Familial hypercholesterolemia in childhood: diagnostics, therapeutical options and risk stratification
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Familial hypercholesterolemia in children

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Purpose of this review
This review provides an update on recent advances in the diagnosis and management of children with familial hypercholesterolemia.

Recent findings
A large cross-sectional cohort study of paediatric familial hypercholesterolemia demonstrated that affected children had a 5-fold more rapid increase of carotid arterial wall intima-media thickness during childhood years than their affected siblings. This faster progression led to a significant deviation in terms of intima-media thickness from the age of 12 years and onwards. Low-density lipoprotein cholesterol was a strong and independent predictor of carotid artery intima-media thickness in these children, which confirms the pivotal role of low-density lipoprotein cholesterol for the development of atherosclerosis. In this condition lipid lowering by statin therapy is accompanied by carotid intima-media thickness regression in familial-hypercholesterolemic children, which suggests that initiation of low-density lipoprotein cholesterol-reducing medication in childhood already can inhibit or possibly reduce the faster progression of atherosclerosis. Furthermore, these trials demonstrated that statins are safe and do not impair growth or sexual development in these children. Conversely, products containing plant sterols reduced low-density lipoprotein cholesterol levels by 14%, but did not improve endothelial dysfunction as assessed by flow-mediated dilatation.

Summary
Children with familial hypercholesterolemia clearly benefit from lipid-lowering strategies. Statins are safe agents and have been proven to reduce elevated low-density lipoprotein cholesterol levels significantly. In addition, statins improve surrogate markers for atherosclerosis. Therefore these agents should become the pivotal therapy in children with familial hypercholesterolemia.
Familial hypercholesterolemia

Introduction

Familial hypercholesterolemia is a common and inherited metabolic disorder of lipoprotein metabolism. Clinically, familial hypercholesterolemia is characterized by elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) from birth onwards, due to mutations in the LDL receptor gene. The elevated levels of total cholesterol and LDL-C strongly predispose to the early initiation of atherogenesis and premature cardiovascular disease (CVD), which can already be observed in children with familial hypercholesterolemia.

In this review we describe recent advances in the diagnosis and management of children with familial hypercholesterolemia which have been published since early 2003. In previous years, most studies focused on treatment of these children. This resulted in a paradigm shift from screening, diagnosis, and treatment with bile acid-binding resins to better risk stratification and improved treatment through 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitors (statins) and cholesterol-absorption-inhibitor (ezetimibe, plant sterols and stanols) therapy.

Risk stratification

Although familial hypercholesterolemia is a monogenic disorder, mortality varies to a large degree among adult patients with the disorder. Additional genetic and environmental risk factors for CVD might determine the variable expression in patients with this disorder. Identification of these risk factors could lead to a more efficacious intervention strategy with lipid-lowering drugs or modification of lifestyle at a young age. Wiegman et al. assessed the diagnostic value of LDL-C levels and were the first to determine the best available cut-off value to diagnose familial hypercholesterolemia in a cohort of more than 1000 children of familial hypercholesterolemia relatives. LDL-C levels below 3.5mM were only found in 4.3% of children with a mutation in the LDL-receptor gene. Therefore, in familial hypercholesterolemia families, the determination of LDL-C levels can reliably establish a diagnosis of familial hypercholesterolemia in children. Furthermore, Wiegman et al. observed that variations
in LDL-C but also in high-density lipoprotein cholesterol (HDL-C) and lipoprotein (a) in these children were associated with higher incidence of premature CVD in relatives. Familial-hypercholesterolemic children with LDL-C levels \( \geq 6.2 \text{ mM} \) had a familial-hypercholesterolemic parent with premature onset of CVD 1.7 times more often. Children with HDL-C levels below 1.0 mM had a familial-hypercholesterolemic parent with premature onset of CVD 1.8 times more often, and children whose lipoprotein (a) was \( \geq 300 \text{ mg/dl} \) had a familial-hypercholesterolemic parent with premature CVD 1.5 times more often. So, children with premature CVD among first relatives had higher LDL-C, lower HDL-C and higher lipoprotein (a) levels. This suggests that when a diagnosis of familial hypercholesterolemia is certain in a family, simple measurement of the most important lipoproteins, LDL-C, HDL-C and lipoprotein (a), allows not only an accurate diagnosis of familial hypercholesterolemia in childhood but also can lead to identification of familial-hypercholesterolemia families with the highest risk of premature CVD.

