Paediatric guidelines for lipid reduction

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Due to the fact that atherogenesis starts even in early childhood there is no doubt that the primary prevention of atherosclerotic diseases is a paediatric problem and therefore must start as early as possible in childhood. Thus, there is now indeed strong support for increasing efforts toward identifying those subjects with elevated total cholesterol or low density lipoprotein (LDL)-cholesterol levels and for providing appropriate treatment in order to achieve a substantial and pertinent reduction of those levels.

Based on the data from the Lipid Research Clinics Program, the diagnosis of hypercholesterolaemia during infancy and childhood can easily be made, using the 95th percentiles for total cholesterol and for LDL-cholesterol.

Today there is no doubt that elevated plasma cholesterol levels should be lowered first by dietary modification even in early childhood, beginning at the age of two years. Most authors report an average cholesterol reduction of about 10–15% by a low cholesterol–low fat diet. Our group had the opportunity to study 11 hypercholesterolaemic children consuming a type II diet containing 15–20 g soybean-protein, which resulted in a reduction of 32% in total cholesterol and 37% in LDL-cholesterol.

In an individual patient who does not respond adequately to diet, drug treatment should be started. Bile acid-binding resins in a dose of 4–8 g are the drugs of choice at this time. A further 15–20% reduction of total plasma cholesterol can be achieved in most children. It is concluded that detection and adequate treatment of disorders of lipoproteins should be carried out early in childhood, in particular in families with a cardiovascular history. Current knowledge supports the suggestion that early intervention might reduce the risk of later cardiovascular diseases.

The close relationship between atherosclerotic disease and certain lipid components was discovered at the end of the last century. German scientists first identified this lipid component as 'cholesterol'; later on Anitschkow was the first to describe that animals who were fed a cholesterol-rich diet developed atherosclerotic lesions.

Since that time a vast body of knowledge concerning the associations between nutritional factors and the induction of disturbances of lipoprotein metabolism and the inborn errors of lipoproteins has accumulated. Today scientists have been able to advance in the molecular-biological field of lipoprotein and apoprotein metabolism and have provided us with fascinating new data about new aspects of genetics of lipoprotein disorders.

Clinical, experimental and epidemiological studies carried out in the last two decades have established that reducing elevated plasma cholesterol levels can reduce the risk of coronary heart diseases in men. The data of the Lipid Research Clinics Coronary Primary Prevention Trial clearly show that a reduction of serum total cholesterol by treatment with cholestyramine is associated with a decreased incidence of primary endpoint of fatal and nonfatal heart attacks by an average of 19% after seven years.

In addition to epidemiological data there is much evidence about the cardiovascular risk of subjects affected with an inherited metabolic disorder of lipoproteins, especially with the heterozygous form of hypercholesterolaemia, which is estimated to be the most frequent inborn error of metabolism (incidence 1:500). The probability of a manifestation of a cardiovascular disease in the form of angina pectoris, myocardial infarction or sudden cardiac death in heterozygous males aged 60 years is estimated at 60% compared to 13% in healthy subjects. A recent genetic study from Utah reported that out of 1134 persons examined those

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males who were affected with familial hypercholesterolaemia had their first myocardial infarction at an average age of 42 years and died at the age of 45 years. On the other hand clinicians had to learn from severe forms of hypercholesterolaemia, that is the homozygous form, which is characterized by a defect of LDL-receptor activity, that clinical manifestations of cardiovascular disease may occur in the pediatric age groups, even in the first decade of life. Moreover, a recently published paper by Newman and coworkers first provided clear evidence that even in adolescents a statistically significant relationship exists between the extent of fatty streaks in the great arteries of deceased subjects and the total cholesterol and low density lipoprotein (LDL)-cholesterol concentrations which have been estimated in earlier life.

The sum of these findings strongly support the importance of (1) a diagnosis of disturbances of lipoprotein metabolism as early as possible during childhood, and (2) a subsequent, effective lowering of elevated plasma cholesterol. In this respect clear recommendations of numerous scientific committees, particularly the National Institutes of Health in Behesda, have been issued in the last few years.

