, metabolic syndrome (MetS), hypertension, dyslipidemia, type 2 diabetes, and abdominal obesity [5,6]. Indeed, those people with NAFLD have been reported to have an increased risk for CVD as assessed by a variety of outcomes such as coronary artery calcium scoring [4,6], coronary angiography [8,9], endothelium-dependent flow mediated dilation [10], left ventricular mass index [11] and carotid intima media thickness (IMT) [12]. In addition, those with NAFLD have a two-fold

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risk of CVD mortality, independent of the MetS and other established CVD risk factors [13]. As the majority of these studies have been limited to high risk individuals with features of the MetS, it is not clear if these results are applicable to healthy or low risk populations. In fact, Kim et al. did not find an independent association between LF and carotid atherosclerosis in those without the MetS [12]. Many of these studies have only included subjects diagnosed with NAFLD or healthy controls and did not use LF as a continuous measure. Also, they used indicators of LF and NAFLD such as ultrasound and liver enzymes which are less accurate than determination through more sophisticated imaging techniques and may limit the ability to determine robust associations.

The objective of our study was to determine whether there is an independent association between LF and sub-clinical carotid atherosclerosis, an early marker of CVD, in a predominantly healthy multi-ethnic cohort of Aboriginal, Chinese, European, and South Asian men and women. In addition we evaluated the relationship between LF, body fat measures, and the presence of the MetS to determine if LF provides any additional information of increased CVD risk beyond simple measures of obesity: body mass index (BMI), waist circumference (WC), and percent body fat.

2. Subjects and methods

2.1. Participants

Participants for this investigation were from those enrolled in the Multicultural Community Health Assessment Trial (M-CHAT). The M-CHAT study is an ongoing investigation on body fat distribution and cardiovascular disease risk in four different ethnic groups and has already been described in detail [14]. Between 2004 and 2005, a total of 829 apparently healthy individuals of Aboriginal, Chinese, European or South Asian (Indian sub-continent) background between 35 and 60 years of age were recruited across three ranges of body mass index (18.5–24.9, 25–29.9, and $\geq$30 kg/m^2) [14]. Participants were excluded if they self-reported having CVD, had undergone recent weight change (greater than 2 kg in 3 months prior to assessment date), if they were on medication known to affect type 2 diabetes and CVD risk factors (lipid-lowering, antihypertensive, hypoglycemic, hormone replacement therapy, or insulin), were abusing alcohol and/or narcotics or if they had diagnosed HIV, metabolic disorders, or immuno compromised conditions, significant prosthetics or amputations. A total of 546 participants returned after five years to undergo a follow-up assessment which included a computed tomography (CT) scan to assess LF and an ultrasound of the carotid arteries to assess indicators of sub-clinical atherosclerosis. The current investigation is limited to 492 participants (71 Aboriginals, 148 Chinese, 141 European and 132 South Asians) who had data for both the LF CT scans and the carotid artery ultrasound scan. All participants provided informed consent. This study was approved by the Simon Fraser University and Providence Health Care Research Ethics Boards.

2.2. Demographics and body composition

At the five year follow-up, participants were assessed for demographic factors including age, education, income, and smoking status by self-report. Weight in kilograms and height in meters were assessed with participants in light clothing (or hospital gowns), footwear removed and pockets emptied, and used to calculate body mass index (BMI). Waist circumference (WC) was recorded in centimeters as the average of two measures taken against the skin at the point of maximal narrowing of the waist between the lower rib and the iliac crest as viewed from the anterior following a normal expiration. Total body fat was evaluated by dual energy X-ray absorptiometry with a Norland XR-36 scanner (Norland Medical Systems, White Plains, NY) using Host Software Version 3.9.4 and Scanner Software 2.1.0 and percent body fat was calculated.

Fasting blood samples were collected and analyzed for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose. All measurements were taken at the same clinical laboratory using standard procedures. The inter- and intra-assay precision of this laboratory meets the stringent criteria of the Canadian Reference Foundation Laboratory. LDL-C was calculated using the Friedewald equation [15]. Blood pressure (BP) was recorded as the average of five successive measures following 10 min of seated rest using the BpTRU model BPM-200 oscillometric office blood pressure monitor (VSM MedTech, Coquitlam, British Columbia, Canada). Subjects were classified as either those with or those without MetS. MetS was defined by the presence of three or more of the following features: (i) larger WC defined by WC $\geq$ 102 cm in men and $\geq$88 cm in women, (ii) triglycerides $\geq$1.7 mmol/L (iii) HDL cholesterol $<$1.0 mmol/L in men and $<$1.3 mmol/L in women, (iv) impaired fasting glucose defined by fasting plasma glucose $\geq$5.6 mmol/L, and (v) hypertension defined by blood pressure $\geq$130/85 mm Hg [16].

2.3. Liver fat assessment

LF was assessed by CT with a CTi Advantage scanner (General Electric, Milwaukee, Wis). A single cross-sectional 10-mm slice of the abdomen at the T12/L1 intervertebral disc was obtained. Computation of LF was conducted via the use of medical imaging software: SliceOmatic v4.2 (TomoVision, Montreal, Quebec, Canada). Three 100 mm^2 regions of interest (ROI's) in the liver were randomly placed in the parenchyma of the right lobe of the liver to avoid blood vessels and areas of focal fatty infiltration in the setting of heterogeneous liver attenuation (Fig. 1) [17]. We followed methodology put forward previously: the average attenuation in Hounsfield units (HU) of these three ROI was used as a measure of LF [17,18]. Testing was carried out to determine whether three versus more ROI's were a better indicator of LF; additional ROI's

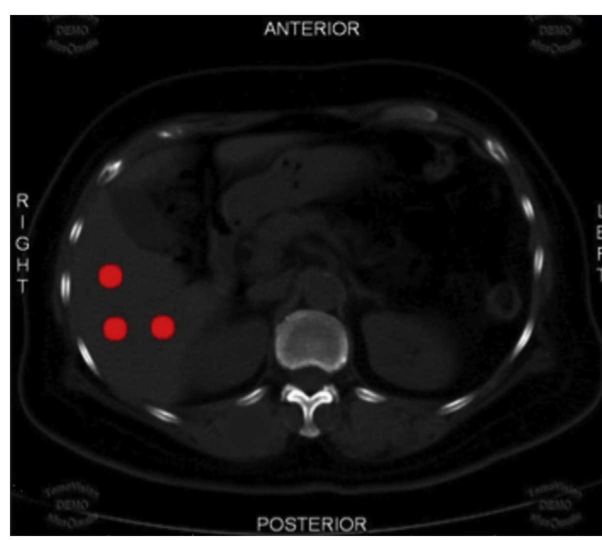

Fig. 1. Computed tomography scan: cross-sectional 10-mm slice of the abdomen at the T12/L1 intervertebral disc. The mean of three 100 mm^2 ROI's (red circles) was used and averaged to compute one number corresponding to LF in Hounsfield units. LF: liver fat, ROI: region of interest. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)