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Lipoprotein particle subclass profiles among metabolically healthy and unhealthy obese and non-obese adults: Does size matter?

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ABSTRACT

Objectives: No data regards lipoprotein particle profiles in obese and non-obese metabolic health subtypes exist. We characterised lipoprotein size, particle and subclass concentrations among metabolically healthy and unhealthy obese and non-obese adults.

Methods: Cross-sectional sample of 1834 middle-aged Irish adults were classified as obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2). Metabolic health was defined using three metabolic health definitions based on various cardiometabolic abnormalities including metabolic syndrome criteria, insulin resistance and inflammation. Lipoprotein size, particle and subclass concentrations were determined using nuclear magnetic resonance (NMR) spectroscopy.

Results: Lipoprotein profiling identified a range of adverse phenotypes among the metabolically unhealthy individuals, regardless of BMI and metabolic health definition, including increased numbers of small low density lipoprotein (LDL) ($P < 0.001$) and high density lipoprotein (HDL) particles ($P < 0.001$), large very low density lipoprotein (VLDL) particles ($P < 0.001$) and greater lipoprotein related insulin resistance ($P < 0.001$). The most significant predictors of metabolic health were lower numbers of large VLDL (ORs 2.72–3.13 and 2.49–3.86, $P < 0.05$ among obese and non-obese individuals, respectively) and small dense LDL particles (ORs 1.78–2.39 and 1.50–1.94, $P < 0.05$) and higher numbers of large LDL (ORs 1.82–2.66 and 2.84–3.27, $P < 0.05$) and large HDL particles (ORs 1.88–2.58 and 1.81–3.49, $P < 0.05$).

Conclusions: Metabolically healthy adults displayed favourable lipoprotein particle profiles, irrespective of BMI and metabolic health definition. These findings underscore the importance of maintaining a healthy lipid profile in the context of overall cardiometabolic health.

1. Introduction

Obesity prevalence is increasing worldwide and is predicted to affect more than one billion people by 2030 [1]. Obesity represents a major public health concern as it promotes insulin resistance (IR) and is associated with increased risk of developing co-morbidities including metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [2,3], leading to increased risk of premature death and higher all-cause mortality. However not all obese subjects are at increased cardiometabolic risk. Despite their excess body fat a subset of metabolically healthy (MH) individuals have been described [4,5]. Unlike the metabolically unhealthy obese (MUO) phenotype metabolically healthy obesity (MHO) is characterised by favourable lipid and inflammatory profiles, preserved insulin sensitivity and normal blood pressure [6–9]. Despite a more favourable metabolic profile examination of the prevalence of subclinical CVD according to MH and weight status has produced conflicting findings [10–12]. Furthermore prospective data on CVD development and all-cause mortality in MHO is limited and where follow-up has occurred results have been inconsistent [13,14].

Obesity and IR are linked with alterations in the lipoprotein particle profile, which may influence CVD and T2DM risk [15,16]. Lipoprotein particle size, in particular small, dense low density lipoprotein (LDL) and high density lipoprotein (HDL) particles and large very low density lipoprotein (VLDL) particles are associated with increased risk for atherosclerosis and premature CVD [15,17,18]. Traditional lipid tests quantify the cholesterol or triglyceride content of lipoproteins. In contrast, nuclear magnetic resonance (NMR) spectroscopy simultaneously quantifies the number and size of lipoprotein particles [19]. Recent data suggests altered expression of lipid metabolism genes in MHO and MUO

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individuals [20]. Limited data regarding lipoprotein particle profiles in MHO exists. To date the focus has been solely on LDL subclass determined by electrophoretic methods, with the rest of the lipoprofile ignored [21–23]. Therefore the main objective of this paper is to fully examine lipoprotein particle size and concentration, determined by NMR, in a cross-sectional sample of middle-aged metabolically healthy and unhealthy obese and non-obese adults.

2. Methods

2.1. Study design and subject recruitment

The Cork and Kerry Diabetes and Heart Disease Study (Phase II) was a single centre, cross-sectional study conducted between 2010 and 2011 [24]. A population representative random sample was recruited from a large primary care centre in Mitchelstown, County Cork, Ireland (Mitchelstown cohort). Full details have been published elsewhere [24]. In brief 3807 potential Mitchelstown cohort participants were randomly selected from all registered attending patients in the 50–69 year age group. Following exclusion of duplicates, deaths and ineligibles, 3043 were invited to participate in the study and of these 2047 individuals (49.2% male) completed the questionnaire and physical examination components of the baseline assessment (response rate 67%). Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork. All participants provided written informed consent. Following exclusion of individuals taking lipid-lowering medications and those with incomplete lipoprotein particle profiles the remaining 1834 participants were included in the analyses.

