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Body mass index correlates with atherogenic lipoprotein profile even in nonobese, normoglycemic, and normolipidemic healthy men

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OBJECTIVE: To establish a relationship between body mass index (BMI), lipid, and lipoprotein parameters among nonobese, normoglycemic, and normolipidemic healthy men without any cardiovascular, metabolic, or chronic diseases.

METHODS: A total of 297 healthy, nonsmoking males between 20 and 75 years were recruited. Exclusion criteria included familial hypercholesterolemia, any chronic diseases, and BMI $\geq$ 30 kg/m^2. Lipid and lipoprotein particles were determined by standard methods, with the use of ultracentrifugation and nuclear magnetic resonance (NMR). Cholesterol in remnant-like particles (RLPc) was also determined.

RESULTS: These healthy volunteers were separated into two groups: normoweight (BMI $>$ 19 kg/m^2 and $<$25 kg/m^2 [n = 143]) and overweight (BMI $\geq$ 25 kg/m^2 and $<$30 kg/m^2 [n = 154]). Overweight participants were older ($P < .001$) compared to normoweight. Both groups had low-density lipoprotein (LDL) cholesterol levels ($<$130 mg/dL) considered as desirable, and although both groups had plasma triglyceride levels within the nonpathological range, overweight participants presented with 30% higher triglyceride levels ($P < .001$) and 9% lower high-density lipoprotein cholesterol ($P < .001$) compared to normoweight individuals. Although LDL was comparable between groups, NMR analysis showed that overweight participants had 27% more total LDL particles due to a 16% decrease in large LDL ($P < .001$) and 70% increase in the smaller subclasses ($P < .001$). In overweight participants, NMR analysis also showed a 2-fold increase in large very low–density lipoprotein ($P = .001$), and 30% more medium very low-density lipoprotein particles ($P = .020$). Overweight participants also had 70% more intermediate-density lipoprotein particles ($P = .010$), a 30% decrease in large high-density lipoprotein particles ($P < .001$), and a 39% increase in RLPc levels ($P = .005$). Results were adjusted for age and fat intake.

The authors declare that there are no conflicts of interest.

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CONCLUSION: BMI correlates with a shift toward a more proatherogenic lipoprotein profile even in individuals whose lipid levels were not elevated.

Introduction

The combination of high triglycerides (TGs) and low high-density lipoprotein cholesterol (HDLc) accompanied by nonpathological or moderately elevated low-density lipoprotein cholesterol (LDLc) is typically associated with obesity[1] and insulin resistance,[2] and the lipid pattern also linked to the term adiposopathy or adipose tissue dysfunction.[3] Detailed analysis of the lipoprotein profile by sequential ultracentrifugation or nuclear magnetic resonance (NMR) reveals that atherogenic dyslipidemia is characterized by increased numbers of large very low–density lipoproteins (VLDLs) and intermediate-density lipoproteins (IDLs), and smaller low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. In addition, the concentrations of remnant lipoprotein cholesterol in plasma (RLPc) are normally increased with atherogenic dyslipidemia and are an independent cardiovascular disease risk factor.[4]

Abundant scientific evidence demonstrates that clustering of these proatherogenic lipoprotein subclasses is associated with increased cardiovascular risk.[5] For example, we have recently described that the atherogenic subclasses correlate with circulating proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of LDLc concentrations, and are associated with two of the most informative polymorphisms in a key gene regulating TG in circulation, the apolipoprotein A5.[6,7]

The effect of obesity on lipoprotein subclass distribution has been described.[8–11] Similar associations have also been found in healthy subjects. The atherogenic lipoprotein profile determined by ultracentrifugation is correlated with increased cardiovascular risk in healthy overweight subjects[12] and is described to be associated with coronary calcification in postmenopausal women[13] and intima media thickness in healthy men.[14]

We hypothesize that the shift toward an atherogenic lipoprotein profile can be observed even among healthy normoweight subjects.

Therefore, we studied the ultracentrifuge and NMR lipoprotein profiles of a group of nonobese men specifically selected to be free of any clinical conditions.

Methods

Subjects

In this cross-sectional study, 297 healthy, nonsmoking men (0 cigarettes/day for >6 months), aged 20 to 75 years (evenly stratified by age), were recruited in Clermont-Ferrand, France (n = 97), Graz, Austria (n = 100), and Reus, Spain (n = 100) as part of a European Commission–funded research and technology development project of the 5th Framework Program.[15]

Methodology was standardized between recruitment centers. A physician conducted a personal interview with the potential participant to gather anthropometric data, personal history, lifestyle, medications, physical activity, smoking habits, and use of dietary supplements containing vitamins or trace elements.

Obesity was an exclusion criterion in our study, and body mass index (BMI) ranged from 18.9 to 30 kg/m^2. We separated the participants into two groups: normoweight (BMI > 19 kg/m^2 and <25 kg/m^2 [n = 143]) and overweight (BMI ≥ 25 kg/m^2 and <30 kg/m^2 [n = 154]).

BMI was calculated as weight in kilograms divided by height in squared meters. Body weight and height were measured using calibrated scales and a wall-mounted stadiometer, with subjects wearing light clothes and no shoes.

Exclusion criteria included familial hypercholesterolemia, chronic diseases (including diabetes, cancer, cardiac insufficiency, neurological diseases, inflammatory diseases and chronic diseases of the liver, lung, or thyroid, unstable hypertension, dementia, and infectious diseases known to affect the immune system such as human immunodeficiency virus and hepatitis C), vaccination during the previous 2 months, alcohol abuse or drug addiction, and competitive sports activities. The consumption of fat, special diets, or dietary supplements in the previous 3 months was evaluated with a food frequency questionnaire and a face-to-face discussion with a dietician. The study protocol was approved by the ethics committees of all three recruiting centers, and written informed consent was obtained from all participants.

Standard lipid profile and biochemical analyses

Glucose was measured using an enzymatic assay based on a trinder GOD-POD method (Spinreact, SA, Spain), adapted to a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Spain). Glycosylated hemoglobin levels were measured using high-performance liquid chromatography (model D-10; Bio-Rad, Hercules, CA), according to the manufacturer's instructions.

Standard laboratory methods were used to quantify total cholesterol, TGs, and HDLc. LDLc was calculated by the Friedewald formula.[16] Apolipoproteins were measured with immunoturbidimetry using antisera specific for apoAI,