Regulation of Serum Cholesterol Level in Middle-Aged and Elderly Men

Relation of Cholesterol Absorption and Synthesis to Lipoprotein Metabolism

Helena Gylling, Timo Strandberg, Reijo Tilvis, Tatu A. Miettinen

Abstract The aim of the present study was to investigate cholesterol absorption and cholesterol and bile acid synthesis and relate these values to kinetics of low-density lipoprotein (LDL) apoprotein (apo) B in 50- and 75-year-old men to find out why and by which mechanism serum cholesterol level decreases with advancing age under normal home-living conditions. The daily caloric, fat, and cholesterol intakes were lower in the 75-year-old men because the physiological requirements of daily energy are reduced in old age. However, absolute body weight was identical in the two groups, indicating isocaloric energy intake. Serum levels of total and LDL cholesterol were insignificantly lower but those of LDL apo B significantly lower, so that the LDL cholesterol/apo B ratio was higher in the elderly men. The mean reduction of LDL apo B by 26% (P<.05) in the old men was associated with a 30% (P<.05) decrease in transport rate (TR) and a 3% (P=NS) decrease in removal rate (FCR) for LDL apo B. However, at the comparable apo B levels, both TR and FCR for apo B were significantly lower in the old than in the younger men.

In population-based epidemiological studies, serum total and low-density lipoprotein (LDL) cholesterol increases in males up to 64 years of age, followed by a decline for unknown reasons. In the Finnish male population the values tend to decrease after as early as 50 years of age. The effect of aging on LDL metabolism has been evaluated in kinetic studies including young, middle-aged (55±8 years, mean±SD), and old (68±2 years) men. In these studies fractional catabolic rate (FCR) of LDL apoprotein (apo) B was diminished by age. However, LDL cholesterol was significantly higher in the elderly; accordingly, results did not solve the mechanism of age-associated decline in LDL cholesterol. Because of the well-known association of LDL cholesterol with coronary artery disease and the high prevalence of coronary artery disease in the aged, it was important to expand the metabolic studies of LDL to include the elderly.

Cholesterol absorption efficiency, bile acid synthesis, fecal neutral and total sterol excretion, and cholesterol turnover but not synthesis were reduced in the elderly men. Cholesterol absorption efficiency was positively correlated with LDL cholesterol and apo B, TR for LDL apo B, and dietary fat, cholesterol, and energy intakes and inversely with cholesterol synthesis, so that at the comparable absorption efficiency and low absolute absorption, cholesterol synthesis was surprisingly low in the older men, lower than in the younger men. Thus, low LDL level in the old men is contributed by reduced cholesterol absorption, which insufficiently stimulates cholesterol synthesis, and is related to low LDL apo B transport and to low but isocaloric food intake. LDL level is mainly influenced by reduced LDL apo B transport rate, the contribution of decreased removal rate being less consistent. (Arterioscler Thromb. 1994;14:694-700.)

Key Words • cholesterol • LDL • turnover • elderly • cholesterol absorption • cholesterol synthesis

Aging affects the concentration and metabolism of cholesterol in the whole body. Age-associated atherosclerotic lesions are rich in cholesterol. In addition, in several tissues, eg, muscles, adipose tissue, skin, and tendons, the concentration of cholesterol is markedly increased by age. These findings suggest impaired elimination of cholesterol from the body. Thus, age-related changes in the formation and composition of bile are important because bile is the major excretory pathway of body cholesterol. The proportion of cholesterol in bile is elevated by age, resulting in increased lithogenicity and risk of stone formation. Supersaturation of bile in the aged may reflect an increased absolute or relative rate of hepatic secretion of cholesterol or a decreased rate of bile acid synthesis. In fact, both normal and decreased bile acid turnover and synthesis have been observed in aged human subjects, but daily biliary bile acid or cholesterol secretion and fecal elimination, absorption, and synthesis of cholesterol have not been measured.

