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Comprehensive lipid and metabolite profiling of children with and without familial hypercholesterolemia: A cross-sectional study

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ABSTRACT

Background and aims: Individuals with familial hypercholesterolemia (FH) have elevated low-density lipoprotein cholesterol (LDL-C), accelerated atherosclerosis, and premature cardiovascular disease. Whereas children with lifestyle-induced dyslipidemias often present with complex lipid abnormalities, children with FH have isolated hypercholesterolemia. However, to the best of our knowledge, a comprehensive profiling of FH children is lacking. Therefore, we aimed to characterize the lipid-related and metabolic alterations associated with elevated LDL-C in children with FH and healthy children.
Methods: We measured plasma metabolites in children with FH (n = 47) and in healthy children (n = 57) using a high-throughput nuclear magnetic resonance (NMR) spectroscopy platform, and compared the differences between FH and healthy children.
Results: Both statin treated (n = 17) and non-statin treated FH children (n = 30) had higher levels of atherogenic ApoB-containing lipoproteins and lipids, and lipid fractions in lipoprotein subclasses, compared to healthy children (n = 57). FH children displayed alterations in HDL particle concentration and lipid content, compared with healthy children. Interestingly, the small HDL particles were characterized by higher content of cholesteryl esters, and lower levels of free cholesterol and phospholipids. Furthermore, plasma fatty acids were higher in non-statin treated FH children, particularly linoleic acid. Finally, acetoacetate and acetate were lower in FH children compared with healthy children.
Conclusions: Hypercholesterolemia in children associates with diverse metabolic repercussions and is more complex than previously believed. In particular, we found that hypercholesterolemia in FH children was paralleled not only by increased atherogenic ApoB-containing lipoproteins and lipid fractions, but also alterations in HDL subfractions that suggest impaired reverse cholesterol transport.
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1. Introduction

Cardiovascular disease (CVD) is the main cause of mortality worldwide [1]. Most CVD is caused by atherosclerosis: a lifelong process of sub-endothelial lipid retention and inflammation [2].

Abbreviations: IDL, intermediate density lipoprotein; L-HDL, large high density lipoprotein; M-HDL, medium high density lipoprotein; S-HDL, small high density lipoprotein; VLDL, very low density lipoprotein; XL-HDL, very large high density lipoprotein.

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The most important risk factor for atherosclerosis is elevated plasma cholesterol, which may be lifestyle-induced or caused by genetic disposition, such as familial hypercholesterolemia (FH). FH is a common, autosomal disorder characterized by reduced hepatic clearance of low-density lipoprotein cholesterol (LDL-C), usually resulting from a mutation in the LDL receptor (*LDLR*), proprotein convertase subtilisin/kexin 9 (*PCSK9*), or apolipoprotein B (*APOB*) [3]. Individuals with FH have hypercholesterolemia from birth, and CVD often occur prematurely [3–5]. In fact, recent registry studies from Norway show that 93% of all FH individuals experience CVD during life, and die in average 15 (men) to 21 (women) years earlier than the general population [4,5]. Clinically, young children with FH already have increased carotid intima-media thickness and activation of the inflammatory arm of atherosclerosis [6]. However, if successfully implemented, cholesterol-lowering treatment with statins may halt or even normalize atherosclerotic development in FH children, and is thereby believed to affect mortality and morbidity later in life [7]. Current guidelines therefore recommend initiation of lifelong statin treatment for FH children from 8 to 10 years of age [3,8,9].

Whereas children with obesity or other lifestyle-induced dyslipidemias often present with multicomponent lipid abnormalities, FH children generally have isolated hypercholesterolemia [10]. However, to the best of our knowledge, a comprehensive profiling of lipid-related and metabolic measures in FH children is lacking. This is highly warranted since it is unknown whether FH children display subtle changes in other sub fractions of the lipoprotein spectrum. Furthermore, it is unknown to which extent hypercholesterolemia affects other parts of metabolism, such as the fatty acid (FA), amino acid, or glucose metabolism. Therefore, an integrated and broad examination of the hypercholesterolemia-associated metabolic aberrations in children with and without FH can provide a better understanding of the disease. In time, such knowledge can potentially aid researchers and clinicians to improve future treatment of FH and hypercholesterolemia in children, and thereby also be important for the prevention and treatment of atherosclerosis in a more general term.

