Familial hypercholesterolemia in childhood: diagnostics, therapeutical options and risk stratification
Rodenburg, J.

Citation for published version (APA):
Plant stanols do not restore endothelial function in pre-pubertal children with familial hypercholesterolaemia despite reduction of total and LDL cholesterol

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Submitted for publication
Abstract

Objective
Children with familial hypercholesterolaemia (FH) exhibit high cholesterol levels from birth onwards, resulting in early atherogenesis. The latter is reflected by impaired endothelial function. This emphasizes the need for early intervention in children with FH. Currently, options for treating high cholesterol levels in these children are limited. Therapy with HMG-CoA reductase inhibitors (statins) has been shown to restore endothelial function in FH children, but statins have not been approved in Europe for use in children. Plant sterols or stanols also lower cholesterol levels by inhibiting cholesterol absorption in the small intestine. We therefore examined the effect of plant stanols on lipids and endothelial function in pre-pubertal children with FH.

Study design
A total of 42 FH children, aged 7-12 years, were enrolled in a double-blind crossover trial consuming 500 ml of a low-fat yoghurt enriched with 2.0 g of plant stanols (mainly sitostanol) and 500 ml of a low-fat placebo yoghurt for 4 weeks, separated by a 6-week wash-out period. Lipid profiles and endothelial function were assessed after both periods of consumption. Endothelial function was measured as flow-mediated dilation (FMD) of the brachial artery by means of ultrasonography and a wall tracking system.

Results
This daily intake of 2.0 g stanols decreased total cholesterol (TC) by 7.5% and LDL cholesterol (LDL-C) by 9.2% as compared to placebo. However, this reduction of LDL-C did not improve FMD, which was 10.5 ± 5.1% after plant stanol and 10.6 ± 5.0% after placebo consumption, respectively (p = 0.852).

Conclusions
In conclusion, the present study confirms that plant stanol consumption reduces LDL-C in children with FH. Nevertheless, plant stanols do not improve endothelial function in children with FH, in contrast to statins. This might be due to insufficient LDL-C reduction to improve endothelial function. Another explanation is that statins improve endothelial function irrespective of LDL-C lowering, and plant sterols might lack these pleiotropic effects.
Introduction

Familial hypercholesterolaemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism due to a variety of mutations in the LDL-receptor gene. The disorder is associated with elevated cholesterol levels from birth onwards and premature atherosclerosis. In general, affected persons show symptoms of cardiovascular disease at relatively young age. Although children with FH are almost always clinically asymptomatic, development of atherosclerosis has already started, as reflected by increased intima-media thickness and endothelial dysfunction.

Endothelial dysfunction has emerged as a marker of an early, but reversible, stage in the development of atherosclerosis and can be measured as flow mediated dilation (FMD) of the brachial artery. FMD correlates well with known risk factors and other markers of coronary artery disease. Children with FH indeed exhibit impaired endothelial function, which supports the view that prevention of atherosclerotic development should be initiated in early childhood. In a previous study, de Jongh et al demonstrated that treatment with statins improves endothelial dysfunction towards normal levels in children with FH.

Statins appear to be safe and effective in children, as evaluated in a randomised controlled setting for up to two years. However, as their long-term safety in children is still under investigation, statins are presently not registered for children with FH in Europe. This is in contrast to the USA, where statins can be prescribed to hypercholesterolaemic children from 10 years onward. In addition, ezetimibe, a new cholesterol-lowering drug, has been approved worldwide for prescription to hypercholesterolaemic children older than 10 years of age. Strikingly however, clinical trials testing the effect and safety of ezetimibe in children are completely lacking.

Therefore, the common lipid-lowering strategy for children with FH presently consists of dietary and lifestyle-interventions and, if considered necessary, bile-acid binding resins. It has been shown, however, that the efficacy of a cholesterol-lowering diet alone is limited and that resins are poorly tolerated, resulting in poor compliance. Despite the emergence of new lipid-lowering strategies, non-pharmacological interventions currently remain the only therapeutic option for pre-pubertal children with FH.