In previous studies cholesterol absorption efficiency was involved in the regulation of cholesterol homeostasis and LDL cholesterol concentration and metabolism in middle-aged men. In these studies cholesterol absorption efficiency was positively related to LDL cholesterol levels and inversely to FCR for LDL apo B and to overall cholesterol synthesis. At the moment it is not known whether cholesterol absorption efficiency is related to cholesterol metabolism or kinetics of LDL.
apo B in elderly subjects. Thus, our first aim was to
study cholesterol absorption efficiency, the whole-body
cholesterol metabolism, and bile acid synthesis in 50-
and 75-year-old men to find out the effect of age on
these functions and whether these variables are related
to decreases of serum cholesterol with advancing age.
Second, we investigated LDL kinetics to find out
whether cholesterol absorption and metabolism are
similarly related to lipoprotein metabolism in these two
groups and whether the lipoprotein kinetics is related to a
mechanism by which age regulates serum cholesterol
level. So, in addition to serum lipids, lipoproteins, and
cholesterol absorption, we measured fecal elimination
of cholesterol as bile acids and neutral sterols, choles-
terol synthesis=(fecal neutral sterols+bile acids)-dietary
cholesterol absorbed=cholesterol absorption efficiency x dietary cho-
sterol synthesis=(fecal neutral sterols+bile acids); dietary choles-
terol absorption efficiency x dietary cholesterol; dietary choles-
terol absorbed=cholesterol absorption efficiency x dietary chole-
terol; total cholesterol absorbed=cholesterol absorption efficiency x total cholesterol flux; cholesterol turnover or transport=fecal endogenous neutral sterols+fecal bile acids; cholesterol synthesis=(fecal neutral sterols+bile acids); dietary cholesterol.

For the turnover studies autologous LDL from hydrated
densities 1.019 to 1.063 g/mL was collected, resuspended, and
ultracentrifuged to remove contaminating proteins. Approxi-
mately 1.0 to 1.5 mg of LDL was labeled with \(^{125}\text{I}\) by the iodine
monochloride method.\(^{22}\) Ninety-eight percent of the label in
LDL was recovered in LDL apo B. The labeled LDL was
mixed with 5% human serum albumin, filtered through pyro-
gen-0.22-μm Millipore filters, and injected intravenously
into the subjects. After the injection, 10-mL blood samples
were collected and counted for radioactivities over a 14-day
period. The die-away curves were constructed in whole plasma
for the radioactivities, of which FCRs were determined by use
of a two-pool model.\(^{23}\) The TR for LDL apo B was calculated by multiplying the pool sizes of corresponding apoproteins by
the FCR. Pool size was calculated from a plasma pool of 4.5% of
body weight.
The data are presented as mean±SEM. The significance of
differences was analyzed with two-tailed Student’s t test and
Fisher’s exact \(\chi^2\) test. Correlations were tested by calculating
the Pearson’s correlation coefficient. Regression analyses
were constructed for comparison of kinetic and metabolic data, and
regression coefficients were estimated. A value of \(P<.05\) was
considered statistically significant.

Results

Dietary Intakes

Fat intake (36.3±1.7% versus 39.2±1.1% of calories) and
the ratio of polyunsaturated to saturated fatty acids (0.32±0.07 versus 0.33±0.03) were similar in the 75-
and 50-year-old men, while the intakes of cholesterol (273±22 versus 480±26 mg/d), fat (71±5 versus 105±5
g/d), and energy (35±2 versus 23±1 kcal/kg) were significantly higher in the younger than in the older men

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Height, m</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Apo E phenotype</td>
</tr>
<tr>
<td>3/3</td>
</tr>
<tr>
<td>4/3</td>
</tr>
<tr>
<td>Dietary calories, kcal/kg/d</td>
</tr>
<tr>
<td>Fat intake, g/kg/d</td>
</tr>
<tr>
<td>Fat intake, % of calories</td>
</tr>
<tr>
<td>P/S ratio in dietary fat</td>
</tr>
<tr>
<td>Dietary cholesterol, mg/kg/d</td>
</tr>
</tbody>
</table>

Apo indicates apoprotein; P/S, polyunsaturated to saturated. Values are mean±SEM. *P<.05.
TABLE 2. Serum Lipids and Lipoproteins

