Atherosclerosis 241 (2015) 664–670

Contents lists available at ScienceDirect

Atherosclerosis

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

Relationship of pericardial fat with lipoprotein distribution: The Multi-Ethnic study of atherosclerosis

Kwok-Leung Ong [a, *], Jingzhong Ding [b], Robyn L. McClelland [c], Bernard M.Y. Cheung [d], Michael H. Criqui [e], Philip J. Barter [a, f], Kerry-Anne Rye [a, f], Matthew A. Allison [e]

[a] Centre for Vascular Research, University of New South Wales, Sydney, NSW 2025, Australia
[b] Sticht Center on Aging, Wake Forest University School of Medicine, Winston-Salem, NC, United States
[c] Department of Biostatistics, University of Washington, Seattle, WA, United States
[d] Department of Medicine, University of Hong Kong, Hong Kong, China
[e] Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA, United States
[f] Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Received 18 April 2015
Received in revised form
19 May 2015
Accepted 9 June 2015
Available online 18 June 2015

Keywords:
Cardiovascular disease
Lipids
Lipoproteins
Pericardial fat
Subclinical atherosclerosis

ABSTRACT

Objective: Pericardial fat and lipoprotein abnormalities contribute to increased risk of cardiovascular disease (CVD). We investigated the relationship between pericardial fat volume and lipoprotein distribution, and whether the association of pericardial fat volume with subclinical atherosclerosis and incident CVD events differs according to lipoprotein distribution.

Methods: We analyzed data from 5407 participants from the Multi-Ethnic Study of Atherosclerosis who had measurements of pericardial fat volume, lipoprotein distribution, carotid intima-media thickness (IMT), and coronary artery calcium (CAC). All participants were free of clinically apparent CVD at baseline. Incident CVD was defined as any adjudicated CVD event.

Results: After adjusting for demographic factors, traditional risk factors, and biomarkers of inflammation and hemostasis, a larger pericardial fat volume was associated with higher large VLDL particle (VLDL-P) concentration and small HDL particle (HDL-P) concentration, and smaller HDL-P size (regression coefficients = 0.585 nmol/L, 0.366 μmol/L, and −0.025 nm per SD increase in pericardial fat volume respectively, all $P < 0.05$). The association of pericardial fat volume with large VLDL-P concentration and HDL-P size, but not small HDL-P concentration, remained significant after further adjusting for each other as well as LDL cholesterol, HDL cholesterol, and triglycerides. The relationship of pericardial fat volume with incident CVD events, carotid IMT, and prevalence and severity of CAC did not differ by quartiles of large VLDL-P concentration, small HDL-P concentration, or HDL-P size (P for interaction>0.05).

Conclusion: Pericardial fat is associated with atherogenic lipoprotein abnormalities. However, its relationship with subclinical atherosclerosis and incident CVD events does not differ according to lipoprotein distribution.

1. Introduction

An excess of ectopic fat deposition, such as in the pericardium, is often found in obese subjects [1]. As pericardial fat is anatomically close to the myocardium, it may contribute to cardiovascular disease (CVD) events by paracrine pathways, with adipokines secreted from pericardial fat acting to promote local vascular inflammation and progression of atherosclerosis [2,3]. Immunohistological studies have identified an association of the extent of inflammation in pericardial adipose tissue with the presence of coronary artery disease [4]. Epidemiological studies have also revealed the association of pericardial fat with CVD events [5–7]. In this regard, recent studies suggest pericardial adipose tissues may contribute to the presence of coronary plaque [8], as well as coronary artery calcification independent of body fat composition, anthropometric measures and traditional cardiovascular risk factors [9,10]. Pericardial fat is also associated with carotid stiffness [11] and atrial

* Corresponding author.
E-mail address: oklws@yahoo.com.hk (K.-L. Ong).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.06.027
0021-9150/

fibrillation [12].

Lipoprotein particle subclass and size may affect CVD risk independently of overall cholesterol levels [13–15]. Adipocytokines, such as interleukin-6 (IL-6), that are secreted by pericardial adipose tissue, may lead to insulin resistance [16], which is known to be associated with alterations in lipoprotein particle size and subclass concentrations [17,18]. Therefore, we hypothesized that atherogenic lipoprotein abnormalities may modify the association of pericardial fat with cardiovascular risk and tested this using data from the Multi-Ethnic Study of Atherosclerosis (MESA). Additionally, we investigated whether the relationship of pericardial fat volume with subclinical atherosclerosis (as assessed by coronary artery calcium [CAC] and carotid intima-media thickness [IMT]) and incident cardiovascular events differ by lipoprotein distribution.