The aim of the present study was to characterize the lipid-related and metabolic alterations associated with elevated cholesterol in children with FH and healthy children.

2. Patients and methods

In the present cross-sectional study, we measured a large number of metabolites in plasma from children with FH, and healthy control children within a normal range of plasma LDL-C (normal-high and normal-low LDL-C), and compared the differences between these groups of children (group differences). Additionally, we investigated the alterations in plasma lipid-related and metabolic measures paralleling alterations in LDL-C (continuous differences).

2.1. Participants and setting

We recruited healthy children as part of a mother-child follow-up study at Departments of Endocrinology and Obstetrics, Oslo University Hospital Rikshospitalet (OUS), and Department of Nutrition, University of Oslo [11]. The cholesterol concentration and self-reported family history of CVD suggested that the healthy children did not have FH. In sub-analyses, we separated the healthy children into two groups based on their LDL-C level: normal-high and normal-low LDL-C, defined as greater than, and less than or equal to the median LDL-C (2.13 mmol/L), respectively. Furthermore, we recruited children with a definite FH diagnosis, as verified by clinical or genetic diagnosis, from The Lipid Clinic at OUS. We collected data from all the children, including plasma samples for metabolomics analyses, in the period September 2013 to October 2015. Seventeen children were on current statin treatment, of whom eleven used atorvastatin (three children on 10 mg; six children on 20 mg and two children on 40 mg); five used rosuvastatin (three on 5 mg, one child on 10 and 20 mg each) and one child used simvastatin (10 mg) treatment.

All children, and their parents when the child was under 16 years, gave written informed consent to participate in the study, and the Regional Committee for Research Ethics in South East Norway approved the study.

2.2. Variables

We assessed clinical and biochemical variables at the time of visit for both groups of children, including weight, height and medication use (statins). For the FH children, we performed genetic testing at the Department of Medical Genetics, OUS. Clinical diagnosis was based on the Dutch Lipid Clinic Network Score (World Health Organization publication no WHO/HGN/FH/CONS/99.2) or Simon Broome criteria [9]. We measured standard biochemistry for both groups, including lipid profile, in heparin-plasma at the Department of Medical Biochemistry, OUS.

2.3. Quantitative NMR metabolomics

We used a high-throughput serum nuclear magnetic resonance (NMR) spectroscopy platform (Nightingale Health, Finland) to measure a large number of metabolites involved in human metabolism-related health and disease [12]. The method has been extensively described and used in several recent papers [12–16]. Briefly, the metabolomics profiling includes particle concentration and lipid content of 14 subclasses of lipoproteins, as well as plasma FAs, amino acids, glucose metabolites, and various other metabolites.

2.4. Statistical analyses

Descriptive data are presented as mean (standard deviation, SD) or median (25th − 75th percentile or interquartile range, IQR) for continuous variables, or as counts (%) for categorical variables. We tested baseline differences between groups using Independent Samples *t*-test for parametric data, Mann-Whitney *U* test for non-parametric variables, and Pearson's Chi square test for categorical variables. The number of participants with missing data was low; whereas all lipid sub-classes were detectable in FH children, a few healthy children had undetectable levels of chylomicrons and large VLDL. Missing values were excluded test by test.

For all lipid-related and metabolic measures, we log-transformed to account for skewed distributions, and we scaled to SD to aid comparison of magnitudes and to aid visualization of the results. We constructed linear regression models fitted for each of the 148 metabolites (outcome variables), using either group affiliation (dichotomous variable) or differences in LDL-C (per 1.0 mmol/L increment, continuous variable) as the main exposures. In the main analyses, we separated on statin use and adjusted for age and gender. In sensitivity analyses, we adjusted for other possible confounders and competing exposures, including weight, height, BMI, triglycerides, HDL-C and sex hormones. In addition, we examined possible effect modification of gender and mutation type (LDL receptor negative mutations versus other mutations). Because of a high correlation between metabolic measures, the number of components that explained 99% of the variance in the metabolites was 22 (calculation not shown). Therefore, to adjust for multiple tests, we set significance level at $0.05/22 = 0.002$.

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