Visceral/epicardial adiposity in nonobese and apparently healthy young adults: Association with the cardiometabolic profile

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ABSTRACT

Objective: We investigate associations of regional adipose tissues with cardiometabolic profile of non-obese and apparently healthy young adults.
Methods: Four hundred twenty-five nonobese and apparently healthy individuals were assessed for blood pressure and fasting lipid profile, blood glucose and adiponectin. Subcutaneous abdominal adipose tissue (SAT) and ectopic fat depots (visceral abdominal adipose tissue [VAT], epicardial adipose tissue [EAT] and hepatic fat fraction [HFF]) were quantified by magnetic resonance imaging.
Results: According to anthropometric measurements, blood pressure and blood markers, the population (18−35 years, 54% women) had a low cardiometabolic risk. Compared to women, men had more VAT, EAT and HFF, but less SAT. Regional adipose tissues were positively correlated with each other. VAT and EAT carried significant correlations with all markers of cardiometabolic risk, while SAT and HFF correlated variably with these markers. While taking into account age and gender, SAT, VAT and EAT were associated with most cardiometabolic markers, while HFF was only associated with total cholesterol/high-density lipoprotein ratio (TC/HDL-C) and triglycerides (TG). When comparing SAT, VAT and EAT head-to-head, VAT was the only adipose tissue location maintaining significant association with most markers of cardiometabolic risk. Greater VAT (≥50th percentile) was associated with a worse car-diometabolic profile, whether individuals were overweight or normal weight.
Conclusion: Even in nonobese and apparently healthy young women and men, accumulation of ectopic visceral adiposity in general, and of VAT in particular, is associated with a worse cardiometabolic profile whether individuals were overweight or normal weight.

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1. Introduction

Cardiovascular disease is extremely common in the general population, affecting more than one out of three adults in the United States [1]. Among the risk factors for cardiovascular disease, obesity is one of the most significant [2]. However, exact mechanisms linking excess adiposity to cardiovascular disease are not completely understood. It is believe that it is not obesity *per se*, but rather specific localizations and dysfunction of adipose tissue, through the associations with metabolic alterations (increased blood pressure, altered lipid profile, elevated blood glucose, decreased adiponectin), that promotes subclinical atherosclerosis and future cardiovascular disease [3]. Indeed, visceral abdominal adipose tissue (VAT) is thought to be more pathological than subcutaneous abdominal adipose tissue (SAT) because of its adverse biologic functions [3–5]. Similarly, other ectopic fat depots may play a role in cardiometabolic risk. Indeed, epicardial adipose tissue (EAT) is proposed to promote a proin-flammatory and proatherogenic environment for coronary ar-teries [6–8] while adipose tissue accumulation in the liver (fatty liver) is associated with several deleterious pathophysio-logical processes leading to a dysfunctional cardiometabolic phenotype [9].

Manifestations of cardiovascular disease typically appear after the fourth or fifth decades of life. However, atherosclerosis underlying the lion's share of cardiovascular disease is known to begin years before symptoms appear, and is present in a majority of young and apparently healthy adults [10–12]. It has been shown in young adults that an adverse cardiometabolic profile (high blood pressure, altered lipid profile, elevated blood glucose) is associated with a higher extent and a significant progression of subclinical atherosclerosis [13,14]. Studies have also reported that this adverse cardiometabolic profile during early adulthood has a powerful predictive value on long-term risk of cardiovascular disease morbidity and mortality [15,16]. Therefore, there is now convincing evidence that cardiometabolic risk consideration in young adults is relevant.

To the best of our knowledge, little is known about the accumulation of SAT, VAT, EAT and hepatic fat fraction (HFF) in nonobese and otherwise healthy young adults. The contribution of regional adipose tissues to cardiometabolic profile of this specific population remains uncertain. We hypothesized that SAT, VAT, EAT and HFF carry different relationships to markers of cardiometabolic profile, and that accumulation of ectopic adiposity (VAT, EAT and HFF) is associated with an adverse orientation of cardiometabolic profile in this population. Thus, we aimed to investigate the associations of regional adipose tissues with markers of cardiometabolic profile (blood pressure, lipid profile, blood glucose and adiponectin) and to identify which adipose tissue has the strongest association with cardiometabolic profile in a specific cohort of nonobese and otherwise healthy young individuals.