<table>
<thead>
<tr>
<th>Variables, mmol/L</th>
<th>75-Year-Old Men (n=11)</th>
<th>50-Year-Old Men (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>5.43±0.17</td>
<td>5.79±0.18</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>0.41±0.07</td>
<td>0.39±0.04</td>
</tr>
<tr>
<td>IDL cholesterol</td>
<td>0.18±0.03</td>
<td>0.25±0.02</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.51±0.21</td>
<td>3.88±0.17</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.33±0.15</td>
<td>1.36±0.06</td>
</tr>
<tr>
<td>HDL₂ cholesterol</td>
<td>0.71±0.14</td>
<td>0.49±0.06</td>
</tr>
<tr>
<td>HDL₃ cholesterol</td>
<td>0.45±0.02*</td>
<td>1.03±0.06</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>1.47±0.17</td>
<td>1.24±0.10</td>
</tr>
<tr>
<td>VLDL triglycerides</td>
<td>0.97±0.15*</td>
<td>0.58±0.06</td>
</tr>
<tr>
<td>IDL triglycerides</td>
<td>0.09±0.01</td>
<td>...</td>
</tr>
<tr>
<td>LDL triglycerides</td>
<td>0.27±0.02*</td>
<td>0.36±0.02</td>
</tr>
<tr>
<td>HDL triglycerides</td>
<td>0.14±0.01</td>
<td>0.15±0.01</td>
</tr>
</tbody>
</table>

VLDL indicates very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean±SEM.

*(P<.05.

(Table 1). However, the similar body weight, height, and body mass index indicated that both groups were eucaloric and in a steady state during the metabolic studies.

Serum Lipids

Table 2 shows that serum total and lipoprotein cholesterol and triglyceride levels were otherwise similar in the 75- and 50-year-old men except that HDL₃ cholesterol and LDL triglycerides were significantly lower and very-low-density lipoprotein triglycerides higher in the older men. Intermediate-density lipoprotein tended to be decreased in the aged. LDL apo B was lower (Table 3) and the LDL cholesterol/apo B ratio was higher in the elderly, suggesting that the LDL particle was less dense.

Turnover Studies

LDL apo B concentration was significantly lower in the elderly because of a lower TR of LDL apo B (Table 3) and insignificantly decreased FCR for LDL apo B. In the older men LDL apo B was 26%, TR 30%, and FCR only 3% lower than in the younger men. In the elderly men LDL cholesterol and apo B contents were related to TR (Fig 1, lower panels) but not to FCR (Fig 1, upper panels). In the younger men LDL apo B was regulated by its catabolism and TR, whereas the LDL cholesterol level was related only to FCR (Fig 1, upper panel). The mean FCR and TR for the similar LDL apo B concentrations were lower and the corresponding LDL cholesterol/apo B values were higher in the elderly than in the younger men (Fig 1 and Table 4). Thus, the 21% lower TR and 10% lower removal rate of LDL apo B in the old men kept the LDL cholesterol and apo B levels similar to those in the younger men. The LDL cholesterol/apo B ratio was insignificantly related to FCR but significantly (r = -.506) to TR for LDL apo B.

Intestinal Cholesterol Fluxes and Bile Acid and Cholesterol Synthesis

Cholesterol absorption efficiency, bile acid synthesis, and fecal neutral and total steroid excretion were significantly reduced in the elderly men (Table 5). Calculations showed that biliary and total cholesterol fluxes into the intestine, absolute total and dietary cholesterol absorption, and cholesterol turnover but not synthesis were also lower in the older men. It is interesting to note that despite markedly reduced relative and absolute absorption of cholesterol, cholesterol synthesis tends even to be reduced in the older men. Fig 2 shows that the correlation between cholesterol absorption and synthesis was significant in both groups but that at the comparable absorption efficiency cholesterol synthesis was lower in the older than younger men. The amount of dietary cholesterol and fat and energy intake were not related to any variables of cholesterol metabolism separately in the two groups. In the combined groups (n=45) cholesterol absorption efficiency was significantly related to the daily intakes of energy (r = -.332), dietary fat (r = -.322), and cholesterol (r = -.318) (Table 6). Dietary calories and cholesterol but not fat were also weakly related to bile acid (but not cholesterol) synthesis (r = -.337 and -.327, respectively).

