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Predominance of small dense LDL differentiates metabolically unhealthy from metabolically healthy overweight adults in Korea

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ABSTRACT

Objective. The purposes of this study were (1) to determine the association between lipoprotein subfraction profiles and metabolically healthy overweight (MHO) phenotype, as defined by visceral adiposity; and (2) to identify the strongest predictor of metabolic health among the lipoprotein measurements.

Materials/Methods. This cross-sectional study was comprised of 462 overweight patients, who were classified as MHO or non-MHO based on their visceral adipose tissue (VAT) area to subcutaneous adipose tissue area (SAT) ratio (VAT/SAT ratio). Serum lipoprotein subfraction analyses and other metabolic parameters were measured.

Results. Among the overweight participants, two hundred fifty-five individuals (53.7%) had the MHO phenotype. After adjusting for age, sex, medication, lifestyle factors, and confounding metabolic characteristics, the non-MHO group showed significantly higher lipid levels and a greater prevalence of unfavorable lipid profiles. LDL subclass pattern type B was the most significant predictor of the non-MHO phenotype (odds ratio 2.70; 95% CI 1.55–4.69), while serum LDL cholesterol level was not a significant predictor of the non-MHO phenotype.

Conclusions. Lipoprotein subfraction particle measurements were significantly associated with the non-MHO phenotype and a higher VAT/SAT ratio, with small dense LDL predominance being the most significant predictor of MHO phenotype. These findings will help identify MHO and non-MHO phenotypes and perhaps lead to a development of cost-effective individualized treatments.

Abbreviations: MHO, metabolically healthy overweight; non-MHO, metabolically unhealthy overweight; VAT/SAT ratio, visceral adipose tissue area to subcutaneous adipose tissue area ratio; sdLDL, small, dense low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; CT, computed tomography; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; HTN, hypertension; DM, diabetes mellitus; hsCRP, high sensitive C-reactive protein; MetS, metabolic syndrome.

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1. Introduction

Obesity is a major public health concern that leads to increased cardiovascular disease and mortality [1]. About 1.7 billion people worldwide are currently classified as overweight, and the health care costs associated with obesity and related diseases have increased [1,2]. Therefore, identifying overweight patients with an unhealthy metabolic profile may help develop cost-effective individualized prevention and treatment of obesity-related metabolic consequences [3].

Evidence suggests that not all overweight or obese individuals show the metabolic dysfunction associated with an increased risk of metabolic comorbidities [4–6]. Overweight or obese people who do not have metabolic abnormalities such as diabetes (DM), hypertension (HTN), or other cardiovascular risks have a metabolically healthy overweight (MHO) phenotype [7]. Prevalence of MHO worldwide is surprisingly high as shown in recent studies, accounting for as much as 50% of the overweight and 30%–47% of the obese population [8,9]. MHO is associated with less visceral adiposity, as recent studies show that abdominal visceral fat is a critical variable in determining metabolic disturbance [10,11]. Moreover, the visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) ratio, a reflection of the relative distribution of VAT and SAT accumulation and a strong correlate of cardiovascular disease risk, should be accounted for in overweight or obese populations [12–14].

Lipid metabolism dysregulation is closely related to the cluster of metabolic profile abnormalities in patients with visceral obesity [15]. Moreover, atherogenic dyslipidemia, a group of lipoprotein abnormalities assessed through lipoprotein subfraction particle profile analyses, is an important predictor of cardiovascular disease and may be more clinically significant than traditional plasma lipid parameters, such as hypercholesterolemia or elevated LDL-cholesterol levels [16]. To date, few studies have used lipoprotein subfraction profiles of atherogenic dyslipidemia to determine the metabolic health of overweight patients [17,18].

The purpose of this study was to determine the association between lipoprotein subfraction parameters and MHO versus non-MHO phenotypes, as defined by visceral adipose tissue (VAT) area, and to identify which lipoprotein was the strongest predictor of the MHO phenotypes.

2. Methods

2.1. Study participants

Four hundred seventy-two patients who visited the obesity clinic at Severance Hospital in Seoul, Korea from January 2008 to July 2012 were enrolled in this study. The study was approved by the Institutional Review Board of Severance Hospital.

The study participants were overweight (body mass index (BMI) $\geq$ 23 kg/m^2), according to Asia-Pacific criteria, and sedentary (defined as participating in structured exercise fewer than two times per week) [19]. No participants had undergone dietary therapy before beginning this study. Patients with a history of dyslipidemia or those who had used lipid-lowering medications or hormone replacement therapy were excluded from the study. Patients with a history of malignancy; abnormal liver, renal, or thyroid function; acute or chronic inflammatory disease; or clinical or electrocardiographic evidence of cardiovascular disease were also excluded.

Among the overweight participants, the MHO group was defined as having an abdominal VAT/SAT ratio, of < 0.4 and the non-MHO group as having a VAT/SAT ratio $\geq$ 0.4, as measured by computed tomography (CT) scan [20].

2.2. Clinical and anthropometric evaluation

Data on past and current medical conditions and medications were collected from medical records. Body weight was measured to the nearest 0.1 kg using an electronic scale, and height was measured to the nearest 0.1 cm using a stadiometer to calculate BMI of each participant. Waist circumference was measured midway between the lowest rib and the iliac crest while standing. Blood pressure was measured two times using a mercury sphygmomanometer after more than 10 min of seated rest, and the average of the two measurements was recorded. Intra-abdominal visceral and subcutaneous fat areas were measured via computed tomography (Tomoscan 350; Philips, Mahwah, NJ, USA) as described previously [21]. Participants provided information on lifestyle factors such as smoking status and alcohol consumption through questionnaires. Smoking status was considered to be yes if the participant indicated that he or she was a current smoker. Alcohol consumption was defined as a positive factor if the participant consumed 72 g or more per week.

2.3. Biochemical analyses

Biochemical analyses were performed on blood samples collected after an overnight fast (>12 h). Serum levels of fasting glucose (Hitachi 7600; High-Technologies Corporation, Hitachi, Tokyo, Japan) and fasting insulin (Roche; Indianapolis, IN, USA) were measured. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [fasting insulin (mUI/L) × fasting glucose (mg/dl)/405] [22]. Insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI) [1/{log fasting insulin (μU/mL) + log fasting glucose (mg/dL)}] [23]. Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and high sensitive C-reactive protein (hsCRP) were measured using the Hitachi 7600 Automatic analyzer (High-Technologies Corporation, Hitachi, Tokyo, Japan). Non-HDL cholesterol was defined as the difference between total cholesterol and HDL-cholesterol.

Metabolic syndrome was defined using the criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute, with waist circumference criteria modification based on the following World Health Organization-Asian Pacific region criteria for abdominal obesity [19,24]: (1) a waist circumference $\geq$ 90 cm for men and $\geq$ 85 cm for women; (2) triglycerides $\geq$ 150 mg/dl; (3) serum HDL cholesterol < 40 mg/dl for men and < 50 mg/dl for women; (4) systolic blood pressure $\geq$ 130 mmHg, diastolic