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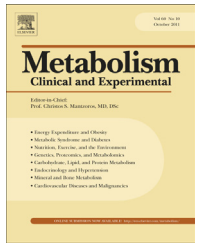

Familial hypercholesterolemia affects microvascular autoregulation in children

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ABSTRACT

Objective. Familial hypercholesterolemia (FH) impairs macrovascular endothelial function in childhood and causes an increase of cardiovascular risk in later life. Whether microvascular function is affected in children with FH is unknown. The aim of this study was to investigate the impact of FH on microvascular autoregulation in children by post occlusive reactive hyperemia (PORH).

Methods. PORH of the skin was assessed using laser Doppler fluxmetry. Baseline perfusion, biological zero, defined as no-flow laser Doppler signal during suprasystolic occlusion, peak perfusion after release of suprasystolic occlusion, as well as time to peak perfusion and recovery time, defined as time until baseline perfusion is resumed, were measured in 16 children, who were diagnosed with FH according to current guidelines, and in 91 healthy controls.

Results. In children with FH, peak perfusion was higher (FH: 1.60±0.68 vs. controls: 1.26±0.50 AU [arbitrary units], $p=0.02$), recovery time was longer (110±42.61 vs. 83.18±35.08 s, $p=0.01$) and biological zero was lower than in controls (0.12±0.04 vs. 0.18±0.05 AU, $p<0.001$). Baseline perfusion and time to peak were not different between children with FH and controls (baseline perfusion: 0.43±0.21 vs. 0.38±0.15 AU, $p=0.18$; time to peak: 15.44±12.25 vs. 18.18±17.79 s, $p=0.56$).

Conclusion. For the first time the present study reveals an impact of FH on microvascular autoregulation in children: the differences of PORH between children with FH and controls indicate an affected autoregulation of microvascular blood flow in FH, which has its onset in childhood.

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Abbreviations: AU, arbitrary units; BMI, body mass index; BMI-SDS, body mass index standard deviation score; FH, familial hypercholesterolemia; HDL, high density lipoprotein; LDL, low density lipoprotein; PORH, post occlusive reactive hyperemia.

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1. Introduction

Familial hypercholesterolemia (FH) is a common metabolic disorder, which is caused by mutations of the gene encoding the low-density lipoprotein (LDL)-receptor. More than 1000 mutations of the LDL-receptor have been described so far [1], however, most of them are classified into five categories. Class one mutations are alternatively referred to "null" or "receptor-negative" mutations, whereas mutations from classes two to five are classified as "receptor defective" [2–4], leading to increased LDL-cholesterol concentrations in plasma. Thereby, FH affects endothelial function in macrocirculation, which subsequently results in an increase of cardiovascular risk in future life [5].

Focusing on microcirculation, previous studies have demonstrated that metabolic disorders, such as type 1 diabetes mellitus and morbid obesity, independently cause microvascular injury, which seems to have its onset in childhood [6,7]. Referring to dyslipidemia, in middle-aged subjects it has been shown that elevated serum cholesterol levels potentially affect regulation of microvascular perfusion [8]. These data raised concerns about the onset of microvascular impairment, in particular, regarding children with FH.

Microvascular function can be assessed by post occlusive reactive hyperemia (PORH) using laser Doppler fluxmetry. Laser Doppler fluxmetry of the skin gathers perfusion signals deriving from the terminal microcirculatory network of the papillary dermis [9,10]. Perfusion of this terminal microcirculatory network is regulated by the tone of precapillary arterioles [10]. Constriction of these precapillary arterioles prevents terminal microcirculation from hyperperfusion. Accordingly, it has been suggested that the rapid increase of blood flow during PORH elicits constriction of precapillary arterioles, which thereby adjust capillary homeostasis [11]. Microvascular impairment upon metabolic disorders has been attributed to an impaired regulatory ability of these precapillary arterioles [6,7,11,12]. Regarding FH, as most frequent hereditary metabolic disease, we hypothesized that microvascular autoregulation might already be affected in childhood. Therefore, the aim of this study was to assess microvascular autoregulation by means of PORH in children with FH and in healthy controls to reveal early alterations of microvascular regulatory function.

2. Methods

2.1. Study subjects and design

This study was performed according to the recommendations of the Declaration of Helsinki and the ICH-GCP guidelines. Approval of the institutional ethics committee had been obtained before the study was initiated. All children included gave informed assent and written informed consent was obtained from their parents.

Children, in whom pediatric primary health care providers suspected a congenital hyperlipidemia, were referred to the Department of Pediatrics and Adolescent Medicine at the Medical University of Vienna. At the specialized metabolic outpatients clinic of the Department of Pediatrics and Adolescent Medicine the diagnosis of heterozygous FH was established – in accordance with current guidelines – based on recommended clinical criteria or genetic testing [2,13,14]. A restricted fat and cholesterol diet was recommended in all children with heterozygous FH [15]. According to current recommendations a pharmacological treatment with statins or ezetimibe was considered in children with FH who showed no improvement of LDL-cholesterol levels upon a previously initiated restricted fat and cholesterol diet [15].

Controls were recruited from an epidemiological project, which was undertaken at Austrian secondary schools. In detail, in pupils aged between 10 and 18 years a medical history was taken, blood pressure, height and weight were measured and the respective body mass index (BMI) was calculated. Further, blood lipids as well as blood glucose levels were determined in all children. To be eligible for the control group of the present study blood lipid levels as well as blood glucose had to be within the normal range. Accordingly, body mass index (BMI) had to be normal referring to the age- and sex-matched percentiles [16]. Furthermore, none of the controls had a history of any cardiovascular, metabolic or other chronic disease. Controls had to be free of any continuous medication. No smoking subjects were included in either group.

2.2. Clinical data

All study participants were weighed and height was measured to determine BMI. According to age- and sex-dependent percentiles BMI-standard deviation scores (BMI-SDS) were calculated. After a resting period of 20 minutes in a supine position blood pressure was measured on both arms with appropriate cuff sizes. For further analyses the mean value of both blood pressure values was used. Subsequently, z-scores were calculated for systolic and diastolic blood pressure to account for the influence of sex, age and height. In children with FH a detailed family history was obtained and the continuous use of any lipid-lowering drugs was recorded.

2.3. Laboratory data

Regarding laboratory tests, all blood samples were drawn by the same trained investigator. In children with FH fasting blood samples were drawn and serum lipids (total cholesterol, triglycerides, LDL-cholesterol and high density lipoprotein (HDL)-cholesterol) as well as fasting blood glucose were determined at the institutional laboratory. In healthy controls, fasting levels of blood lipids and glucose were determined from whole blood obtained by finger pricks using the Cholestech LDX System (CHOLESTECH, Hayward®). This device utilizes enzymatic solid-phase technology to measure blood lipid levels. Referring to the manufacturer's specification, the intra-day coefficients of variations range between 2.4 and 2.5% for total cholesterol, 3.4 and 4.8% for HDL-cholesterol, 1.6 and 3.6% for triglycerides, 3.8 and 4.9% for LDL-cholesterol as well as 4.5 and 6.2% for blood glucose. According to the Cholesterol Reference Method Laboratory Network the Cholestech LDX System meets the criteria of the National Cholesterol Education Program for accuracy and precision and is comparable to centralized laboratory testing.

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