Lipoproteins and Cholesterol Metabolism

In the combined groups the LDL cholesterol and apo B levels were significantly related to FCR (r = -.501 and -.417) and TR (r = -.369 and -.787) for LDL apo B (Fig 1) and to cholesterol absorption (Table 6). Cholesterol synthesis, in turn, was positively correlated with FCR for LDL apo B (r = .348). Dietary fat intake was significantly related to LDL apo B concentration and TR for LDL apo B. Virtually similar associations were found separately in the two age groups as in Table 6 except that cholesterol synthesis and transport were positively related to TR for LDL apo B (r = .717 and .682) only in the elderly men and to FCR for LDL apo B in the middle-aged men (r = .342 and .356, respectively).

Discussion

The present study evaluating the age-related lowering of serum cholesterol investigated cholesterol absorption and metabolism and simultaneously LDL apo B kinetics for the first time in a population-based study of men at 50 and 75 years of age. Since the lipid levels are determined to some extent by the dietary conditions the subjects have been used to at home all their lives, the present studies were performed under home conditions with unchanged dietary habits. Therefore, the dietary conditions represent a steady-state situation and, despite the outpatient basis, had a fairly similar composi-
tion in the two groups. The lower calorie intake in the old men, 23 versus 33 kcal · d⁻¹ · kg body wt⁻¹ in the younger men, was physiological, however, since the requirements of daily energy are reduced in old age by about 1% per year of age.³⁰ Despite the low calorie intake of the older men, the relative and absolute body weights were identical in the two groups, indicating isocaloric energy intake. The amounts of daily dietary fat and cholesterol intakes were lower in the elderly, yet the relative dietary fat intake, type of fat, and plant sterol consumption were identical.

According to earlier absorption studies,¹⁴⁻¹⁷,³¹,³² the low cholesterol intake should not explain the reduced absorption efficiency of cholesterol in the older men because, in contrast to the positive correlation between absorption and intake (Table 6), addition of cholesterol to the diet is usually considered to reduce absorption efficiency.¹⁶,³³ However, the positive correlation of cholesterol absorption with dietary fat intake, observed also in a normal population,¹⁵ might indicate that the low absolute fat intake of the old men reduced cholesterol absorption efficiency. A reduction of dietary fat and cholesterol intake in younger men reduced cholesterol absorption efficiency.¹⁵ In addition, the low bile acid synthesis may have decreased intestinal micellar formation and subsequent absorption through reduced intestinal bile acid concentration in the elderly men. Dietary plant sterols, which in amounts present in normal diets also inhibit cholesterol absorption,¹⁴ were similar in the two groups. The reduced calorie intake of the elderly men, although isocaloric to the body requirements, may have decreased cholesterol absorption because the latter was positively correlated with the energy intake. On the other hand, low energy and food intake may reduce intestinal mass and diminish gut motility, a factor known, in fact, to increase cholesterol absorption.³⁴ Finally, it is possible that an age-dependent impairment of intestinal mucosal function could be a contributory factor, even though the normal fecal fat indicates that the general absorptive function is impaired only to a limited degree, if at all. The low cholesterol absorption in the elderly men modifies cholesterol and lipoprotein metabolism and may actually be a major factor for the age-related decrease in serum cholesterol.