LDL-C levels vary between children with familial hypercholesterolemia, as a result of both environmental and genetic factors. In the general population the variability of LDL-C levels is partly influenced by polymorphisms in the Apo \( \varepsilon \) gene \(^5\). In particular, the \( \varepsilon 4 \) allele is associated with higher, and the \( \varepsilon 2 \) with lower, total cholesterol and LDL-C levels \(^6\text{-}^8\). Variation at the apoE gene locus might account for as much as 14% of the genetically determined variation in total cholesterol \(^5\text{-}^9\). However, in children with familial hypercholesterolemia, the presence of the \( \varepsilon 4 \) allele did not contribute to the differences in LDL-C levels \(^10\) but, strikingly, the \( \varepsilon 4 \) allele did explain 73% of the variance in HDL-C levels. The presence of an \( \varepsilon 4 \) allele was also associated with lower HDL-C levels in an affected sib-pair analysis, which suggested that the \( \varepsilon 4 \) allele carries an additional disadvantage for familial-hypercholesterolemic children \(^10\). This inconsistency between adult and paediatric studies might be explained by the fact that in an affected sib-pairs analysis the results are independent of additional familial factors.

**Surrogate markers for atherosclerosis**

Endothelial dysfunction and increased intima-media thickness (IMT) have both been validated as predictive for future CVD \(^11\). In children with familial hypercholesterolemia
endothelial function is impaired\textsuperscript{12,13}, particularly in those children with a positive family history of premature CVD\textsuperscript{14}. Furthermore, children with familial hypercholesterolemia are also characterized by an increased IMT when compared with healthy controls\textsuperscript{15-18,19}. In fact, familial-hypercholesterolemic children had a 5-fold more rapid increase of carotid arterial wall IMT during childhood years than their affected siblings\textsuperscript{19}. This increase led to a significant deviation in terms of IMT values from the age of 12 years onwards. LDL-C proved a strong and independent predictor of carotid artery IMT, highlighting the pivotal role of this lipoprotein for the development of atherosclerosis in this condition already at a young age\textsuperscript{19}. Therefore, it might be suggested to measure carotid artery IMT as a marker of the increased atherosclerotic burden. This might assist in the decision of when to start lipid-lowering medication in children with familial hypercholesterolemia\textsuperscript{19}.

\section*{3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins)}

By far the preferred drugs in the treatment of hypercholesterolemia in adults are HMG-CoA reductase inhibitors (statins). The use of these agents has been proven to be effective and safe in adults, and therefore they could also be beneficial for hypercholesterolemic children. Yet, most statins have not been registered for children and the recommended lipid-lowering therapy for familial-hypercholesterolemic children above 10 years consists of diet and bile acid-binding resins\textsuperscript{20}. However the lipid-lowering efficacy of bile acid-binding resins is modest (10-15\%) and the long-term compliance is poor, mostly due to side effects\textsuperscript{21-23}.

In previous years, several controlled and uncontrolled trials\textsuperscript{24-32} have demonstrated the efficacy and short- and longer-term safety of statin therapy in children and adolescents with heterozygous familial hypercholesterolemia (Table 1). In the past year, two additional trials have been published with statins in hypercholesterolemic children. First, it was shown that 40 mg of atorvastatin reduced LDL-C by 40\% after 26 weeks of treatment as compared with placebo\textsuperscript{33}. Second, in a 1-year uncontrolled trial, 5 mg of simvastatin reduced LDL-C by 25\%, 10 mg reduced LDL-C by 30\% and
20 mg reduced LDL-C by 36% \(^{34}\). This study demonstrated that even low doses of statins reduce LDL-C levels effectively. Taken together, these data \(^{24-34}\) show that statin therapy is both effective and safe in the short term in children with familial hypercholesterolemia.

