SHORT COMMUNICATION

Changes in cholesterol metabolism with dietary cholesterol in children with familial hypercholesterolaemia

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Summary

1. Possible defects in cholesterol metabolism were sought in children with familial hypercholesterolaemia.

2. In nine affected children (eight heterozygotes and one homozygote) and in five healthy children, cholesterol synthesis and bile acid synthesis were determined from the excretion of steroids in the faeces during a low cholesterol diet. Cholesterol synthesis of $10.1 \pm 4.4$ mg day$^{-1}$ kg$^{-1}$ in the hypercholesterolaemic children was similar to that in these and other normal children. Mean bile acid synthesis of $4.0 \pm 2.1$ mg day$^{-1}$ kg$^{-1}$ also resembled normal values though three severely affected heterozygotes excreted substantially less.

3. The response to 4 weeks' additional 450 mg of dietary cholesterol/day led to variable changes in the plasma cholesterol and in the sterol balance. On average the affected children showed a rise in plasma cholesterol which resembled that in healthy subjects. The sterol balance fell in most, suggesting a reduction in cholesterol synthesis, which is the normal response to dietary cholesterol.

4. The response to dietary cholesterol was therefore at least qualitatively similar in the hypercholesterolaemic children to that reported in healthy subjects.

Key words: cholesterol, hypercholesterolaemia.

Introduction

Few studies of cholesterol metabolism have been carried out in children with familial hypercholesterolaemia; although a few children with the heterozygous form of the disease have apparently not shown any abnormality in sterol metabolism (Carter, Connor & Bhattacharyya, 1975; J. H. Zavoral, W. Krivit, R. D. Ellefson & B. A. Kotke, personal communication), the findings in the much less common homozygous form have been contradictory in that both reduced bile acid synthesis (Carter et al., 1975) and increased cholesterol turnover (Bilheimer, Goldstein, Grundy & Brown, 1975) have been reported. In adults, the synthesis, turnover and absorption of cholesterol have generally been found to be normal (Nestel, 1974; Myant, 1971), the major abnormality being that of reduced clearance of low-density lipoproteins (Langer, Strober & Levy, 1972; Brown & Goldstein, 1974) and possibly reduced excretion of bile acids (Einarsson, Hellström & Kallner, 1974; Nestel & Hunter, 1974).

We report further studies of children with familial hypercholesterolaemia: cholesterol and bile acid excretion have been measured during two dietary periods that differed in cholesterol content.

Methods

Subjects

Nine hypercholesterolaemic children with strong family histories of hypercholesterolaemia and five normolipidaemic children aged 5–18 years were studied. All were of normal body height and weight.
for their ages. Cholesterol-lowering drugs were suspended for 6 weeks beforehand. One child (no. 9) had the rare homozygous form of the disease.

**Diets**

Studies were carried out outside the hospital. Extensive instruction was given and complete food diaries were obtained beforehand so that test diets conformed closely to usual eating habits. Supervision was maintained by frequent visits to the home, when all fat- and cholesterol-containing foods were delivered in pre-weighed packages. Further diaries of food consumed were kept throughout the studies, which comprised two dietary periods each of 4 weeks' duration, although in five subjects (nos. 8, 9, 12, 13 and 14) only the low cholesterol diet was studied. The latter provided 80-190 mg of cholesterol daily. The cholesterol intake was then increased by 450 mg/day from egg yolk. The polyunsaturated to saturated fatty acid ratio in each diet was 2.0.

Fasting plasma samples were collected throughout the study for cholesterol and triglyceride estimations. Sterol balances were determined on pools of faeces collected during the final 8 days of each period by methods described by Miettinen, Ahrens & Grundy (1965) and Grundy, Ahrens & Miettinen (1965), which quantify the excretion of neutral and acidic steroids. The daily sterol balance is calculated as the difference between total steroid excretion and the intake of cholesterol. Chromium oxide capsules were used to correct for differences in faecal flow.