### Table 4. Relative Lipoprotein and Kinetic Values in Old and Middle-Aged Men With Similar and Higher Low-Density Lipoprotein Apoprotein B Levels

<table>
<thead>
<tr>
<th>Variables</th>
<th>75-Year-Old Men (n=11)</th>
<th>Low Apo B⁺ (n=16)</th>
<th>High Apo B⁺ (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL apo B, mg/dL</td>
<td>100±7</td>
<td>109±5</td>
<td>158±2t</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>100±6</td>
<td>93±6</td>
<td>124±5t</td>
</tr>
<tr>
<td>LDL cholesterol/apo B</td>
<td>100±2</td>
<td>87±5</td>
<td>79±5t</td>
</tr>
<tr>
<td>FCR LDL apo B, pools/d</td>
<td>100±3</td>
<td>112±4t</td>
<td>97±4</td>
</tr>
<tr>
<td>TR LDL apo B, mg · kg⁻¹ · d⁻¹</td>
<td>100±6</td>
<td>126±3t</td>
<td>155±4t</td>
</tr>
</tbody>
</table>

Apo indicates apoprotein; LDL, low-density lipoprotein; FCR, fractional catabolic rate; and TR, transport rate. Mean values of 75-year-old men in Table 3 were converted to 100, to which the respective mean values of 50-year-old men were related.

*Represents values of the men with less than or equal to the highest (81 mg/dL) LDL apo B level for 75-year-old men in Fig 1.

†Represents values of the men with greater than the highest (81 mg/dL) LDL apo B level for 75-year-old men in Fig 1.

‡P<.05 from older men.
Table 5. Cholesterol Absorption, Fecal Sterols, and Cholesterol Metabolism

<table>
<thead>
<tr>
<th>Variables</th>
<th>75-Year-Old Men (n=11)</th>
<th>50-Year-Old Men (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol absorption, %</td>
<td>34.4±2.9*</td>
<td>45.9±1.4</td>
</tr>
<tr>
<td>Fecal bile acids, mg · kg⁻¹ · d⁻¹</td>
<td>4.4±0.4*</td>
<td>5.9±0.4</td>
</tr>
<tr>
<td>Neutral sterols, mg · kg⁻¹ · d⁻¹</td>
<td>8.1±0.6*</td>
<td>9.9±0.4</td>
</tr>
<tr>
<td>Total sterols, mg · kg⁻¹ · d⁻¹</td>
<td>12.5±0.9*</td>
<td>15.8±0.6</td>
</tr>
<tr>
<td>Plant sterols, mg · kg⁻¹ · d⁻¹</td>
<td>3.5±0.6</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>Dietary cholesterol, mg · kg⁻¹ · d⁻¹</td>
<td>3.5±0.2*</td>
<td>6.0±0.3</td>
</tr>
<tr>
<td>Total cholesterol flux, mg · kg⁻¹ · d⁻¹</td>
<td>12.3±0.6*</td>
<td>18.4±0.6</td>
</tr>
<tr>
<td>Biliary cholesterol flux, mg · kg⁻¹ · d⁻¹</td>
<td>8.8±0.8*</td>
<td>12.4±0.7</td>
</tr>
<tr>
<td>Dietary cholesterol absorbed, mg · kg⁻¹ · d⁻¹</td>
<td>1.2±0.1*</td>
<td>2.7±0.2</td>
</tr>
</tbody>
</table>
| Total cholesterol flux = fecal neutral sterols/(1 − cholesterol absorption efficiency); biliary cholesterol flux = total cholesterol flux − dietary cholesterol; dietary cholesterol absorbed = cholesterol absorption efficiency × dietary cholesterol; total cholesterol absorbed = cholesterol absorption efficiency × total cholesterol flux; biliary cholesterol transport = fecal endogenous neutral sterols + fecal bile acids; and cholesterol synthesis = (fecal neutral sterols + bile acids) − dietary cholesterol. Values are mean±SEM. *P<.05.

