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Lipoprotein particle profiles compared with standard lipids in association with coronary artery calcification in the general Japanese population

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ABSTRACT

Objective: The utility of lipoprotein particle profiles measured by nuclear magnetic resonance (NMR) spectroscopy beyond standard serum lipids remains inconclusive. Furthermore, few studies have compared NMR measurements with standard lipids in association with coronary artery calcification (CAC) in Japanese, where the coronary atherosclerotic burden is low. We examined whether NMR-based lipoprotein particle profiles are associated with CAC, and compared them with standard lipid and lipid ratios in the Japanese general population.

Methods and Results: We conducted a cross-sectional study in 851 men aged 40–79 years without cardiovascular diseases and lipid-lowering therapies. Adjusted odds ratios (ORs) (95% confidence intervals) for the top versus the bottom quartile of NMR-measured particle concentrations were 2.01 (1.24–3.23) for low-density lipoprotein (LDL-P), 1.04 (0.62–1.75) for high-density lipoprotein (HDL-P), 1.82 (1.13–2.95) for very-low-density lipoprotein (VLDL-P), and 1.92 (1.18–3.17) for LDL-P/HDL-P ratio. Similarly adjusted ORs of NMR-measured particle sizes were 0.59 (0.36–0.97) for LDL-P, 0.66 (0.40–1.10) for HDL-P, and 0.67 (0.40–1.12) for VLDL-P. The corresponding ORs were 1.82 (1.14–2.90) for total cholesterol (TC), 2.06 (1.28–3.30) for low-density lipoprotein cholesterol (LDL-C), 0.56 (0.34–0.91) for high-density lipoprotein cholesterol (HDL-C), 2.02 (1.24–3.29) for triglycerides, 2.08 (1.29–3.36) for non-high-density lipoprotein cholesterol (non-HDL-C), 2.27 (1.37–3.78) for TC/HDL-C ratio, and 1.73 (1.06–2.85) for LDL-C/HDL-C ratio. After mutual adjustment for total LDL-P concentration and TC/HDL-C ratio or non-HDL-C, LDL-P was no longer associated, whereas TC/HDL-C ratio remained significantly associated with CAC.

Conclusions: In community-based Japanese men, the overall association of CAC with NMR-measured lipoprotein indices is comparable, but not superior, to that with standard lipids.

1. Introduction

Lipoprotein particle profiles assessed by proton nuclear magnetic resonance (NMR) spectroscopy [1] are heterogeneous with respect to size and density, having a differential effect and strong

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connection with their atherogenic properties [2,3]. NMR-based lipoprotein profiles have thus been suggested as alternative lipoprotein measures for improved risk assessment of cardiovascular disease (CVD). These profiles have also been reported to be associated with an increased risk of CVD outcomes or subclinical atherosclerosis [4–8].

However, how well NMR-based lipoprotein indices predict CVD or subclinical atherosclerosis compared with standard serum lipids remains uncertain. Only a few prospective population-based studies have directly compared the predictability of clinical CVD risk between various NMR-based lipoprotein profiles and standard lipids including ratio measures [5,6]. In those studies, the association of CVD risk with NMR measures was statistically significant, yet of a lesser magnitude than that with standard lipids. Interestingly, the studies that compared these indices in association with subclinical atherosclerosis reported a stronger relation of NMR-based indices than standard lipids [7,8]. Additionally, these epidemiological studies were mainly conducted in Western countries.

The burden of coronary atherosclerosis in Japan has remained lower compared with that in Western populations. This has been confirmed with multiple levels of evidence, including comparative studies for clinical coronary artery disease (CAD) [9], an autopsy study [10], and studies on the subclinical stage of coronary atherosclerosis as measured by coronary artery calcification (CAC) [11–13]. More recently, however, the overall levels of total cholesterol (TC) in Japan have now become similar to or even higher than those in US [9,14,15]. The level of high-density lipoprotein (HDL) cholesterol (HDL-C) among Japanese adults is higher than that of the US [16], and has increased in recent years [17,18]. Literature is scarce on comparison of NMR-based lipid profiles among community-based samples from Japan and other countries. However, we have reported considerable differences in this profile among samples of Japanese men and Caucasians from the US [19]. To the best of our knowledge, no studies have examined the association of NMR-measured lipoproteins with subclinical atherosclerosis in the general Japanese population.

Therefore, we conducted a cross-sectional study of the general Japanese population to examine whether NMR-based lipoprotein particle profiles are associated with CAC, a marker of subclinical atherosclerosis, and compared them with standard lipid and lipid ratios. A community-based Japanese population tends to have a lower burden of CAD and subclinical atherosclerosis compared with Western populations. Therefore, this Japanese population would be useful for examining lipid profiles for CVD assessment in low-risk populations.

