Familial hypercholesterolemia in childhood: diagnostics, therapeutical options and risk stratification
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Citation for published version (APA):
General Introduction and Outline of this Thesis
Familial Hypercholesterolemia

Heterozygous familial hypercholesterolemia (FH) is a common inherited autosomal dominant metabolic disorder of lipoprotein metabolism. In the Netherlands the frequency of heterozygous FH is 1:400, and the underlying molecular defect consists of mutations in the gene encoding for the low-density lipoprotein (LDL) receptor protein. Clinically, FH is characterized with elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL), from birth onwards, and at an older age by the presence of tendon xanthomas, xanthelasmas and/or an arcus cornealis (Figure 1 and 2). The elevated LDL-C levels strongly predispose for premature atherosclerosis and cardiovascular disease (CVD). Untreated, approximately 75% of male patients suffer from coronary artery disease before the age of 60 years. Typically, the mean age of CVD onset is between 40 and 45 years in male FH patients and about 10 years later in female patients.

Diagnosis

In adult patients the clinical diagnosis of FH is based on a positive family history of premature CVD, physical examination and laboratory findings. In children, the disorder is mostly asymptomatic. Less than 10% of the children have tendon xanthomas and these are primarily found in the second decade of life. Therefore the diagnosis in children is based on LDL-C levels above the 95th percentile for gender and age (Table 1) and a positive family history for premature CVD. However, a considerable number of false-negative and false-positive diagnosis might be expected as shown among adults in families with FH.
Table 1: 95th Percentile Plasma Lipid Values of Healthy Subjects in the First Two Decades of Life.

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Total Cholesterol</th>
<th>LDL-Cholesterol</th>
<th>HDL-Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.91</td>
<td>3.26</td>
<td>1.01</td>
<td>1.14</td>
</tr>
<tr>
<td>Female</td>
<td>5.12</td>
<td>3.45</td>
<td>0.85</td>
<td>1.19</td>
</tr>
<tr>
<td>10-14 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5.25</td>
<td>3.37</td>
<td>0.96</td>
<td>1.41</td>
</tr>
<tr>
<td>Female</td>
<td>5.33</td>
<td>3.47</td>
<td>0.91</td>
<td>1.48</td>
</tr>
<tr>
<td>15-19 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5.10</td>
<td>3.86</td>
<td>0.75</td>
<td>1.67</td>
</tr>
<tr>
<td>Female</td>
<td>5.38</td>
<td>3.78</td>
<td>0.85</td>
<td>1.40</td>
</tr>
</tbody>
</table>

* Levels are 5th percentile. LDL=low-density lipoprotein, HDL=high-density lipoprotein. Values are expressed in mmol/L. To convert cholesterol levels in mg/dl multiply by 38.67; to convert triglyceride levels to mg/dL multiply by 88.57.

Therefore, a molecular diagnosis based on mutations in the LDL-receptor gene is more accurate and the only unequivocal diagnosis.

**Therapy**

Until currently, the recommended therapy for children with FH consists of dietary intervention and life-style changes. However, the long-term efficacy of stringent dietary interventions in children is very poor. The National Cholesterol Education Program (NCEP) for children recommends that pharmacological therapy can be considered in children above 10 years whose LDL-C is above 4.1 mmol/L and when other cardiovascular disease risk factors are present, or above 4.9 mmol/L when no other risk factors are present. Bile acid sequestrants are considered the drugs of choice in the pharmacological treatment of children with heterozygous FH, but the lipid lowering efficacy is modest and the long term compliance is poor. In adult patients with FH, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the first choice in pharmacological lipid-lowering strategies. Statins have proven to reduce the incidence of CVD, stroke and peripheral vascular disease. Therefore in the last decade several trials have been conducted to establish the safety and efficacy of statin in children with FH.
Detection of sub-clinical atherosclerosis

In children with FH the disorder is mostly asymptomatic. Nevertheless, autopsy reports of healthy children shows atherosclerotic lesions at a young age, even in the general population. Another autopsy study demonstrated a prevalence of 3.2% of coronary stenosis in adolescents between the age of 15-19 years, which indicates that atherosclerotic changes already starts in early FH childhood.

Surrogate markers are able to assess sub-clinical atherosclerosis. They are predictive for CVD, and improvement of these markers correlates with improvement of the atherosclerotic process. The strength of a validated surrogate marker is enhanced by the fact that it may yield pathophysiological information at an early stage of the atherosclerotic process. Intima media thickness (IMT) ultrasound measurements and the endothelial function as measured by flow-mediated dilatation (FMD) are both surrogate markers for detection of early atherosclerotic disorders.