**Results**

The changes in the plasma cholesterol as a result of adding 450 mg of cholesterol to the diet/day are shown in Table 1. Although there was a mean increase of 0.39 mmol/l, there were variations in individual responses: in two the plasma cholesterol even fell slightly and in only one (no. 6) did the observed rise in the plasma cholesterol substantially exceed the expected rise (derived from equations obtained in studies of adults (Hegsted, McGandy, Myers & Stare, 1965)).

The sterol balances are also shown in Table 1. In the hypercholesterolaemic children the mean sterol balance during the low cholesterol periods (approximating endogenous cholesterol synthesis) was $10.1 \pm 4.4$ (SD) mg day$^{-1}$ kg$^{-1}$, similar to that

<table>
<thead>
<tr>
<th>Subject no. (age in years)</th>
<th>Cholesterol intake (mg/day)</th>
<th>Serum cholesterol (mmol/l)</th>
<th>Neutral steroid excretion (mg/day)</th>
<th>Acidic steroid excretion (mg/day)</th>
<th>Total steroid excretion (mg/day)</th>
<th>Cholesterol balance (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (8)</td>
<td>130</td>
<td>8.76</td>
<td>319</td>
<td>147 (6.1)</td>
<td>466</td>
<td>336</td>
</tr>
<tr>
<td>2 (6)</td>
<td>580</td>
<td>8.63 (-0.13)</td>
<td>322</td>
<td>110 (4.6)</td>
<td>432</td>
<td>-148</td>
</tr>
<tr>
<td>3 (5)</td>
<td>120</td>
<td>7.11</td>
<td>271</td>
<td>134 (6.4)</td>
<td>405</td>
<td>280</td>
</tr>
<tr>
<td>4 (5)</td>
<td>120</td>
<td>7.81 (+0.70)</td>
<td>462</td>
<td>110 (5.8)</td>
<td>318</td>
<td>198</td>
</tr>
<tr>
<td>6 (7)</td>
<td>135</td>
<td>9.35</td>
<td>176</td>
<td>47 (2.0)</td>
<td>223</td>
<td>88</td>
</tr>
<tr>
<td>7 (18)</td>
<td>130</td>
<td>9.20 (-0.15)</td>
<td>313</td>
<td>75 (3.3)</td>
<td>388</td>
<td>-197</td>
</tr>
<tr>
<td>8 (5)</td>
<td>110</td>
<td>9.77</td>
<td>190</td>
<td>66 (2.8)</td>
<td>256</td>
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</tr>
<tr>
<td>9 (5)</td>
<td>10.21 (+0.44)</td>
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<td>375</td>
<td>98 (1.7)</td>
<td>573</td>
<td>443</td>
</tr>
<tr>
<td>10 (10)</td>
<td>10.11 (+0.26)</td>
<td>532</td>
<td>8.32 (-0.18)</td>
<td>96 (1.8)</td>
<td>922</td>
<td>126</td>
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<tr>
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<td>210</td>
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<td>12 (11)</td>
<td>145</td>
<td>3.50 (+0.26)</td>
<td>308</td>
<td>73 (4.0)</td>
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</tr>
<tr>
<td>13 (12)</td>
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<td>503</td>
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<td>613</td>
<td>468</td>
</tr>
<tr>
<td>14 (12)</td>
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<td>4.97</td>
<td>545</td>
<td>137 (2.9)</td>
<td>682</td>
<td>542</td>
</tr>
</tbody>
</table>

