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ORIGINAL ARTICLE

Prediction of future risk of insulin resistance and metabolic syndrome based on Korean boy's metabolite profiling

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KEYWORDS
Childhood obesity;
Metabolic profiling;
Insulin resistance;
Metabolic syndrome

Summary
Objective: Childhood obesity is strongly related to future insulin resistance and metabolic syndrome. Thus, identifying early biomarkers of obesity-related diseases based on metabolic profiling is useful to control future metabolic disorders. We compared metabolic profiles between obese and normal-weight children and investigated specific biomarkers of future insulin resistance and metabolic syndrome.
Methods: In all, 186 plasma metabolites were analysed at baseline and after 2 years in 109 Korean boys (age 10.5 ± 0.4 years) from the Korean Child Obesity Cohort Study using the AbsoluteIDQ™ p180 Kit.

Abbreviations: 2-AAA, alpha amino adipic acid; AAA, aromatic amino acids; BCAA, branched-chain amino acids; HOMA-IR, homeostasis model assessment for insulin resistance; IR, insulin resistance; PC, phosphatidyl-choline; SM, sphingomyelin.

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Results: We observed that levels of 41 metabolites at baseline and 40 metabolites at follow-up were significantly altered in obese children ($p < 0.05$). Obese children showed significantly higher levels of branched-chain amino acids (BCAAs) and several acylcarnitines and lower levels of acyl—alkyl phosphatidylcholines. Also, baseline BCAAs were significantly positively correlated with both homeostasis model assessment for insulin resistance (HOMA-IR) and continuous metabolic risk score at the 2-year follow-up. In logistic regression analyses with adjustments for degree of obesity at baseline, baseline BCAA concentration, greater than the median value, was identified as a predictor of future risk of insulin resistance and metabolic syndrome.
Conclusion: High BCAA concentration could be ''early'' biomarkers for predicting future metabolic diseases.
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Introduction

The prevalence of childhood obesity is increasing worldwide. Obesity in childhood is associated with the future development of insulin resistance (IR), which appears to be the primary mediator of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease [1]. Thus, identifying children with IR could be an effective strategy for the prevention and treatment of metabolic syndrome and cardiovascular disease.

The gold standard tests for IR are the hyperinsulinemic—euglycemic clamp and oral glucose tolerance test (OGTT), which are invasive and expensive [2]. Homeostasis model assessment for insulin resistance (HOMA-IR) provides an estimate of IR derived from fasting glucose and insulin levels [3], with higher scores representing a greater degree of IR. HOMA-IR has been validated as a surrogate marker of IR for clinical and epidemiological studies of children and adolescents [4,5].

Metabolomics is a technique for identifying and quantifying the metabolome [6]. Recently, metabolomics has been used to examine changes in metabolic profiles according to obesity and metabolic syndrome [7,8]. Changes in metabolites in biofluids/tissues are direct indicators of variation in physiology and pathology [8].

Among the different metabolites, branched-chain amino acids (BCAAs; isoleucine, leucine, and valine) have been suggested to play key roles in obesity, IR, and diabetes [9—12]. In adults without apparent abnormalities in glucose homeostasis, elevated BCAA levels are associated with an increased future likelihood of developing type 2 diabetes mellitus [11]. However, few studies have examined obesity-related changes in the blood metabolome in children, both cross-sectionally and prospectively.

In the present study, we used a targeted metabolomic approach to prospectively identify blood metabolites associated with obesity and IR in Korean children, which is useful to control future metabolic disorders. First, we compared metabolic profiles between obese and normal-weight children. Then, we investigated whether specific biomarkers could predict the risk of future metabolic disorders, high HOMA-IR, and metabolic risk score at the 2-year follow-up.

Methods

Study subjects

This study was conducted as part of the Korean Children and Adolescent Cohort Study, which is still in the process of following a student cohort in Seoul and Kyunggi province, Korea, from entry into elementary school at age 7 years to graduation at age 19 years. The overall objective of the whole cohort study is to identify early risk factors for obesity and associated metabolic disease in Korean children. Body weight and body fat percentage were measured using a body composition analyser (BC418; Tanita, Tokyo, Japan) and height was measured using an automatic stadiometer (DS-102; Jenix, Seoul, Korea). Obese children were defined as those with a BMI (body mass index) greater than the 85th percentile (≥85th) for age and gender, based on Korean child growth standards; normal-weight children were those with a

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