2. Methods

2.1. Participants

The MESA study is a longitudinal cohort of 6814 men and women of four major racial/ethnic groups, Caucasian, African American, Hispanic American, and Chinese American [19]. All participants aged 45–84 years of age were free of clinically apparent CVD at baseline [19]. They were recruited from six United States communities between July 2000 and August 2002. Participants were followed up in person at four clinic visits over a 10-year period. Venous blood samples were collected after a 12-h fast, then shipped to the MESA central laboratory for lipid and glucose measurement. The study was approved by the institutional review boards at all participating centers and informed written consent was obtained from all participants. The study was performed in compliance with the principles of the Declaration of Helsinki. Details of the study objectives, design, and protocol have been described previously [19].

Among 6814 participants at baseline, data on pericardial fat volume were available on 6788 participants, of whom 6760 had their lipoprotein profile measured by nuclear magnetic resonance (NMR) spectroscopy. As lipid-lowering medications can affect lipid and lipoprotein concentrations, 1112 participants taking any lipid-lowering medication (statins, fibrates, niacin, and/or bile-acid sequestrants), or with missing data on lipid-lowering medications, were excluded from this study. After further excluding participants with triglycerides >400 mg/dL (n = 64), and missing data on carotid IMT (common and/or internal carotid IMT), CAC, or incident CVD events (n = 177), a total of 5407 participants were included in the analysis.

2.2. Lipid and lipoprotein measurement

High-density lipoprotein (HDL) cholesterol was measured using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) after precipitation of non-HDL cholesterol with magnesium/dextran sulfate. Triglyceride levels were measured using a glycerol-blanked enzymatic method with the Triglyceride GB reagent (Roche Diagnostics) on the Roche COBAS FARA centrifugal analyzer. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula in plasma samples having a triglyceride value <400 mg/dL [20]. Lipoprotein particle subclasses and concentrations were measured at LipoScience, Inc. (Raleigh, North Carolina) by NMR spectroscopy using the LipoProfile-3 algorithm as described previously [15,21,22]. Particle concentrations of lipoprotein subclasses of different sizes were measured using the amplitudes of their lipid methyl group NMR signals. Lipoprotein particle diameters were classified as HDL (7.3–14 nm), LDL (18–23 nm) and very-low-density lipoprotein (VLDL) (>29 nm), with HDL subclassified as small HDL (7.3–8.2 nm), medium HDL (8.2–9.4 nm) and large HDL (9.4–14 nm); LDL were subclassified as small LDL (18–20.5 nm) and large LDL (20.5–23 nm). Intermediate-density lipoprotein (IDL) were 23–29 nm, and VLDL were subclassified as small VLDL (29–35 nm), medium VLDL (35–60 nm) and large VLDL (>60 nm). The mean particle sizes were the weighted average of the related subclasses.

2.3. CAC and carotid IMT

Detailed procedures for the measurement of CAC have been described previously [23]. Briefly, all the MESA participants underwent computed tomography (CT) scans of the chest for CAC using either an electron-beam CT scanner at 3 field centers. A multidetector row helical CT scanner was used at the other 3 field centers. Participants were scanned twice at the same visit at one of the field centers, and these scans were read independently at a centralized reading center using a standard protocol. The results of the two scans were averaged to provide a more accurate estimate of the amount of calcium present than a single scan. Calcification was identified as a plaque of $\geq$1 mm^2 with a density of $\geq$130 Hounsfield units (HU) and quantified using the previously described Agatston scoring method [24].

Carotid IMT assessment was performed using high-resolution B-mode ultrasound as previously described for the Cardiovascular Health Study [25]. The Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin) was used to record images of the left and right carotid arteries at all centers. A single longitudinal lateral view of each common carotid artery (CCA) and 3 longitudinal views in different imaging planes of each internal carotid artery (ICA) were obtained. The maximal IMT of the internal and common carotid sites was then measured as the mean of the maximum IMT of the near and far walls of the right and left sides at the ultrasound reading center as described previously [26,27].

2.4. Pericardial fat measurement

The CT scans used to ascertain the presence and extent of CAC were analyzed for pericardial fat volume as described previously [5,11]. Briefly, the CT slices within 15 mm above and 30 mm below the superior extent of the left main coronary artery were analyzed by three experienced CT analysts. This region of the heart was selected because it includes the pericardial fat located around the proximal coronary arteries (left main coronary, left anterior descending, right coronary, and circumflex arteries). The anterior border of the volume was defined by the chest wall and the posterior border by the aorta and the bronchus. Pericardial fat volume was defined as the sum of all voxels containing fat based on volume analysis software (GE HealthCare, Waukesha, WI), which could discern fat from other tissues with a threshold of −190 to −30 Hounsfield units.

2.5. CVD event ascertainment

CVD end-points included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina associated with coronary revascularization, stroke, stroke death, coronary heart disease death, other atherosclerotic death, and other CVD death. At intervals of 9–12 months, a trained telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Some additional medical encounters were identified occasionally through follow-up visits, participant call-ins, medical