TABLE 1. Serum cholesterol concentrations and cholesterol and bile acid metabolism
The mean values for acidic steroid excretion were in the normal children (11.5 ± 2.9 mg day⁻¹ kg⁻¹). The mean values for acidic steroid excretion were also similar: 4.0 ± 2.1 mg day⁻¹ kg⁻¹ in hypercholesterolaemic children and 3.8 ± 1.4 mg day⁻¹ kg⁻¹ in normolipidaemic children. However, in three of the nine hypercholesterolaemic children (nos. 5, 7 and 8), who were the most severely affected heterozygotes, acidic steroid excretion was only half of that seen in the others. Acidic steroid excretion was on average similar during the high and low cholesterol diets. Neutral steroid excretion increased on the high cholesterol diet, which represented unabsorbed dietary as well as re-excreted cholesterol. The sterol balance, which in the steady state would be equivalent to cholesterol synthesis, was substantially lower on the high cholesterol diet (264 ± 121 mg/day on low, and 22 ± 197 mg/day on high, cholesterol diet). However, the degree of apparent suppression of cholesterol synthesis varied markedly: in six there were substantial reductions in sterol balance, in subjects nos. 5, 7 and 8 (who showed the highest increase in plasma cholesterol concentration) the sterol balance rose. Though negative values for sterol balance were observed in four children, indicating net retention of dietary cholesterol with increased cholesterol consumption, this did not unduly raise the plasma cholesterol concentration.

**Discussion**

Although the major genetic defect in familial hypercholesterolaemia lies in the catabolism of low-density lipoprotein protein (Brown & Goldstein, 1974), there is evidence for reduced bile acid excretion that may be secondary to diminished low-density lipoprotein removal (Einarsson et al., 1974; Nestel & Hunter, 1974). The absorption, synthesis and turnover of cholesterol have, however, generally been found to be in the normal range (Nestel, 1974), though a single child with homozygous hypercholesterolaemia was reported to have shown increased cholesterol turnover (Bilheimer et al., 1975).

Comparison of the present data with those obtained in children by others (Carter et al., 1975; J. H. Zavoral et al., personal communication; Huang, Rodriguez, Woodward & Nichols, 1976) and ourselves (Nestel, Poyser & Boulton, 1978) shows that, on average, acidic steroid excretion in the hypercholesterolaemic children was in the normal range. Nevertheless, the three most severely affected children (nos. 5, 7 and 8) showed acidic steroid excretion of 2.0 mg day⁻¹ kg⁻¹ or less, suggesting that, as in some adults, diminished synthesis of bile acids may occur.

The values for sterol balance on the low cholesterol diet (cholesterol synthesis) in the hypercholesterolaemic children (Table I) resembled that reported in adults eating little cholesterol (Grundy & Ahrens, 1969, 1970; Quintao, Grundy & Ahrens, 1971; Whyte, Nestel & MacGregor, 1977). The child with homozygous hypercholesterolaemia showed normal values for steroid excretion.

The responses to dietary cholesterol were variable, resembling findings in normal infants (Nestel et al., 1978) and adults (Quintao et al., 1971; Nestel & Poyser, 1976). As previously demonstrated in adults, increased intakes of cholesterol commonly lead to a reduction in sterol balance, interpreted (in the steady state) as suppression of cholesterol synthesis. Although one criterion of a steady state, a constant plasma cholesterol concentration, was demonstrable in the present study (two measurements made during the final 8 days of the high-cholesterol diet showed similar values), the finding of retention of dietary cholesterol in some children showed that a steady state had not been reached in all. Assuming 50% cholesterol absorption and proportional suppression of cholesterol synthesis, sterol excretion should have risen during the high cholesterol diet by an average of 225 mg/day (50% of 450 mg), a value similar to that actually observed for the group (208 mg/day), though the individual values fluctuated considerably.

The sterol balance fell substantially with cholesterol feeding in four of seven hypercholesterolaemic children, suggesting that cholesterol synthesis was at least partly inhibited. As in our previous studies in adults (Nestel & Poyser, 1976), failure to reduce sterol balance (indicating inadequate suppression of synthesis and/or increased re-excretion of cholesterol, a second metabolic response to cholesterol feeding) could result in a greater than expected rise in the plasma cholesterol concentration and this was observed in child no. 6.

The nature of the changes in the sterol balance with added dietary cholesterol seen in the hypercholesterolaemic children therefore resembled the changes seen in normolipidaemic children and adults. They also reflected the variable response in the plasma cholesterol concentration to the high cholesterol diet, which, however, on average showed a rise in the cholesterol level of 0.39 ±
0.12 mmol/l that was only a little less than the expected change of 0.52 mmol/l (from the equation of Hegsted et al., 1965).

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References