**Table 1. Trials with Statins in Children with Familial Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Trial (year published)</th>
<th>Treatment</th>
<th>No of subjects randomised</th>
<th>placebo</th>
<th>statin</th>
<th>mean age (range)</th>
<th>follow-up (week)</th>
<th>Mean LDL-C reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athyros (2002) (letter)</td>
<td>atorvastatin 10-20-40 mg</td>
<td>16 (male)</td>
<td>13 (10-17)</td>
<td>156</td>
<td>45%</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Couture (1998)</td>
<td>simvastatin 20 mg</td>
<td>16</td>
<td>47 (8-17)</td>
<td>6</td>
<td>31-38%</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Mc Crindle (2003)</td>
<td>atorvastatin 10-20 mg</td>
<td>47</td>
<td>140 (10-17)</td>
<td>26</td>
<td>40%</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Dirisamer (2003)</td>
<td>simvastatin 5-10-20 mg</td>
<td>20</td>
<td>13 (10-17)</td>
<td>52</td>
<td>25-36%</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Ducobu (1999) (letter)</td>
<td>simvastatin 10-20-40 mg</td>
<td>32 (male)</td>
<td>&lt;17</td>
<td>104</td>
<td>37%</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>de Jongh (2002)</td>
<td>simvastatin 10-20-40 mg</td>
<td>69</td>
<td>106 (10-17)</td>
<td>48</td>
<td>31-41%</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Knipscheer (1996)</td>
<td>pravastatin 5-10-20 mg</td>
<td>18</td>
<td>54 (8-16)</td>
<td>12</td>
<td>23-33%</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Lambert (1996)</td>
<td>lovastatin 10-20-30-40 mg</td>
<td>69 (male)</td>
<td>12,8</td>
<td>8</td>
<td>21-36 %</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Sinzinger (1992) (letter)</td>
<td>lovastatin 20 mg</td>
<td>9</td>
<td>- (6-13)</td>
<td>208</td>
<td>28%</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Stein (1999)</td>
<td>lovastatin 10-20-40 mg</td>
<td>65 (male)</td>
<td>67 (10-17)</td>
<td>48</td>
<td>17-27%</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Stefanutti (1999)</td>
<td>simvastatin 10 mg</td>
<td>8</td>
<td>8 (4-12)</td>
<td>52</td>
<td>29%</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

LDL-C = Low-density lipoprotein cholesterol, y = year
Furthermore, statins not only reduce LDL-C levels, but also improve surrogate markers of atherosclerosis. Reversal of endothelial dysfunction as well as regression of IMT upon lipid reduction reflects an improvement of the atherosclerotic process. Statin therapy significantly improved endothelial dysfunction in children with familial hypercholesterolemia after 28 weeks of therapy. In adult familial-hypercholesterolemia patients, aggressive lipid lowering by statins was even accompanied by carotid IMT regression. This suggested that initiation of lipid-lowering medication in childhood inhibits progression or might even lead to regression of atherosclerosis. Therefore, a placebo-controlled trial in 214 children (8-17 years) with familial hypercholesterolemia was performed, to measure the effect of 2-year pravastatin therapy on IMT. As expected, pravastatin (20-40 mg) reduced LDL-C levels by 24% but, strikingly, 2 years of pravastatin led to regression of carotid IMT compared with placebo. This shows that the increased arterial wall thickness, and similarly endothelial dysfunction as present in children with familial hypercholesterolemia, are reversible.

Pharmacokinetics and pharmacodynamics of statins

The pharmacokinetics of statins have been widely studied in healthy adults and patients with hypercholesterolemia. In order to formulate a rational dosing regimen for children, such studies had to be carried out in children as well. In fact, two trials have now described the single-dose pharmacokinetics of pravastatin in children; one with a single dose of 10 mg pravastatin in 20 children with familial hypercholesterolemia, aged 5-16 years, and another with a daily dose of 20 mg pravastatin in 24 children with familial hypercholesterolemia, aged 8-16 years. In fact, pravastatin 10 mg was absorbed rapidly and the mean maximum concentration was 15.7 ng/ml. The mean half-life of pravastatin was 1.6 h and the plasma levels were below the detection limit 10 h after dosing. Pravastatin (20 mg) showed a mean maximum concentration of 52.1 ng/ml in 8-10-year-old children and 31.7 ng/ml in 11-16-year-olds. The mean half-life was 2.5 h in both groups. The investigators of both studies concluded that the pharmacokinetic profile of pravastatin in children was similar to that reported in adults. However, these data cannot be extrapolated to other statins, since pravastatin is not metabolized by cytochrome P450, in contrast to most other statins.
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Psychosocial aspects of statin use in children

In the more distant past, numerous studies have shown that the emotional impact of premature death of an affected parent is much greater than having familial hypercholesterolemia per se. As lipid reduction is a life-long prerequisite for familial-hypercholesterolemic children, the question arises about what the consequences of statin therapy in these children are with respect to anxiety, quality of life and concerns. A recent study evaluated the influence of simvastatin on psychosocial functioning in 69 children with familial hypercholesterolemia (mean age, 15.3 years). They demonstrated that 46% of the children with familial hypercholesterolemia suffer from the fact that they have the disease, but 62% felt safer by taking the medication and 81% expressed that they would not mind taking the medication for their whole life. So, statin treatment does not seem to negatively influence the psychosocial functioning of children with familial hypercholesterolemia.