Based on the data from the Lipid Research Clinics Program, which also included a healthy young population, it is not difficult to evaluate a patient's serum lipid value (see Tables 1 and 2). Using strict criteria for diagnosing a hypercholesterolaemia the 95th percentiles for total and for LDL-cholesterol can be used. In general, in the age group between 1 and 20 years every total cholesterol...

### Table 1 Normal plasma lipid concentrations in the first two decades of life*

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>No.</th>
<th>Cholesterol (mg/dl)</th>
<th>Triglyceride (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5th</td>
<td>Mean</td>
</tr>
<tr>
<td>0-4 M</td>
<td>238</td>
<td>114</td>
<td>155</td>
</tr>
<tr>
<td>F</td>
<td>186</td>
<td>112</td>
<td>156</td>
</tr>
<tr>
<td>5-9 M</td>
<td>1253</td>
<td>121</td>
<td>160</td>
</tr>
<tr>
<td>F</td>
<td>1118</td>
<td>126</td>
<td>164</td>
</tr>
<tr>
<td>10-14 M</td>
<td>2278</td>
<td>119</td>
<td>158</td>
</tr>
<tr>
<td>F</td>
<td>2087</td>
<td>124</td>
<td>160</td>
</tr>
<tr>
<td>15-19 M</td>
<td>1980</td>
<td>113</td>
<td>150</td>
</tr>
<tr>
<td>F</td>
<td>2079</td>
<td>120</td>
<td>158</td>
</tr>
</tbody>
</table>

*Data are given are from the Lipid Research Clinic Data Book. Lipids were determined on plasma from 11,219 fasting, white subjects (5,749 boys, 5,470 girls) who were studied in seven North American Lipid Research Clinics using common protocols and laboratory methodology.

### Table 2 Normal plasma lipoprotein concentrations in the first two decades of life*

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>No.</th>
<th>High-density lipoprotein</th>
<th>Low-density lipoprotein</th>
<th>Very low-density lipoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>Cholesterol (mg/dl)</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5th</td>
<td>Mean</td>
<td>95th</td>
</tr>
<tr>
<td>5-9 M</td>
<td>145</td>
<td>38</td>
<td>56</td>
<td>75</td>
</tr>
<tr>
<td>F</td>
<td>127</td>
<td>36</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>10-14 M</td>
<td>298</td>
<td>37</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>F</td>
<td>248</td>
<td>37</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>15-19 M</td>
<td>300</td>
<td>30</td>
<td>46</td>
<td>63</td>
</tr>
<tr>
<td>F</td>
<td>297</td>
<td>35</td>
<td>52</td>
<td>74</td>
</tr>
</tbody>
</table>

*Data are from the Lipid Research Clinic Data Book. Lipoproteins were determined on plasma from 1415 fasting white subjects (743 boys, 672 girls) who were studied in seven North American Lipid Research Clinics, using common protocols and laboratory methodology.
level higher than 200 mg dl⁻¹ and LDL-cholesterol higher than 135–140 mg dl⁻¹ must be considered to be elevated[18]. However, it should be emphasized that subjects with cholesterol and LDL-cholesterol concentrations exceeding the 90th percentile in the pediatric age group are very likely to show elevated plasma lipid levels during adolescence and early adulthood. Thus, a high tendency for tracking has been shown in various longitudinal studies for total cholesterol and for LDL-cholesterol[19-21].

**Familial hypercholesterolaemia (FH)**

Familial hypercholesterolaemia is characterized by one of several genetic defects in a cell surface receptor that normally controls the degradation of plasma LDL. The disorder results clinically in a lifelong elevation of the concentration of LDL-bound cholesterol in blood[19].

Detection of a newborn affected with FH is possible from cord blood cholesterol determination, however, hypercholesterolaemia must also be present in one of the parents[22]. If there is a family history of hypercholesterolaemia and/or premature coronary artery disease at latest with the age of two years a blood cholesterol determination should be performed. In many cases due to other reasons (such as suspected anemia etc.) blood specimens were drawn during that period. If two laboratory tests reveal cholesterol levels higher than the 75th percentile, the introduction of a diet low in cholesterol and saturated fat is desirable.

If the diagnosis of familial hypercholesterolaemia has been confirmed by family testing, a strict diet should be prescribed, in order to lower elevated plasma cholesterol levels towards normal range. The classical type II-diet consists of restriction of total fats (max. 30% of total energy) and restriction of saturated fats and cholesterol (less than 250 mg per day).