2.2. Clinical, anthropometric and lifestyle data

Blood pressure was measured using an Omron M7 Digital BP monitor on the right arm, after a 5 min rest in the seated position. The average of the second and third measurements was used for analyses. Hypertension was defined as average systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg or being on hypertensive medication. Body weight was measured in kilogrammes without shoes, to the nearest 100 g, using a Tanita WB100MA weighing scales (Tanita Corporation, IL, USA). Height was measured in centimetres to 1 decimal place using a Seca Leicester height gauge (Seca, Birmingham, UK). Waist circumference (defined as mid-way between lowest rib and iliac crest) was measured in centimetres to 1 decimal place using a Seca 200 measuring tape (Seca, Birmingham, UK). The average of two measures were used for analyses. BMI was calculated and individuals with a BMI $\geq$30 kg/m^2 were defined as obese. Three existing MH definitions [9,25] (Supplemental Table 1) were used to define the MHO, MUO, metabolically healthy non-obese (MHNO) and metabolically unhealthy non-obese (MUNO) subjects. Participants completed a General Health Questionnaire (GHQ), the short form International Physical Activity Questionnaire [26] (IPAQ) and a food frequency questionnaire (FFQ) validated for use in the Irish population. Physical activity levels were determined by frequency, duration and intensity of activity. Smoking status was defined as never, former and current smokers. Alcohol consumption included questions based on weekly intake to define never, moderate and heavy drinkers. A dietary score (the Dietary Approaches to Stop Hypertension (DASH)) was calculated using the FFQ responses, as previously described [27].

2.3. Biological analyses

Blood samples were taken following an overnight fast. Fasting plasma glucose (FPG), serum total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C) and triglyceride (TG) levels were measured by Cork University Hospital Biochemistry Laboratory. FPG concentrations were determined using a glucose hexokinase assay and serum lipids were analysed using enzymatic colorimetric tests (Olympus Life and Material Science Europa Ltd., Lismeehan, Co. Clare, Ireland) on an Olympus 5400 automatic analyzer (Olympus Diagnostica Gmbh, Hamburg, Germany). Serum insulin, adiponectin and C reactive protein (CRP) were determined using a biochip array system (Evidence Investigator; Randox Laboratories, Antrim, UK). Liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) were determined were measured by Cork University Hospital Biochemistry Laboratory. Homeostasis model assessment (HOMA), a measure of IR, was calculated [28].

2.4. Lipoprotein particle profiling

Lipoprotein subclass particle concentrations and average VLDL, LDL, and HDL particle diameters were measured on serum specimens by NMR spectroscopy at LipoScience, Inc (Raleigh, NC). LDL, HDL, and VLDL subclasses were quantified based on the amplitudes of their spectroscopically-distinct lipid methyl group NMR signals [19]. Weighted-average VLDL, LDL, and HDL particle sizes (in nanometre diameter units) were computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its NMR signal. The following 9 subclass categories were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (42–60 nm), small VLDL (29–42 nm), large LDL (20.5–23 nm), small LDL (18–20.5 nm), large HDL (9.4–14 nm), medium HDL (8.2–9.4 nm), and small HDL (7.3–8.2 nm). Particle concentrations are expressed as nanomoles per litre (VLDL and LDL) and micromoles per litre (HDL). A Lipoprotein Insulin Resistance score (LP-IR), ranging from 0 (least) to 100 (most) insulin resistant, which is a weighted combination of the 6 lipoprotein subclass and size parameters most closely associated with IR, was calculated [29].

2.5. Statistical analysis

Statistical analysis was conducted using PASW Statistics version 20 for Windows (SPSS Inc, Chicago, IL). Continuous variables are expressed as means $\pm$ SD and categorical variables as percentages. Lipoprotein variables were assessed for normality of distribution, and skewed variables were normalised as appropriate. Differences between groups were analysed by independent *t*-tests or Mann Whitney U tests for continuous variables and by Chi-Square test for categorical variables. Logistic regression was used to determine associations between lipoprotein status (categorized as below and above median level for each biomarker) and metabolic health among obese and non-obese subjects. Multivariate logistic regression analysis was performed including age, gender, physical activity, dietary quality, smoking status, alcohol consumption, liver enzymes and adiponectin concentrations as confounding factors. For all analyses a *P*-value of <0.05 was considered significant.

3. Results

3.1. Clinical characteristics

The prevalence of metabolically healthy and unhealthy obese and non-obese phenotypes in the sample are presented in Fig. 1. Demographic and clinical characteristics are shown in Table 1. MH individuals were generally younger and more likely to be female than their unhealthy counterparts. Both total cholesterol and LDL-C