Familial hypercholesterolemia in childhood
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Chapter 10

Summary and General discussion
The chapters in this thesis regard the clinical presentation and consequences of familial hypercholesterolemia in childhood. In overview, five main issues have been addressed:

- Optimal diagnostic strategy for FH in childhood
- Heterogeneity of cardiovascular risk in FH children
- Detection of sub-clinical atherosclerosis in FH children
- Efficacy and safety of lipid-lowering therapy in FH children
- Effect of lipid-lowering-therapy on surrogate endpoints in FH children

In this chapter, the different studies presented in this thesis are summarized with regard to these issues. Additionally, the rationale, clinical implications and suggestions for future investigation are also discussed.

**Optimal diagnostic strategy for FH in childhood**

Although FH children are characterized by elevated plasma levels of LDL-C, they rarely have clinical symptoms of atherosclerosis. Therefore, the most accurate method to identify FH in childhood is the determination of a defect in the LDL-receptor gene. Unfortunately, DNA sequencing is only available to a limited number of physicians. A more simple and broadly available method is the measurement of the LDL-C levels in blood plasma.

This raises the question what cut-off level should be used to make the diagnosis ‘FH’ in children of FH families? The 12-year referral data of our pediatric lipid outpatient clinic supports the use of a LDL-C cut-off level of 3.5 mmol/L at minimal loss of specificity and sensitivity (chapter 2). Naturally, choosing a cut-off level will always result in a small percentage of missed diagnosis.

Consequently, this implicates the greatest cautions in diagnosing children as not having FH based on LDL-C level below the cut-off level. Hence, especially in families with a history of premature CVD, follow-up of LDL-C plasma levels and/or determination of the LDL receptor mutation should be recommended.
Heterogeneity of cardiovascular risk in FH children

Analyses of mortality show a large variation in the onset and severity of CVD in FH. Specifically, the risk of atherosclerosis in young adults with FH varies significantly between families. Early identification of children in the highest risk category could assist in the identification of FH children in need for early therapeutic intervention.

Which parameters in FH children are associated with the occurrence of premature atherosclerosis in their families? In chapter 2 we observed that severely increased LDL-C, Lp(a) and decreased HDL-C plasma levels in FH children are associated with a positive family history for CVD. In line, children with a positive family history have a more pronounced impairment of endothelial function, assessed as flow-mediated dilatation, than patients with a negative family history (chapter 3). Summarized, these data underscore the potential importance of extremely increased LDL-C and decreased HDL-C levels and a positive family history for CVD for placing the FH children in the highest risk category for future CVD.

These findings emphasize the importance of lipid-lowering therapy in early childhood, especially in those children belonging to the highest-risk category. Particularly, because of the aggressive nature of FH in adults and the limited time-span to prevent these children for future CVD. Ongoing research in adult FH patients will have to determine which other genetic and environmental factors play a role in the susceptibility for CVD in FH. Hopefully, this will provide additional tools for the early and reliable identification of FH children at the highest cardiovascular risk.

Detection of sub-clinical atherosclerosis in FH children

In the general population autopsy studies of healthy subjects have shown that atherosclerotic changes are already present in adolescents. Given that adult FH patients are often characterized by premature atherosclerosis, it is safe to assume that atherosclerotic changes begin in early childhood. The process of atherosclerosis starts with the reversible stage of endothelial dysfunction even before the onset of morphological changes. In recent years, assessment of endothelial function (e.g. flow-mediated dilatation; FMD) and arterial wall thickness
Summary and general discussion

(intima media thickness of the carotid artery; IMT) have emerged as surrogate markers for atherosclerosis with clear predictive value for future CVD \(^9,10\).

Comparisons of FMD (chapter 7 and 9) and IMT \(^11\) of FH children to healthy controls, demonstrated that young FH children are already characterized by an impaired FMD and increased IMT, indicating the onset of atherogenesis in FH at a very young age. In view of the reversibility of the early stage of atherogenesis, these data support the early initiation of lipid-lowering therapy when endothelial dysfunction throughout the vascular bed is still amenable to complete normalization.

Efficacy and safety of lipid-lowering therapy in FH children

The present therapeutic guidelines for the treatment of FH children include lifestyle advice and, when the lipid-lowering response is inadequate, bile acid binding resins \(^12\). The lipid-lowering efficacy of such therapy is modest and compliance is often poor \(^13;14\). Cholesterol synthesis inhibitors (statins) are efficacious in lipid-lowering and reduce the incidence of CVD in adults and are therefore the therapy of choice in adults \(^15\).

Does statin therapy have similar lipid-lowering efficacy in children and are they safe for the use in these growing young children?