Inhibitors of cholesterol absorption

In contrast to statins, which inhibit cholesterol synthesis in the liver, drugs are now available that reduce cholesterol absorption in the intestine. Ezetimibe is a novel cholesterol-lowering agent that prevents the absorption of cholesterol and plant sterols at the brush border of the small intestine by inhibiting the passage of sterols of dietary and biliary origin across the intestinal wall. Two target mechanisms for this drug have recently been proposed, namely the Niemann-Pick C1-like 1 protein (NPC1L1) and the annexin-caveolin 1 complex; both seem to be associated with the regulation of intestinal sterol metabolism. Other agents that reduce cholesterol absorption are plant sterols and stanols, which inhibit the solubility of cholesterol in micelles and thereby decrease its absorption. The reduction in cholesterol absorption leads to a decrease in the amount of intestinal cholesterol presented to the liver. As a result, there is a compensatory increase in the production of endogenous cholesterol and an increase of the LDL-receptor expression. The net effect is a reduction of LDL-C levels.
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A daily intake of 10 mg of ezetimibe reduces LDL-C levels by approximately 18% in adults. Although ezetimibe has already been registered for familial hypercholesterolemia children older than 10 years, it has not been adequately studied in this group of patients. Therefore, such studies are needed to assess the efficacy and safety of ezetimibe in children with familial hypercholesterolemia and confirm the data obtained in adults.

A new trend is the enrichment of food products with plant sterols and stanols. A daily consumption of 2 g of plant sterols or stanols reduces cholesterol levels by approximately 10% in adults as well as in children with familial hypercholesterolemia. In short-term studies plant sterols and stanols seemed to be safe in children with familial hypercholesterolemia. In line with these data, de Jongh et al. showed that an intake of 2.3 g/day of plant sterols decreased LDL-C by 14% as compared with the placebo in young familial-hypercholesterolemic children (5-12 years). However, in contrast to statin therapy, plant sterol consumption did not improve endothelial dysfunction in these children. The authors suggested that the absence of vascular effects during sterol therapy might imply a threshold of LDL-C reduction before improvement of endothelial function can occur. Also, statins might exert direct 'pleiotropic' effects on the vasculature and the absence of an effect on flow-mediated dilatation of the brachial artery during sterol use might also be the consequence of a lack of pleiotropic effects of sterols.

As the chemical structures of plant sterols and stanols are very similar to cholesterol, absorption of these compounds might be atherogenic. However, the absorption of plant sterols and stanols is at least less than 5% and less than 1%, respectively, whereas that of cholesterol varies from 35 to 70%. Furthermore, plant sterols and stanols cannot be synthesized in the body, and generally the serum concentrations of plant sterols and stanols are very low; less than 1% plant sterols are found in the serum sterol fraction in healthy humans. Earlier studies demonstrated that plant sterol consumption increased plasma plant sterol concentrations in children whereas plant stanol consumption decreased plasma plant sterol concentration. Therefore, Ketomaki et al. investigated the changes in ratios of plant sterols and stanols to cholesterol in red cells and plasma after consumption of plant sterols and stanols in
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hypercholesterolemic children. Plant sterol consumption increased and plant stanol consumption decreased the ratios of plant sterols to cholesterol in red cells. The authors suggest that even though the safety of plant sterol ester spreads has been evaluated in long-term and short-term studies, the long-term effects on red cells and vascular endothelial cells need further investigation.