Plant sterols are synthesized in plants and are structurally similar to cholesterol. Plant sterols are naturally present in the diet, and β-sitosterol, campesterol and stigmasterol are the most common ones. Plant stanols are the saturated counterparts of plant sterols.
sterols. Over the past decade, food products enriched with plant sterols and stanols have been introduced to reduce cholesterol levels. Plant sterols and stanols inhibit the absorption of cholesterol in the small intestine by decreasing the incorporation of dietary and biliary cholesterol into micelles. Plant stanols also impede absorption of plant sterols, resulting in both lower serum cholesterol and plant sterol levels. Sterols and stanols have been shown to safely reduce total cholesterol (Total-C) and low-density-lipoprotein cholesterol (LDL-C) by approximately 10% in FH adults and children. However, it is uncertain whether the LDL-C reduction by plant sterols and stanols improves endothelial function.

Therefore, we previously evaluated the effect of 2.3 g of plant sterols on LDL-C and endothelial function for four weeks in children with FH. Although LDL-C decreased with 14%, endothelial dysfunction did not improve. This is probably due to insufficient reduction of LDL-C before restoration of endothelial function can be realized. However, one cannot exclude a possible untoward effect of plant sterols on the vascular endothelium. Daily consumption of approximately 2.0 g of sterols is known to increase serum plant sterol concentration by 39-96% in both adults and children. Raised serum plant sterol concentrations have been suggested as a potential risk factor for coronary heart disease. Hence, the increase in serum plant sterol concentrations could attenuate the beneficial effect of plant sterol-induced cholesterol reduction on endothelial function. However, this should not apply to plant stanols, which are not only hardly absorbed, but actually lower serum plant sterol concentrations.

Therefore, we designed a study to evaluate the effect of short-term consumption of plant stanols on LDL-cholesterol and to evaluate whether the presumed LDL-C reduction will improve endothelial function in pre-pubertal children with FH.

Subjects and Methods

Subjects

Children were recruited from the outpatient lipid clinic at the Emma Children's Hospital in Amsterdam. Each subject, as well as each subject's parents or guardians, gave written informed consent for the child's participation in this study, which was approved by the Institutional Review Board of our centre.

We enrolled 42 prepubertal FH-children between 7 and 12 years of age. All subjects
met the following inclusion criteria: A personal diagnosis of FH by detection of a mutation in the LDL-receptor gene or LDL-C above the 95th percentile for age and gender and one parent with a confirmed diagnosis of FH. None of the children showed clinical signs of hypercholesterolaemia. Three subjects used drugs against asthma and one boy used medication for his attention deficit hyperactivity disorder (ADHD). At start of the study, none of the girls had reached menarche. Clinical characteristics at baseline are shown in table 1. Normal ranges of children’s cholesterol and triglyceride levels are shown in table 2.

**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FH subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>41</td>
</tr>
<tr>
<td>Male/female</td>
<td>22/19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.8 (1.5)</td>
</tr>
<tr>
<td>Length (m)</td>
<td>1.43 (0.10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>36.5 (8.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.7 (2.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>108 (12)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>61 (9)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.92 (1.55)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>5.38 (1.69)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.32 (0.31)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.64 [0.51-0.95]</td>
</tr>
</tbody>
</table>

All values are given as means (SD), except for triglycerides as median [interquartile range]
To convert cholesterol levels expressed in mmol/L to mg/dl, multiply by 38.67
To convert triglyceride levels expressed in mmol/L to mg/dl, multiply by 88.57

n, number; FH, familial hypercholesterolaemia; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein.

**Table 2** Normal ranges for lipid levels in children

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-9 years</td>
<td>10-14 years</td>
<td>5-9 years</td>
<td>10-14 years</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.15 (5.26)</td>
<td>4.09 (5.23)</td>
<td>4.22 (5.31)</td>
<td>4.15 (5.21)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.41 (3.26)</td>
<td>2.49 (3.37)</td>
<td>2.59 (3.45)</td>
<td>2.49 (3.47)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.45 (1.01)</td>
<td>1.40 (0.96)</td>
<td>1.37 (0.85)</td>
<td>1.35 (0.91)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.63 (1.14)</td>
<td>0.75 (1.41)</td>
<td>0.68 (1.19)</td>
<td>0.85 (1.48)</td>
</tr>
</tbody>
</table>

Values are given as 50th percentiles (95th percentile) for age and gender, except for HDL cholesterol as 50th percentile (5th percentile)
To convert cholesterol levels expressed in mmol/L to mg/dl, multiply by 38.67
To convert triglyceride levels expressed in mmol/L to mg/dl, multiply by 88.57