2. Methods

2.1. Study population

We studied a sample of 425 apparently healthy young men and women prospectively enrolled at the Institut universitaire de cardiologie et de pneumologie de Québec. Subjects were recruited through posters displayed in public areas, email invitation to local university, and word-of-mouth. Eligibility criteria included French Canadian origin, age 18–35 years and apparently good health defined as the absence of obesity (body mass index [BMI] <30 kg/m^2) and absence of known hypertension, dyslipidemia, diabetes or cardiovascular disease; in addition, renal, hepatic, hematological and systemic inflammatory disorders were ruled-out by questionnaire. Exclusion criteria were exercise habits significantly beyond average for the population (>5 h of aerobic exercise per week), abnormal screening electrocardiogram and pregnancy on urine test. Women within 1 year of childbirth and lactation were excluded. The local Institutional Review Board approved the study, and all participants provided signed informed consent.

2.2. Anthropometric measurements, blood pressure and blood test

During standardized visits, each subject underwent anthropometric measurements (weight, height and waist circumference), blood pressure measurement and fasting blood test. In brief, waist circumference (WC) was obtained in standard standing anatomical position and measurement was made at the end of normal expiration at the midpoint between the last rib and the iliac crest. BMI was calculated (BMI = weight in kg/height in m^2). Systolic (SBP) and diastolic blood pressures (DBP) were measured with a Welch Allyn Vital Signs Monitor-300 Series device. The blood test was performed on overnight fasting plasma and blood was collected into Vacutainer tubes containing ethylene-diamine-tetra-acetic acid. Triglyceride (TG) and total cholesterol (TC) levels were determined in plasma and lipoprotein fractions were obtained

using automated techniques. The high-density lipoprotein cholesterol (HDL-C) was obtained after precipitation of apolipoprotein B (ApoB)-containing lipoproteins in the infranatant with heparin and manganese chloride. Apolipoprotein A1 (ApoA1) and ApoB were obtained in plasma and lipoprotein fractions by nephelometry using polyclonal antibodies on the Behring BN ProSpec (Siemens, Marburg, Germany). Plasma glucose and adiponectin were respectively measured by an enzymatic assay (Roche, Mannheim, Germany) and by an enzyme-linked immunosorbent assay (R&D Systems, Inc., Minneapolis, USA) [13].

2.3. Magnetic resonance imaging and images analysis

ECG-gated 1.5 T magnetic resonance imaging (MRI) was performed with a dedicated cardiac coil for epicardial fat quantification and a body coil for abdominal fat quantification (Philips Achieva 1.5T, operating release 2.6 level 3, Philips Healthcare, Best, The Netherlands). Precise slice positioning was ensured by 3-dimensional localizer sequences. An axial T1-weighted (T1w) spin-echo slice (5 mm thickness, TR = 750 ms, TE = 6–8 ms, resolution = 660 × 660 mm) at the level of mitral valve was obtained during diastole at breath-hold in end expiration according to the evidence showing that EAT area is significantly correlated to EAT volume [17–19]. Images were performed with and then without saturation of the lipid peak to confirm that the disappearing signal is in fact fat. Similarly, abdominal axial T1w slices were obtained with identical parameters with both fat enhancement and then fat saturation. One slice was acquired at the level of the 1st and 2nd lumbar intervertebral space (L1–L2) for quantification of HFF. Another slice was obtained at the level of the 4th to 5th lumbar intervertebral space (L4–L5) to evaluate abdominal adiposity as previously reported by our group [20,21].

Images analysis was performed off-line in a standardized core laboratory (LICA: Laboratoire d'imagerie cardiovasculaire avancée) using dedicated software (Qmass MR version 7.1, Medis, Leiden, The Netherlands) by trained technicians. On fat-enhanced images, the pericardial space is easily identified and manually traced as the dark stripe separating the bright white EAT within, and the bright white pericardial adipose tissue without. On fat-enhanced images the gray abdominal muscles and dark vertebrae are easily identified and manually traced to separate the bright SAT from the bright VAT. A semi-automated approach was developed to minimize observer bias and maximize reproducibility of VAT quantification. A standardized oval region of interest was positioned in the homogeneous adipose tissue devoid of vessels and non-adipose structures served as a reference for fat; any pixel of similar signal intensity (by full width at half-maximum technique) was automatically detected and classified as adipose tissue. Co-registered fat-saturation images were evaluated to ensure that bright fat pixels identified in fat-enhanced T1 imaging effectively darkened with fat saturation to confirm pixels were indeed adipose tissue. EAT, SAT and VAT were measured and reported as volumes normalized to 5 mm length (mL/5 mm). The estimated HFF was calculated as the difference between the signal from the non-fat-saturated image and the signal from the fat-saturated-image divided by the signal from the non-fat-saturated image [22].

2.4. Statistical methodology

Statistical analyses were performed with Stata 11.0 (StataCorp LP, College Station, TX, USA). Distribution of normality was tested using the Kolmogorov–Smirnov test; given that all variables were normally distributed parametric tests have been used for statistical analysis. Student's t-tests were used to compare mean values of cardiometabolic markers and regional adipose tissues between