The baseline characteristics of an international trial, evaluating the safety and efficacy of simvastatin in FH children, showed that the study was performed in a population that was representative for FH (chapter 4). The main results of this study demonstrated that simvastatin is highly efficacious (41% LDL-C reduction) and most importantly that there was no evidence of any adverse effect of simvastatin on growth and pubertal development (chapter 5). Additionally, we demonstrated in chapter 6 that daily statin therapy has no adverse effects on the quality of life and anxiety of the FH children and their parents.

The aggressive nature of FH in adults and the knowledge that these children are already characterized by sub-clinical atherosclerosis supports the need for early intervention in order to delay and/or prevent the development of CVD in these patients. Comparable to adults our data show that simvastatin is an effective therapeutic option in FH children. This trial was performed in pubertal children above the age of 10.

What are the options in even younger patients?

In chapter 9 we evaluated the efficacy of cholesterol absorption inhibitors (e.g.
plant sterols) in pre-pubertal children. Plant sterols were well tolerated in these children and resulted in a LDL-C reduction of 14%.

Both statins and plant sterols are efficacious in lipid-lowering. However, it remains to be established whether they will improve the cardiovascular outcome in these children. It will be a challenge to further evaluate the effectiveness of combinations of lipid-lowering regimes, comprising e.g. statins and cholesterol absorption inhibitors. The additional value of doubling the statin dose has a small effect on lipid-lowering efficacy, whereas it may increase statin-associated side effects. Adding plant sterols or other cholesterol absorption inhibitors to a low dose of statins may result in an increasing efficacy whilst minimizing the chance of statin-associated side effects. Hence, this may prove to be a valuable additive for children who have to be motivated for lifetime lipid-lowering therapy.

**Effect of lipid-lowering therapy on sub-clinical atherosclerosis in FH children**

The lack of clinical endpoint data in FH children thus far makes it difficult to predict the effect of lipid-lowering therapy on the clinical outcome in these children. Surrogate endpoint such as FMD and IMT have predictive value for future CVD and LDL-C reduction induced by statin therapy has been associated with an improved FMD \(^{16}\) and decreased IMT \(^{17}\) in adults.

What is the effect of lipid-lowering therapy on these surrogate endpoints in young FH children, who are already characterized by sub-clinical atherosclerosis? Does lipid-lowering therapy inhibit or even reverse the atherosclerotic process in these young FH children?

Short-term statin therapy significantly restored the endothelial function, assessed as FMD (chapter 7). However, at 1-year follow-up we were not able to show a decrease in the IMT of the carotid arterial wall between the statin and placebo group (chapter 8) in FH children. Several factors may have contributed to the lack of improvement of IMT in these children. The IMT is still very 'thin' in these children compared to the IMT of adult FH patients. A larger sample size and long-term intervention may be required to demonstrate significant changes in IMT. Currently, longer-term data of these children are being collected.

The 14% LDL-C reduction by plant sterols was unable to result in an improvement in endothelial function of pre-pubertal FH children (chapter 9).
These data may be used in favor of the ‘pleiotrophic’ effects of statins beyond their lipid-lowering effect. On the other hand, we did show an inverse relation between improvement in FMD and the LDL reduction of statins (Chapter 7).

Overall our data imply a threshold lipid-lowering effect necessary to improve endothelial function and therefore emphasize the need for aggressive LDL-lowering therapy in FH children. Future research will have to provide evidence if other lipid-lowering drugs (e.g. combination therapy) will be able to reverse the process of sub-clinical atherosclerosis in this high-risk group. To predict the effect on the clinical endpoints in FH children, surrogate endpoints should be incorporated in new lipid-lowering intervention trials in FH children. FMD has proven to be a useful, easily modifiable marker to detect the earliest stages of sub-clinical atherosclerosis, whereas IMT has been accepted as a valuable tool in large long-term intervention trials.

Conclusion

The results of this thesis suggest that early identification and treatment of FH children might change the course of the disease. Whereas their affected parents started therapy at an age where the process of atherosclerosis had already reached an ‘irreversible’ state, institution of effective lipid-lowering in childhood will contribute to improvement of endothelial dysfunction, before irreversible structural changes occur. Although FH children are generally clinically asymptomatic, they are already characterized by functional changes of the arterial wall from early age onwards. Simvastatin is a good therapeutic option, it is effective, well tolerated, does not adversely affect the quality of life and is able to restore the vascular function in FH children. In contrast, modest LDL-C reduction with plant-sterols is unable to improve vascular dysfunction. Overall, the data presented in this thesis provide convincing arguments for early institution of aggressive lipid-lowering therapy in children with FH with the aim of preventing them from the cardiovascular events, from which their family members often suffered.
References


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