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Abdominal obesity and circulating metabolites: A twin study approach

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ABSTRACT

Objective. To investigate how obesity, insulin resistance and low-grade inflammation link to circulating metabolites, and whether the connections are due to genetic or environmental factors.

Subjects and methods. Circulating serum metabolites were determined by proton NMR spectroscopy. Data from 1368 (531 monozygotic (MZ) and 837 dizygotic (DZ)) twins were used for bivariate twin modeling to derive the genetic (r_g) and environmental (r_e) correlations between waist circumference (WC) and serum metabolites. Detailed examination of the associations between fat distribution (DEXA) and metabolic health (HOMA-IR, CRP) was performed among 286 twins including 33 BMI-discordant MZ pairs (intrapair BMI difference ≥3 kg/m^2).

Results. Fat, especially in the abdominal area (i.e. WC, android fat % and android to gynoid fat ratio), together with HOMA-IR and CRP correlated significantly with an atherogenic lipoprotein profile, higher levels of branched-chain (BCAA) and aromatic amino acids, higher levels of glycoprotein, and a more saturated fatty acid profile. In contrast, a higher proportion of gynoid to total fat associated with a favorable metabolite profile. There was a significant genetic overlap between WC and several metabolites, most strongly with phenylalanine (r_g = 0.40), glycoprotein (r_g = 0.37), serum triglycerides (r_g = 0.36), BCAAs (r_g = 0.30–0.40), HDL

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particle diameter (r_g = −0.33) and HDL cholesterol (r_g = −0.30). The effect of acquired obesity within the discordant MZ pairs was particularly strong for atherogenic lipoproteins.

Conclusions. A wide range of unfavorable alterations in the serum metabolome was associated with abdominal obesity, insulin resistance and low-grade inflammation. Twin modeling and obesity-discordant twin analysis suggest that these associations are partly explained by shared genes but also reflect mechanisms independent of genetic liability.

1. Introduction

Obesity is often accompanied by a cluster of metabolic abnormalities including insulin resistance, atherogenic dyslipidemia and chronic low-grade inflammation. Although body mass index (BMI) predicts the incidence of diabetes and coronary heart disease [1], it cannot by itself identify obese individuals who remain metabolically healthy and normal weight individuals who present disturbed lipid or glucose metabolism and increased cardiovascular risk [2,3]. The assessment of body fat distribution can further improve the evaluation of the subject's metabolic risk. Indeed, observational studies have shown that abdominal obesity, especially excess visceral [4,5], together with liver fat [3] accumulation is the main driver of cardiometabolic risk factors and disease independently of BMI. Traditionally, serum lipids, glucose and insulin were used as markers of cardiovascular risk. More recently, the focus has widened to cover a more global serum metabolomics profile, which has predicted the incidence of cardiovascular events [6], type 2 diabetes [7] and all-cause mortality [8] in prospective cohort studies.

Both obesity and serum metabolomics profile are heritable. Genetic factors explain 47%–90% of the interindividual variation in BMI with the remaining variance being attributable to environmental sources and measurement error [9]. Heritability estimates from direct measures of whole-body and regional body fat assessed by dual-energy X-ray absorptiometry (DEXA) are generally similar to the estimates obtained for BMI [10,11]. Genetic and environmental influences on serum metabolite levels were recently described in the Finnish twin cohort. Heritability estimates were moderate and ranged between 23% and 55% for amino acids and other small-molecule metabolites and were higher for serum lipid (range: 48%–62%) and lipoprotein (range: 50%–76%) concentrations demonstrating a genetic basis for individual differences in serum metabolite levels [12].

Given these high heritabilities and the significant association between adiposity and metabolic traits [13], a question of interest is whether associations result from potential causal mechanisms or are confounded by shared genes acting pleiotropically on both phenotypes. A recently published Mendelian randomization study suggests causal adverse effects of adiposity with multiple cardiometabolic risk markers in adolescents and young adults from four population-based cohorts in Finland [13]. Obesity discordant twin analyses and bivariate twin modeling are also well suited to explore the extent to which genetic and potential causal environmental factors explain observed associations. Previous twin studies have documented a moderate overlap of both genetic and unique environmental factors that contribute to adiposity and lipid traits [14,15]. However, to the best of our knowledge, they have not yet been extended to include a more comprehensive set of circulating metabolites. Thus, in this study of healthy twins, we aimed to 1) estimate the extent of genetic and environmental overlap between waist circumference (WC) and the serum metabolome using bivariate twin modeling techniques; 2) investigate which adiposity and insulin resistance measures are most strongly associated with the serum metabolic profile, including lipids, fatty acids (FAs), and amino acids in twin individuals; 3) examine whether these associations are independent of genetic and familial influences, by conducting within-pair analysis in monozygotic (MZ) twins.

2. Research Design and Methods

2.1. The Twin Cohorts

The sample was derived from two population-based cohorts, FinnTwin16 (FT16) and FinnTwin12 (FT12) [16]. Both are longitudinal studies of behavioral development and health habits of Finnish twins enrolled during adolescence and repeatedly assessed by self-report questionnaires. The FT12 study includes five consecutive birth cohorts of Finnish twins born in 1983–1987. The questionnaires were sent to twin individuals at age 12 and subsequent follow-up assessments were made when the twins were aged 14, 17 and as young adults (mean age 22 years). The FT16 study includes five consecutive birth cohorts of Finnish twins born in 1975–1979. The questionnaires were sent to the twin individuals at age 16 and subsequent follow-up assessments were made when the twins were aged 17, 18.5, ~25 and ~34 years. For both the FT12 and FT16, the baseline and follow-up assessments included surveys of health-related behaviors, anthropometric characteristics, symptom checklists, and social relationships. Zygosity was determined initially by a validated questionnaire method and then confirmed by genetic analysis of polymorphic markers at the Paternity Testing unit, National Institute for Health and Welfare, Helsinki, Finland.

The data presented in this article were derived from a clinical assessment for twins selected from both FT12 and FT16 after the fourth wave questionnaire collection. Pregnant women and subjects on cholesterol-lowering drugs were excluded. Our study population for quantitative genetic analysis included 1368 subjects (FT12: n = 725, FT16: n = 543 and TwinFat, see below: n = 100; MZ: 531, DZ: 837; age range: 21.0–31.5; 52.5% female). A venous blood sample for serum metabolite (NMR) analyses was taken in the morning of the assessment. Height was measured to the nearest millimeter