Cholesterol absorption efficiency was positively correlated with LDL cholesterol and apo B levels and negatively with cholesterol synthesis, indicating that cholesterol absorption regulated cholesterol metabolism independently of age. Similar results have been attained in young men. However, reduced return of intestinal cholesterol to the liver apparently weakly stimulated cholesterol synthesis in the old men because, for instance, at a 40% absorption in Fig 2, cholesterol synthesis was 6 mg · kg⁻¹ · d⁻¹ in the old men and about 14 mg · kg⁻¹ · d⁻¹ in the younger men. Under these conditions hepatic sterol balance is maintained by reduced total and LDL cholesterol levels were observed in octogenarians. The age-related decrease in serum cholesterol appears to be slow, as shown in a 12-year follow-up study of 65-year-old subjects, in whom serum cholesterol was actually fairly constant up to 75 years of age, after which it declined nonsignificantly by 6%. In most previous LDL kinetic studies the oldest subjects studied were less than 65 years of age, and in only one study, four subjects were more than 70 years of age. In the large review by Miller, there was only a small difference in the individual FCR values between age groups from 40 to 49 to 60 to 69 years, and, in fact, 40 years of age seemed to be a clear-cut cutpoint for FCR values, which were definitely higher before than after this age. Our present results show reduced LDL receptor activity in the elderly at LDL apo B levels similar to those of the younger men. In in vitro studies, LDL receptor activity is unaffected by age in lymphocytes and fibroblasts.

Advancing age increased the LDL cholesterol/apo B ratio, which could be explained by the low TR and insignificantly diminished FCR for LDL apo B so that the LDL particles become cholesterol rich. These particles could bring sufficient cholesterol to the liver even at a limited receptor activity. A low TR for LDL apo B has been suggested to indicate enhanced receptor activity when effective receptor-mediated removal of remnant particles lowers LDL apo B transport. However, when the two groups were selected to have similar LDL apo B levels, both the removal and transport of LDL apo B were significantly reduced in the elderly, indicating that receptor activity was low but sufficiently effective for cholesterol-rich LDL particles to keep LDL cholesterol unchanged at low LDL apo B transport. It can be expected that with more advanced age the transport rate is even more reduced, resulting finally in significantly decreased LDL cholesterol levels as well.

It is interesting to note that, similar to our results, unaltered total and LDL cholesterol levels were observed in octogenarians. The age-related decrease in serum cholesterol appears to be slow, as shown in a 12-year follow-up study of 65-year-old subjects, in whom serum cholesterol was actually fairly constant up to 75 years of age, after which it declined nonsignificantly by 6%. In most previous LDL kinetic studies the oldest subjects studied were less than 65 years of age, and in only one study, four subjects were more than 70 years of age. In the large review by Miller, there was only a small difference in the individual FCR values between age groups from 40 to 49 to 60 to 69 years, and, in fact, 40 years of age seemed to be a clear-cut cutpoint for FCR values, which were definitely higher before than after this age. Our present results show reduced LDL receptor activity in the elderly at LDL apo B levels similar to those of the younger men. In in vitro studies, LDL receptor activity is unaffected by age in lymphocytes and fibroblasts.

In addition to low cholesterol absorption efficiency, bile acid synthesis was decreased by age in agreement with some but not all previous studies. Since bile acid synthesis is positively related to transport (r=0.761; P<0.001) and synthesis (r=0.634; P<0.001) of cholesterol, the more or less consistent decrease of the two latter variables could have contributed to the reduced bile acid synthesis in the elderly. Low bile acid synthesis may also character-
ize the aging liver, a factor related to the weak positive association of bile acid synthesis with low calorie and cholesterol intake. The findings indicate that, even though cholesterol synthesis data suggested that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity was inconsistently decreased, bile acid synthesis was clearly decreased in the old men. This might indicate that consumption of hepatic hydroxysteroids, known to regulate HMG-CoA and apo B receptor activities,40-42 to bile acids, is also decreased, enhancing their content in the liver. A clinical consequence of the low bile acid output may be constipation, a general complaint of the elderly, known to be worsened by low bile acid output.43

The present findings show that the old age–related decrease in LDL cholesterol is associated with reduced relative and absolute absorption of cholesterol, low cholesterol synthesis and turnover, a low FCR for LDL apo B and cholesterol levels, a markedly reduced TR for LDL apo B, low bile acid synthesis, and a reduced biliary cholesterol secretion. It is debatable whether the low cholesterol absorption and bile acid synthesis are related to reduced though isocaloric energy and nutrient intakes in the elderly. It can be speculated, however, that the resulting reduction of 7a-hydroxylase activity might have reduced bile acid synthesis from hydroxysterols, increased cholesterol synthesis and turnover, a low FCR for LDL output.43

Acknowledgments
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