Most authors who treated pediatric FH patients by diet alone reported on a reduction of total cholesterol of between 10 and 15%[23-26]. Thus, by means of a dietary regimen only in a minority of children plasma cholesterol levels reach the normal age-related range. In contrast, Stein et al. published in 1982 a study performed in Cincinnati, reporting that out of 12 children undergoing a usual diet therapy as outpatients, 11 were within their normal range for plasma cholesterol after three months[26].

Stimulated by reports from adult studies showing that diets enriched with soybean-protein are able to reduce elevated plasma cholesterol to a greater extent, we introduced a dietary regime with soybean-protein (15–20 g per day) in the treatment of hypercholesterolaemic children.

**Patients**

Eleven children (seven boys, four girls, mean age 8.1±4.4 years) were included in the dietary program. All children were healthy, did not show any clinical signs of disease and had been diagnosed as being affected with hypercholesterolaemia according to the LRC-criteria. Nine of the 11 children were diagnosed as familial hypercholesterolaemia, two as polygenic hypercholesterolaemia. Most of the children were transferred to the Outpatient Clinic for Metabolic Disorders from other Clinics due to occasionally detected hypercholesterolaemia or due to a family history of hyperlipidaemia or cardiovascular diseases. The study was designed as a switch-over program, all children first participated in the I-group (diet I) for two months and switched over after a break of two months to the II-group (diet II). Three children dropped out from phase I due to school problems. For the first two weeks all children were admitted to the metabolic ward of the Department of Pediatrics, University of Vienna; later they were treated as outpatients and reviewed at two-week intervals. All children accepted both diets very well; adherence to the diet was controlled by one dietitian by means of biweekly visits and exact diet protocols. No weight changes occurred during the dietary treatment nor were any gastrointestinal symptoms reported. As it can be seen from Table 3, a greater reduction of cholesterol and LDL-cholesterol could be observed in the soybean group; thus, the decrease after two months of total cholesterol and LDL-cholesterol was calculated to be 30 and 37% respectively[27].

**Drug treatment**

In most studies, only a minority of familial hypercholesterolaemic children have their elevated plasma cholesterol concentrations normalized, so many children have to be treated by drugs[28,29,30].

The drugs of choice for children are nonabsorbable bile-acid-binding resins, considered safe since they are not being absorbed from the gastrointestinal tract[29-33]. The administering of these drugs (4–20 g per day in divided doses) usually lowers LDL-cholesterol another 10–25%[34]. In our experience, cholesteryamine (average 8 g per day) is able to reduce total-cholesterol and LDL-cholesterol by 12
Table 3  Serum lipids and lipoproteins (mg/dl) in hypercholesterolemic children undergoing dietary treatment

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Cholesterol</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Apo-B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical type II-diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>8</td>
<td>312 ± 61</td>
<td>253 ± 60</td>
<td>49 ± 16</td>
<td>83 ± 26</td>
<td>142 ± 31</td>
</tr>
<tr>
<td>Two weeks</td>
<td>8</td>
<td>306 ± 29</td>
<td>248 ± 36</td>
<td>44 ± 21</td>
<td>104 ± 51</td>
<td>155 ± 24</td>
</tr>
<tr>
<td>Two months</td>
<td>6</td>
<td>269 ± 19**</td>
<td>209 ± 30</td>
<td>42 ± 4</td>
<td>72 ± 41</td>
<td>134 ± 32</td>
</tr>
<tr>
<td><strong>Soy-bean diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>11</td>
<td>336 ± 76</td>
<td>275 ± 74</td>
<td>47 ± 8</td>
<td>72 ± 22</td>
<td>177 ± 22</td>
</tr>
<tr>
<td>Two weeks</td>
<td>11</td>
<td>297 ± 56</td>
<td>249 ± 46</td>
<td>37 ± 7</td>
<td>81 ± 35</td>
<td>144 ± 45</td>
</tr>
<tr>
<td>One month</td>
<td>8</td>
<td>248 ± 52**</td>
<td>203 ± 51</td>
<td>41 ± 4</td>
<td>71 ± 26</td>
<td></td>
</tr>
<tr>
<td>Two months</td>
<td>8</td>
<td>232 ± 29**</td>
<td>180 ± 29**</td>
<td>40 ± 10</td>
<td>82 ± 31</td>
<td>126 ± 23*</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