LDL, low density lipoprotein; HDL, high density lipoprotein.
Study design

The study was a double-blind placebo controlled cross-over trial. The children started with a two week diet run-in period, in which they were not allowed to consume any plant sterol or stanol enriched food products or dietary vitamin supplements, as short-term treatment with antioxidants has been shown to influence endothelial function in children with FH \(^{22}\). This period was extended to 6 weeks in case subjects were already consuming these products on a regular basis. The children were restricted from these products and supplements during the study. After the run-in period, subjects were randomly assigned to consume either 500 ml of yoghurt containing 2.0 g of plant stanols or 500 ml of the placebo low-fat yoghurt without plant stanols, for four weeks each. Twenty children started with the plant stanol-enriched yoghurt, while twenty-two children first ingested the control-yoghurt during this first study period. A 6-week wash-out period followed, after which the children crossed over to the alternate yoghurt for another four weeks. During the entire study, all children were on a low-saturated fat, low-cholesterol diet, compatible with the National Cholesterol Education Program Step II (NCEP-II) diet \(^{10}\).

Endothelial function was assessed at the end of both consumption periods. After an overnight fasting period of at least 12 hours, capillary lipid profile (Total-C, high-density lipoprotein cholesterol (HDL-C), LDL-C and triglycerides (TG)) was measured at baseline and at the end of both consumption periods. Physical examination, including height, weight, blood-pressure and heart-rate, was performed at baseline and at the end of the study.

Yoghurt composition and administration

The stanol-enriched and the low-fat control yoghurt were both produced and blinded by Campina, Woerden, the Netherlands. The yoghurts were distributed in identical-looking 500 ml jars. The children were instructed to consume one jar daily with their meals. At the start of each consumption period, the children received yoghurt for one week in a cooling bag. For the remaining three weeks, parents collected yoghurt at the hospital on a weekly basis. Compliance was measured at each study-visit by collection and calculation of the empty and full jars of yoghurt.
Endothelial function

Endothelial function was measured as flow mediated dilation (FMD) and performed according to a standardized protocol\textsuperscript{23,24}. In short, children were in the morning fasting state and were studied in the supine position. A blood pressure cuff was placed distal to the elbow of the right arm. After a 10 min rest, the brachial artery in the right antecubital fossa was visualized by use of a 7.5 MHz linear transducer. After obtaining an optimal view of the artery, the lumen diameter was measured by use of a wall tracking system. Three baseline vessel diameter measurements were obtained, after which reactive hyperaemia was induced by inflation of the cuff to a pressure of 220 mmHg for 5 minutes, approximately 10 cm distal to the location of the transducer. Upon release of the cuff, the brachial artery dilates by mediation of endothelial NO-release. Lumen diameter measurements were performed at 20-second intervals, during five minutes after cuff-release. All measurements were performed by the same sonographer and were stored digitally. Off-line analysis was performed by a blinded observer, who was unaware of clinical details and treatment period. Baseline vessel diameter was calculated as the average of the three measurements prior to cuff inflation. Flow mediated dilation is defined as \(\frac{\text{maximal lumen diameter after ischaemia - diameter at baseline}}{\text{diameter at baseline}}\) and is expressed as a percentage. Intrasession and intersession variation coefficients are 1.1% and 3.8% respectively\textsuperscript{24}. The total duration of this measurement was approximately 20 minutes.

Statistical analysis

A power calculation was performed to determine the required number of patients. Assuming that the common standard deviation of FMD is 2.0%, a sample size of 17 children in each group had 80% power to detect a difference in means of 2%. Statistical analyses were performed using SPSS 11.5 for Windows software. The paired Student's \(t\)-test was used to study the differences between treatments. Triglyceride data were skewed and, therefore, log-transformed before statistical testing. \(P<0.05\) was considered statistically significant. The FMD measurements of four children were excluded from analysis due to technical problems during image acquisition.
Chapter 11

Results

Forty-two eligible children were enrolled. One child dropped out of the study after one week, as he was not able to drink the required daily amount of yoghurt. Forty-one children completed the trial. One girl reached menarche during the study. Excluding her data from the analyses did not change the results. Based on the number of returned empty jars, compliance was 98% during plant stanol consumption and 96% in the control period. None of the children experienced any serious adverse events. During the period in which the subjects consumed the plant stanol yoghurt, 6 children complained of stomach aches for several days, compared to 8 children during the placebo period. Consumption of plant stanols for four weeks did not affect blood pressure, length, weight or BMI, if compared to placebo (data not shown).