Diet

Cholesterol-lowering therapy in familial-hypercholesterolemic children starts with dietary intervention and lifestyle modification. However, most trials demonstrated that the lipid-lowering effect of diet is modest and moreover that long-term compliance is poor. In a recent prospective study, Sanchez-Bayle and Soriano-Guillen demonstrated that a fat-restricted diet with a mean duration of 7.4 years in hypercholesterolemic children reduced LDL-C by 24% without affecting growth. In contrast with this unexpectedly high result, Engler et al. showed that a 6-week National Cholesterol Education Program (NCEP) Step II diet reduced LDL-C only by 8% in 15 hyperlipidemic children. The discrepancy between those studies in LDL-C-lowering effect of diet might be due to differences in study design and diet restrictions, which were more stringent in the first study. Apart from the LDL-C reduction, Engler et al. found that supplementation of 500 mg/day of vitamin C and 400 i.u./l of vitamin E improved endothelial function whereas diet alone did not. The authors suggested that antioxidants are beneficial supplements in addition to diet. However, results of antioxidant vitamins in long-term efficacy trials in adults are controversial to say the least, and treatment of familial-hypercholesterolemic children should, in our opinion, be focused on LDL-C reduction rather than on antioxidant treatment, in particular as beta-carotene in adults has been associated with pulmonary cancer.
Conclusion

In the last decade, research in familial hypercholesterolemia in children has focused on the efficacy and safety of statins as well as on the effects of statins on surrogate endpoints of CVD. Several studies have demonstrated excellent LDL-C-lowering efficacy as well as reassuring safety of these drugs in prepubertal and pubertal children with familial hypercholesterolemia (Table 1). LDL-C reductions were of course dependent on the dosage and the particular statin but, more importantly, the reductions were much larger than those obtained with other treatments such as bile acid-binding resins. Furthermore, statins not only reduced LDL-C levels, but also improved surrogate markers of atherosclerosis. Statins had already been shown to improve endothelial function in familial-hypercholesterolemic children, and recently Wiegman et al. showed that 2-year pravastatin treatment also reduced the carotid IMT compared to placebo. All these data together stress the need and opportunity for early treatment of familial hypercholesterolemia children in order to reverse the progress of atherosclerosis as early as possible.

It is still unclear at what age statin therapy should be initiated. The age of the youngest patients in the studies varied from 4 to 10 years (Table 1), which indicates that patients can be treated safely from an age of 10 years onwards. However, as prepubertal children with familial hypercholesterolemia are already characterized with endothelial dysfunction at the age of 5 years and IMT already deviates from normal from an age of 12 years, treatment of children younger than 10 years should be debated and investigated.

Cholesterol-absorption inhibitors such as ezetimibe or plant sterols and stanols coadministered with a statin offer new options in the treatment of adult patients with familial hypercholesterolemia. This combination therapy may also be beneficial for children for a number of reasons. First, low doses of statins coadministered with cholesterol absorption inhibitors may result in an increased efficacy and therefore easier-to-reach target LDL-C levels. Secondly, it may avoid up titration to high doses of statins, thereby minimizing the chance of statin-associated side effects. Unfortunately, to date there are no results on the efficacy and safety of ezetimibe, either combined with statins or alone, in children with familial hypercholesterolemia, and these studies...
are urgently needed. Furthermore, treatment with food products containing plant sterols or stanols alone reduce LDL concentrations by 10-15% in children with familial hypercholesterolemia \cite{37,56,57,83}, but in contrast to statin therapy, plant sterol consumption did not improve endothelial dysfunction \cite{37}. This implies that plant sterol or stanols alone might not be efficacious enough to reduce the progression of atherosclerosis in children with familial hypercholesterolemia, but in combination with statins they might be additive \cite{84}. Therefore, future studies in paediatric familial hypercholesterolemia should focus on combination therapy of statins with cholesterol absorption inhibitors, like ezetimibe, plant sterols or stanols.

Furthermore, the advent of more potent statins will allow us to reach more stringent LDL-C goals in an even-increasing number of children with familial hypercholesterolemia \cite{85,86}. Such low LDL-C levels obtained from a young age onwards might raise the hope that when familial-hypercholesterolemic children reach adulthood their CVD risk is virtually eliminated since they will have normal LDL-C levels, restored endothelial function and normal carotid IMT values. This should be the ultimate goal in the management of paediatric familial hypercholesterolemia.

In summary, statins and cholesterol absorption inhibitors seem efficacious and safe in children with familial hypercholesterolemia; however, more long-term studies are required with statins as well as with combination therapy to restore function and morphology of the arterial walls in these children.

References


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