2. Methods

2.1. Participants and risk factor measurement

Participants eligible for the present study were 1094 Japanese men enrolled at baseline (May 2006 to March 2008) in the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). Detailed methods are described elsewhere [20,21]. In brief, SESSA participants were community-dwelling men aged 40–79 years, who were selected based on an age-stratified random sample from the Basic Residents' Register of the city, which includes information on the name, age, and sex of residents. The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17–19, 17–83).

A total of 243 men were excluded from this analysis for the following reasons: history of CVDs ($n = 103$), use of lipid-lowering medications ($n = 119$), missing information for lipid parameters ($n = 9$), and participants with a triglyceride (TG) level at or above 400 mg/dl ($n = 12$). The last criterion was used to adequately estimate low-density lipoprotein (LDL) cholesterol (LDL-C) levels following Friedewald's formula [22–24]. Therefore, 851 participants were finally included in the present analyses (mean [SD] age, 63.4 [10.0] years).

2.2. CAC

We assessed CAC either by electron-beam computed tomography (EBCT) ($n = 593$, 75.1%) using a C-150 scanner (Imatron, South San Francisco, CA, USA) or 16-channel multidetector-row computed tomography (MDCT, $n = 258$) scans using an Aquilion scanner (Toshiba, Tokyo, Japan). Images were obtained from the level of the root of the aorta through the heart at a slice thickness of 3 mm, with a scan time of 100 ms (EBCT) or 320 ms (MDCT). We acquired images at 70% of the cardiac cycle, using electrocardiogram triggering, during a single breath-hold. Quantification of CAC was performed using a DICOM workstation and AccuImage software (AccuImage Diagnostics, South San Francisco, CA, USA). The presence of CAC was defined as a minimum of 3 contiguous pixels (area = 1 mm^2) with a density $\geq$ 130 Hounsfield units (HU). We placed a region of interest around each high-density lesion in the epicardial coronary arteries. Peak density (HU) and area (mm^2) of the individual coronary calcifications were measured, and then the CAC score was calculated according to the Agatston method [25]. All computed tomography (CT) images were read by one physician who was trained in CT reading at the Cardiovascular Institute of the University of Pittsburgh, and who was blinded to participants' demographics. The protocol described above was adopted from a separate cohort study performed by our research group [21], in which the reproducibility of the scans showed an intraclass correlation of 0.98 [11]. In stratified analysis by type of CT, we found that trends were similar between participants assessed by EBCT and those by 16-channel MDCT (data not shown). Additionally, CAC assessment by EBCT and MDCT has been reported to be comparable [26]. Therefore, we presented the combined results. To define the presence of CAC, a CAC score >0 was used [7].

2.3. Assays for lipids, lipoproteins, and other variables

Venipuncture was performed early in a clinical visit after a 12-h fast. We separated serum by centrifugation (3000 revolutions per min, for 15 min) at 4 °C within 90 min. Samples were sent for routine laboratory tests, including those for lipids and glucose. Plasma glucose levels were determined from NaF-treated plasma using a hexokinase glucose-6-phosphate-dehydrogenase enzymatic assay. Serum TC and TG were determined using enzymatic assays, and HDL-C was measured using a direct method (Determiner-C-TC, Determiner-C-TGL, Determiner-L HDL-C, respectively; Kyowa Medix, Tokyo, Japan). Serum lipids were determined at a single laboratory (Shiga Laboratory; MEDIC, Shiga, Japan) that has been certified for standardized lipid measurements according to the protocol of the Centers for Disease Control and Prevention/US Collaborating Center for Reference Method Laboratory Network Research in Blood Lipids (CDC/CRMLN) [27]. We used Friedewald's formula to estimate LDL-C levels [28]. Non-high-density lipoprotein cholesterol (non-HDL-C) was calculated by subtracting HDL-C from TC.

Serum samples were stored at −80C° and shipped on dry ice to LipoScience Inc, (Raleigh, NC) for lipoprotein particle analysis. NMR spectroscopy [1] was performed to quantify the particle concentrations of very-low-density lipoprotein (VLDL), LDL, and HDL [29]. Additionally, particle concentrations were further determined for 3 VLDL subclasses (large, >60 nm; medium, 35–60 nm; and small, 27–35 nm), 3 LDL subclasses (intermediate-density lipoprotein [IDL], 23–27 nm; large, 21.3–23 nm; small, 18.3–21.2 nm), and 3