After consumption of plant stanols for four weeks, Total-C was significantly reduced by 0.53 mmol/L (95% CI: -0.79 to -0.28 mmol/L) and LDL-C was significantly reduced by 0.48 mmol/L (95% CI: -0.69 to -0.27 mmol/L) as compared to consumption of placebo yoghurt (table 3). Expressed in percentages, these reductions were 7.5% for Total-C and 9.2% for LDL-C. There were no significant changes in HDL-C and triglyceride levels. FMD did not significantly differ between both periods. After plant stanol consumption, the FMD was 10.5% ± 5.1%, compared to 10.6% ± 5.0% after consumption of the placebo yoghurt (p= 0.852) (table 3). Baseline vessel diameter during plant stanol and placebo consumption did not differ significantly (2.9 ± 0.3 mm versus 2.8 ± 0.4 mm, respectively). There were no carry-over effects between the two treatments (data not shown).

Discussion

In the present study we demonstrate that short-term use of 2.0 g of plant stanols reduces Total-C and LDL-C by 7.5% and 9.2%, respectively, in prepubertal children with FH. No serious adverse events were evident. As expected, TG and HDL-C levels remained unaltered during stanol consumption. Despite the reductions in LDL-C levels, endothelial function did not improve.

The reductions in Total-C and LDL-C are in line with previous findings on short-term use of stanols in hypercholesterolaemic adults and children and are
Plant stanols

similar to those observed in patients treated with sterols. Becker et al reported an exceptional and frankly unexpected LDL-C reduction of approximately 30% in FH-children after consumption of 1.5 g stanols for 3 months. However, mean LDL-C levels were very high in this cohort (7.87 mmol/L) and the groups were small. In our study, lipid profiles were obtained by collection of capillary fingerstick samples. Use of this method has been shown to result in an overestimation of TG and HDL-C levels and thereby, an underestimation of LDL-C if compared to venous samples. However, in our study, the change in LDL-C was calculated within subjects. Therefore, use of this method probably did not affect the observed LDL-C reductions. Altogether, plant stanols appear to be an effective cholesterol-lowering strategy in children with FH. The present study is the first to evaluate the effect of plant stanols on endothelial function. We found that a LDL-C reduction of 9.2% after plant stanol consumption was not associated with improvement of endothelial function in children with FH. This is similar to the findings of our previous study with plant sterols, in which we found that consumption of 2.3 g of plant sterols for four weeks did not restore endothelial function, in spite of reducing LDL-C by 14%. Based on the results of the latter study, we then suggested that, regarding the vascular endothelium, the beneficial effect of plant sterols on LDL-C levels may be counteracted by a rise in serum plant sterol concentrations after plant sterol consumption. Although serum plant sterol levels were not measured in our previous study, it is known that serum plant sterol concentrations increase by 39-96% after daily consumption of 2.0 g of plant sterols. 

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Table 3 Lipids and FMD with absolute changes in subjects

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Stanol yoghurt (n=41)</th>
<th>Placebo yoghurt (n=41)</th>
<th>Mean absolute change (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-C (mmol/L)</td>
<td>6.47 (±1.35)</td>
<td>7.00 (±1.49)</td>
<td>-0.53 (-0.79 to -0.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>4.77 (±1.32)</td>
<td>5.24 (±1.45)</td>
<td>-0.48 (-0.69 to -0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.35 (±0.24)</td>
<td>1.38 (±0.27)</td>
<td>-0.03 (-0.13 to 0.06)</td>
<td>0.848</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.61 [0.51-0.84]</td>
<td>0.57 [0.51-0.93]</td>
<td>-0.05 (-0.18 to 0.08)</td>
<td>0.444^a</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>10.5 (±5.1)</td>
<td>10.6 (±5.0)</td>
<td>0.05 (-2.40 to 2.51)</td>
<td>0.852</td>
</tr>
</tbody>
</table>

All values are defined as mean values (±SD), except for the mean absolute change given as mean (95% confidential interval (CI)) and triglycerides as median (interquartile range)

^Difference between treatments was calculated after log-transformation of triglyceride values

Total-C. total cholesterol; LDL-C. low-density lipoprotein cholesterol; HDL-C. high-density lipoprotein cholesterol; TG, triglycerides; FMD, Flow Mediated Dilation.
potential risk factor for coronary heart disease. Even though serum sterol concentrations remain within the normal range after consumption of plant sterols, it is unknown if elevations in serum plant sterol concentrations affect endothelial function. However, the present study shows that neither plant stanols, which are hardly absorbed and actually lower plant sterol concentrations, improve endothelial dysfunction in children with FH. Thus, it is unlikely that raised serum plant sterol concentrations are responsible for the observed lack of effect of plant sterols on endothelial function.

