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Cholesterol efflux mediators in homozygous familial hypercholesterolemia patients on low-density lipoprotein apheresis

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SR-BI

BACKGROUND: Homozygous familial hypercholesterolemia (FH) is a rare disorder that may affect 1 person per million. Early initiation of aggressive cholesterol-lowering therapy is essential to prevent premature coronary heart disease. Selective removal of low-density lipoprotein (LDL) by LDL apheresis is a reliable method of treatment.

METHODS AND RESULTS: Cholesterol efflux mediators of homozygous FH patients on weekly LDL apheresis were compared with those of age- and sex-matched heterozygous FH patients receiving oral medication only and with healthy control subjects. The data show that (1) compared with healthy controls, homozygous FH patients have significantly lower plasma levels of high-density lipoprotein cholesterol and apoA-I and significantly lower cholesterol-acceptor capacity of serum to promote cholesterol efflux from cholesterol-loaded THP-1 cells, combined with significantly lower peripheral blood mononuclear cell gene expression levels of ATP-binding cassette (ABC) transporter G1 and borderline-significantly lower levels of ABCA1 and scavenger receptor class B type I (SR-BI); and (2) compared with pre-LDL apheresis (a day before treatment), postapheresis (15 days later; on the day after the weekly treatment) levels of HDL cholesterol and apoA-I were significantly reduced, with no significant effect on cholesterol-acceptor capacity of serum or on peripheral blood mononuclear cell gene expression levels of the cellular transporters, except for a borderline-significant reduction in ABCA1 mRNA levels.

CONCLUSIONS: The data showing decreased levels of cholesterol efflux mediators in plasma and cells may suggest that the overall cholesterol efflux capacity is impaired in homozygous FH patients.

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However, LDL apheresis may maintain cholesterol efflux capacity, despite a lowering levels of high-density lipoprotein cholesterol and apoA-I.

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder characterized by an elevated plasma concentration of low-density lipoprotein (LDL) cholesterol at birth and increased risk of premature coronary heart disease.[1–3] FH is caused by defects in one of at least three different genes coding either for the LDL receptor, its ligand apolipoprotein (apo) B, and/or for proprotein convertase subtilisin/kexin type 9, an enzyme involved in LDL receptor turnover.[1–3] Most common are the different mutations in the LDL receptor gene, with a frequency of the heterozygous form of 1 in 500 and typically total cholesterol levels 10 to 15 mmol/L. The homozygous FH is a rare disorder, with a frequency of 1 per million, with total cholesterol values typically 15 to 30 mmol/L.

The enhanced cholesterol levels may result in increased uptake of modified LDL by macrophage scavenger receptors in the arterial wall, leading to foam cell formation, a hallmark of atherosclerotic plaques. Removal of cholesterol from macrophages in peripheral tissues back to the liver is facilitated by the ATP-binding cassette (ABC) transporters A1 and ATP-binding cassette transporter G1 (ABCG1) and the scavenger receptor class B type I (SR-BI).[4–7] In this process, high-density lipoprotein (HDL) plays a key role by mobilizing excess cellular cholesterol to lipid-poor plasma apolipoproteins. Thus, cholesterol efflux to lipid-free or lipid-poor apoA-I occurs through ABCA1,[4] whereas free cholesterol efflux to mature HDL particles involves ABCG1 and SR-BI.[5,6] In addition, aqueous diffusion of free cholesterol takes place.[4]

In addition to markedly increased levels of LDL cholesterol, low plasma levels of HDL cholesterol and apoA-I also are frequently encountered in heterozygous FH patients. Previously, we have shown that triglyceride-rich HDL3 particles from heterozygous FH patients had reduced capacity to promote cholesterol efflux from lipid-loaded macrophages.[8] Likewise, Bellanger et al[9] recently showed that large HDL2 particles from heterozygous FH patients displayed a reduced capacity to mediate cholesterol efflux. However, the regulation of other mediators of cholesterol efflux (eg, ABC transporters) in these patients is not well known.

Early initiation of aggressive cholesterol-lowering treatment of homozygous FH is essential to prevent potential fatal cardiovascular complications. Currently, the safest and most reliable method of treatment is selective removal of LDL by LDL apheresis, which in combination with potent statin therapy and other lipid-lowering drugs, is able to reduce plasma LDL cholesterol levels by more than 70%.[10] LDL apheresis acutely affects HDL cholesterol levels, but apparently conflicting results on changes in HDL cholesterol are reported.[11–14] Interestingly, Orsoni et al[14] recently reported an acute lowering effect of LDL apheresis on HDL cholesterol levels and on the capacity of plasma to mediate cellular cholesterol efflux; however, HDL particles exhibited a similar capacity to promote cholesterol efflux before and after treatment. To our knowledge, few if any have tested the effect of LDL apheresis on cholesterol efflux in a group of homozygous FH individuals. The aim of the present study was (1) to examine cholesterol efflux mediators on plasma and cellular levels in homozygous FH patients compared with heterozygous FH patients not on LDL-apheresis treatment and with matched healthy controls and (2) to test whether LDL apheresis in the homozygous FH patients affects these mediators in a short-term perspective.

Subjects and methods

Subjects

The homozygous FH subjects (n = 7), diagnosed with definite homozygous FH as determined by genetic testing, were recruited at the Lipid Clinic, Oslo University Hospital Rikshospitalet, Oslo, Norway. Three of the seven homozygous FH subjects were compound heterozygous, whereas the remaining four homozygous subjects were homozygous. All homozygous subjects had mutations in the LDL receptor gene. All seven patients were treated by LDL apheresis. In addition, they were on maximal-tolerable statin treatment and on ezetemibe comedication (concurrently with statin treatment). Control groups were age- and gender-matched heterozygous FH patients not on LDL-apheresis treatment (n = 7; diagnosed by genetic testing; recruited at the Lipid Clinic) and age- and gender-matched healthy control subjects (n = 7). The criterion for age-matching was that matched heterozygous FH subjects as well as the healthy control should be within ±2 years of the age of the homozygous subjects (one-to-one matching). Six of the seven heterozygous FH subjects had genetically verified FH, whereas one of the heterozygous FH subjects had definite FH as determined by clinical diagnosis.

The diagnostic criteria for FH is based on the Dutch Lipid Clinic network classification (WHO publication no WHO/HGN/FH/CONS/99.2), where definite (certain) FH is defined with a score of 8 or greater. Six of seven heterozygous FH subjects were on statin treatment, and three of