**Intima media thickness**

The intima media thickness is a well validated, noninvasive method for assessment of sub clinical atherosclerosis is intima media thickness. It is measured by B-mode ultrasonography, which visualizes the arterial wall of the carotid and femoral arteries. The edges of the lumen-intima and media-adventitia ultrasound interfaces of the posterior artery walls represent the boundaries of the intima-media complex. The distance between the interfaces is called intima-media thickness (IMT). In patients with FH, IMT is greatly increased as compared to the general population. Furthermore, a previous performed trial in adult patient with FH treated with aggressive lipid lowering strategies resulted in a regression of atherosclerosis as demonstrated with IMT. In children with FH, it was demonstrated in several studies that they have increased IMT as compared to healthy controls.

**Endothelial function**

Endothelial dysfunction is an early reversible stage in the development of atherosclerosis, and it is detectable before morphological changes are present. An impaired endothelial function has a predictive value for future cardiovascular events. In previous years, several studies have shown that children with FH are characterized with impaired...
endothelial function \(^{29-31}\), which indicates that the process of atherosclerosis already starts in young asymptomatic FH children.

Endothelial function is a non-invasive marker and measured as FMD. The technique is based on nitric oxide (NO) availability of the endothelium. Increased arterial blood flow is sensed by the endothelium with a subsequent release of NO and other vasodilators. Using ultrasound sonography one can simply measure the diameter of the vessel before and after ischemia, which is imitated by inflating a blood pressure cuff upon the forearm and releasing it after a few minutes. Statins have been shown to reverse endothelial dysfunction in adult FH patients \(^{32,33}\) as well as in children with FH \(^{31}\).

Outline of this thesis

This thesis provides an update on recent developments in diagnostics, therapeutical options and additional risk factors for atherosclerosis in children with familial hypercholesterolemia.

Part I describes how FH can be diagnosed in children from families with known FH. Chapter 1 is a review on recent advances in the diagnosis and management of children with FH. Chapter 2 gives an overview of the 12-year referral data of a large cohort of FH children from our outpatient clinic. The aims of this study were: first, to establish the LDL-C level that provides the most accurate diagnosis of FH in children from families with known FH; and second, to assess whether lipoprotein variation in these children is associated with premature CVD in relatives. In Chapter 3 we observed at what age morphological arterial wall changes are present in children with FH. Furthermore, we assessed the most important predictors for pre-atherosclerosis in these children. The purposes of Chapter 4 were to test the hypothesis that children with FH provide a better model to perform genotype–phenotype analysis than FH adults and to measure the supposed relationship between LDL receptor genotypes and lipoproteins in a paediatric cohort and their relation with the occurrence of parental CVD. In Chapter 5 we describes the diagnosis of autosomal recessive hypercholesterolemia in a young boy with extremely high cholesterol levels.

In Part II various therapeutical options for children with FH are described. Chapter 6 and 7 both reviewed the various LDL-C lowering strategies in FH children with respect to
efficacy and safety. In Chapter 8 we studied the efficacy and safety of 2-year pravastatin treatment in children with FH. The main objective was to determine the effect of 2 year statin treatment on the progression on carotid IMT in these children. Furthermore, we evaluated the effect of 2-year statin treatment on growth and sexual maturation.

The effect of long-term statin treatment was further evaluated in Chapter 9, in which we followed all children who participated in the trial described in chapter 8. Chapter 10 evaluated whether LDL receptor genotype influences the response to pravastatin treatment in children with FH. The last chapter of this part, Chapter 11, describes the effect of short term consumption of yoghurt enriched with plant stanols on LDL-C levels and the effect on endothelial function in pre-pubertal children with FH.

Part III gives an overview about additional risk factors for (premature) CVD in children with FH as compared to healthy siblings. It also describes the efficacy of statin treatment on those additional risk factors. Therefore, we evaluated the particle concentrations of different lipoprotein subclasses in FH children in Chapter 12 and determined whether statin treatment improves the subclass profile. In the last chapter of this thesis, Chapter 13, we compared the levels of oxidized LDL-C between FH children and healthy siblings, and we also studied the effect of statin treatment on oxidized LDL-C levels.

In summary, the aims of this thesis were

1. to establish the most accurate diagnosis for FH in children
2. to evaluate the efficacy and safety of statin treatment and other therapeutical options in children with FH
3. to assess whether children with FH have additional risk factors for premature CVD besides high LDL-C levels, and whether these risk factors are influenced by early statin treatment.
References