De Jongh et al have demonstrated that endothelial dysfunction in children with FH normalizes after treatment with statins for 28 weeks. Putative explanations for the lack of vascular effects of plant sterols and stanols compared to statins, include that statins reduce LDL-C to a greater extent in hypercholesterolaemic adults, adolescents and children. As previously suggested by de Jongh et al, this implies the presence of a threshold of LDL-C lowering before endothelial function can improve. This is supported by LDL-aphaeresis studies, showing that changes in LDL-C per se are the most important determinant in the correlation between LDL-C levels and endothelial function. Another possibility might be that statins exert direct effects on endothelial cells, independent of their effects on serum cholesterol levels. Some studies showed that short-term use of statins improves endothelial function, without plasma lipid-lowering. Thus, plant sterols and stanols might lack these lipid-independent pleiotropic effects of statins, or their LDL-C reducing effect is not large enough to improve endothelial function.

It is unlikely that consumption of plant stanols for a longer period would have improved endothelial function in children with FH. It has been shown that the maximal effect of plant stanols on LDL-reduction is reached after a period of two weeks and that consumption for a longer period does not further reduce LDL-C. Elevation of the dose of plant stanols also does not result in a larger reduction of LDL-C. Furthermore, FMD is a short-term surrogate marker of arterial disease progression and has previously been shown to improve after only two weeks of statin treatment. Therefore, it is unlikely that consumption for a longer period would have resulted in a stronger LDL-reduction and thereby an improvement of FMD.

Consumption of plant sterols and stanols reduces plasma β-carotene concentration and it is unknown whether this might have affected the endothelial function. A meta-
analysis of 15 trials testing doses of >1.5 g of sterols and/or stanols in adults shows a mean change of -12.1% in serum β-carotene concentrations, adjusted for change in serum Total-C (reviewed in 19). A recent study demonstrates a reduction of α- and β-carotene by 17.4% and 10.9%, respectively, in children with FH after daily consumption of 1.2 g of plant sterols 20. In vitro studies showed that carotenoids exert favourable effects on the vascular endothelium and smooth muscle cells (reviewed in 40). This may suggest that the reduction of plasma carotenoids, caused by plant sterol consumption, might be responsible for the lack of improvement of endothelial function after plant sterol or stanol consumption. However, in vitro human data, particularly on the effect of carotenoids on endothelial function measured as FMD, are lacking. Furthermore, we did not measure plasma β-carotene levels in the present study. Therefore, it is uncertain whether a possible reduction in plasma β-carotene concentration might have affected the vascular function.

Our data imply that strong reduction of LDL-C is likely to be essential in order to improve endothelial function in children with FH. Statins would be the most powerful means for this purpose, possibly combined with plant stanols. Until children with FH reach the age at which they become eligible for more aggressive lipid-lowering strategies, treatment with plant stanols can be a useful non-pharmacological tool for cholesterol-lowering. In addition, the children in our study generally considered the stanol-yoghurt, which is available in almost all supermarkets, as a tasteful addition to their daily diet. This is reflected by the high compliance reported in this study. With respect to safety, plant stanols have presently been evaluated for up to five years. No adverse events were reported (reviewed in 19). Therefore, consumption of plant stanols can be a beneficial, safe, tasteful and easy-accessible tool in order to accomplish early lipid-lowering in pre-pubertal children with FH.

In conclusion, short-term consumption of plant stanols reduces LDL-C in children with FH. Plant stanols do not restore endothelial dysfunction in children with FH, possibly due to insufficient reduction of LDL-C. This advocates more aggressive lipid-lowering in FH-children in the future, by means of statin-treatment or possibly by combining stanols with other lipid-lowering compounds. In the interim, consumption with plant stanols might be a safe and useful cholesterol-lowering strategy in children with FH.
References