Table 4  Lipids and lipoproteins in children heterozygous for familial hypercholesterolaemia treated with cholestyramine (8 g d⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>VLDL-C</th>
<th>Total TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment (mg dl⁻¹)</td>
<td>314 ± 50</td>
<td>263 ± 37</td>
<td>46 ± 10</td>
<td>26 ± 18</td>
<td>85 ± 33</td>
</tr>
<tr>
<td>Resin + diet (mg dl⁻¹)</td>
<td>276 ± 49</td>
<td>207 ± 46</td>
<td>48 ± 19</td>
<td>17 ± 9</td>
<td>87 ± 30</td>
</tr>
</tbody>
</table>

P < 0.01  n.s.  n.s.  n.s.

Subjects: seven male, five female; age 9.8 ± 7.2 years.
Duration of treatment: 2-7 years (0.6-5.7 years).

and 21%, respectively, after a mean duration of therapy of 2-7 years (Table 4). There was no effect of cholestyramine on HDL-cholesterol concentration.

With respect to possible side effects of a long term drug treatment during childhood, Glueck recently reported from his results of a cholesterol-lowering therapy in 73 children (40 children were treated with diet alone, and 33 with diet plus bile-acid-binding resins): There was no effect on growth, all children remained in the same percentile distributions for weight and height over the years. Intake of cholestyramine or colestipol is associated with a major problem in some patients: the drug is a bulky powder, therefore some patients do not follow such a treatment for long.

There are some reports on the effect of fibrates, in particular on fenofibrate, in hypercholesterolaemic children: Steinmetz reported in 17 children aged 4-19 years, most suffering from hypercholesterolaemia, a decrease of cholesterol by 22% and of triglycerides of 39% after three months' fenofibrate treatment. Chicaud et al. treated 12 children, mean age 10 years, with hypercholesterolaemia and observed a 20% reduction of total cholesterol.

Treatment of the homozygous form of familial hypercholesterolaemia

These patients are at very high risk for clinical manifestations of cardiovascular disease during childhood; they do not generally respond adequately to a dietary or drug treatment; therefore intensive treatment with surgical procedures (ileal-bypass, liver transplantation etc) and plasma-exchange have to be performed.

Familial combined hyperlipoproteinaemia

Familial combined hyperlipidaemia is a relatively common autosomal dominant disorder in which
kindred members may have several different types of hyperlipoproteinaemia. Approximately one third of these affected have only hypercholesterolaemia, one third only hypertriglyceridaemia and one third have both. Patients with familial combined hyperlipidaemia may have apolipoprotein-B-rich LDL; a measurement of plasma apolipoprotein B thus may allow the physician to distinguish between this disorder and familial hypertriglyceridaemia. Patients with a variant of this disorder have normal LDL-cholesterol levels but increased concentrations of LDL-apo-B (hyperapobetalipoproteinemia). Approximately one third of kindred members may have several different types of hyperlipoproteinaemia. Approximately one third of these affected have only hypercholesterolaemia, one third only hypertriglyceridaemia and one third have both.

Familial hypertriglyceridaemia

Familial hypertriglyceridaemia is quite common in adulthood but very rare during childhood. Individuals affected with this disorder usually have elevated plasma triglyceride levels between 200 and 500 mg dl$^{-1}$. Many of them are obese, thus, weight reduction and carbohydrate restriction form the therapy of choice and in most cases normalization of their triglyceride levels can be achieved.

Severe forms of hypertriglyceridaemia can also be treated easily by reduction of carbohydrate intake.

In conclusion, it should be emphasized that the detection of hyperlipoproteinaemias which are associated with an increased risk for cardiovascular diseases must be primarily a pediatric objective: first, all attempts should be made to detect the frequent forms of familial hypercholesterolaemia, in particular from families with a cardiovascular history or known hypercholesterolaemia. Today there is enough evidence that starting the treatment of affected children from two years onwards has a beneficial effect in terms of avoiding or delaying the development of clinically manifest atherosclerosis.

References


