Effects of Dietary Medium-Chain Triacylglycerols on Serum Lipoproteins and Biochemical Parameters in Healthy Men

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The objective of this study was to investigate effects of dietary medium-chain triacylglycerols (MCTs) on serum lipid levels, liver function, and hepatic fat accumulations in healthy men. Eleven subjects consumed 2200–2600 kcal daily, of which 70–80 g was fat; the fat included 40 g of MCTs or else 40 g of long-chain triacylglycerols (blended vegetable oil). The diet was followed for 4 weeks in this controlled double-blind study. At the end of the experiment, significant differences were not found in the concentrations of serum total cholesterol, very low density lipoprotein cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol between the groups. Serum triglyceride levels were not significantly different in the groups. Adverse effects from ingestion of MCTs on liver functions, the liver-to-spleen ratio on computed tomography (an index of fatty liver), or results of blood tests were not seen. The results suggest that the long-term effects of dietary MCTs on serum cholesterol were similar to those of unsaturated fatty acids found abundantly in vegetable oil, and that consumption of MCTs in the amount of 40 g/day for a month does not cause liver fat accumulation or liver dysfunction.

Key words: medium-chain triacylglycerols; serum lipids; fatty liver; liver function; human

Medium-chain triacylglycerols (MCTs) are an edible oil that consists of C8 and C10 saturated fatty acids. MCTs were first used in clinical nutrition in the 1950s for dietary treatment of malabsorption syndromes caused by rapid absorption. MCTs are metabolized differently from long-chain triacylglycerols (LCTs). Studies of experimental animals have provided evidence that following diets that include MCTs leads to less body fat deposition than diets with LCTs instead. We have found that MCTs intake reduces body weight and body fat in healthy subjects with a body mass index of >23 kg/m² more than LCTs intake. These results suggest that the substitution of MCTs for LCTs in dietary fat could reduce dietary obesity if the energy intake remained constant.

Replacement of MCTs for LCTs, as in, for example vegetable oil, results in an increase in dietary saturated fatty acids, because MCTs are composed of medium-chain saturated fatty acids. Dietary saturated fatty acids increase the serum cholesterol level. However, several studies have shown that medium-chain saturated fatty acids lower cholesterol in animals. We have found that when 10 g/day of MCT was given to healthy subjects for 12 weeks, the serum total cholesterol levels did not differ significantly from that of the group that received LCTs. However, little is known about the long-term effects of the amount of dietary MCTs on blood lipid levels in healthy subjects. In this study, we investigated the effects in healthy subjects of a 4-week diet calling for 40 g/day of MCTs on serum lipids levels. Substances used for comparison were vegetable oil, blended rapeseed oil, and soybean oil.

When long-chain fatty acids are absorbed, they flow into the venous system via the lymphatic vessels and are transported to peripheral tissues such as adipose tissue and muscle. Most medium-chain fatty acids are transferred to the liver via the portal vein. Medium-chain fatty acids are easily degraded by β-oxidation in the liver, but it is important to find if a large intake of MCTs causes fatty liver. The other purpose of this study was to examine the effects on liver lipid accumulation and liver function when healthy subjects consume 40 g/day of MCTs. In

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Abbreviations: MCTs, medium-chain triacylglycerols; LCTs, long-chain triacylglycerols; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; CT, computed tomography
this study, we set total energy and fat intake at 2200–2600 kcal and 70–80 g/day, on the basis of the 5th Recommended Dietary Allowance for the Japanese.\textsuperscript{13} We set MCTs intake as half or more of total fats by weight.

**Materials and Methods**

**Subjects.** The study subjects were 22 Japanese men aged from 27 to 51 y. All subjects were generally healthy and were without diabetes, hypertension, and hyperlipidemia. Body weight, height, energy intake, fat intake, and daily activity were investigated before the study started. The characteristics of the subjects before the experiment are shown in Table 1. The daily activity level of most of the subjects was 1 (mild) or 2 (medium) by the definition of the 5th Recommended Dietary Allowance for the Japanese.\textsuperscript{13} This study was done in accordance with the Helsinki Declaration of 1964, as revised in 1989, and was approved by the ethics committee of Ochanomizu University. The procedures were fully explained to all volunteers in advance, and all gave their signed informed consent before participating.

**Test diets.** MCTs were purchased commercially (Nisshin Oil Mills, Tokyo, Japan). Common edible oil, blended rapeseed oil, and soybean oil (Nisshin Oil Mills) were used as LCTs. Fatty acid compositions were found by gas-liquid chromatography system. The fatty acid compositions of MCTs and LCTs are given in Table 2. Bread containing LCTs or MCTs was prepared.

**Protocol.** The study was double-blind, and controlled. Twenty-two subjects were randomized by using a personal computer and assigned to one of the diet groups. The subjects were asked to consume 2200–2600 kcal/day energy including 70–80 g/day total fat (24.2–32.7 energy percent), and to keep their daily exercise at a fixed level during the 4-week experiment.

Before starting the study, all subjects were given thorough instructions in dietary regulation. The special bread was to be the staple food at breakfast, lunch, or dinner, and the daily intake of the test oil was set at 40 g. The subjects were asked to consume the bread every day during the experiment. For lunch and dinner every day, the subjects consumed the same packaged meals between the 2 groups for 4 weeks under the guidance of a dietitian. The mean energy content of packaged meals for lunch and dinner was about 360 and 200 kcal, respectively. The mean total fat content of packaged meals for lunch and dinner was about 10 and 8 g, respectively. The subjects were asked to consume 150 g/day fruit and 150 g/day vegetables (together, about 150 kcal/day), and to consume side dishes or snacks containing 0–400 kcal and 0–10 g fat every day. If the subjects were unable to consume the packaged meal for any reason, they were asked to maintain the target intake of energy and total fat with food from the menu of a restaurant or fast-food outlet. If the subjects were unable to consume this alternative food because of personal circumstances, individual directions were given on the basis of the menu given in advance. The daily intake of alcoholic beverages was restricted to the equivalent of 25 ml of ethanol.

The subjects were instructed to record the contents of daily meals, snacks, and beverages in a diet diary for the test period. The diary was collected weekly to confirm meal intake, and if necessary the subject was immediately instructed to adhere more strictly to the dietary regimen. Daily intakes of energy, fat, protein, carbohydrate, and fatty acids were calculated from the diary record by the dietitian on the basis of the 4th Revision of the Standard Tables of Food Composition in Japan.\textsuperscript{14}

**Blood sampling and analyses.** At the base line and of 4 weeks, blood samples were collected from the subjects in the early morning after an overnight fast.
Table 3. Mean Daily Intake of Energy, Fat, Protein, Carbohydrate, Medium-chain Fatty Acids and Cholesterol During the 4-week Experiment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Long-chain triacylglycerol diet</th>
<th>Medium-chain triacylglycerol diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/d)</td>
<td>2330±101</td>
<td>2320±67</td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>70.0±1.6</td>
<td>70.2±1.4</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>74.8±6.8</td>
<td>74.5±5.9</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>340±21</td>
<td>336±15</td>
</tr>
<tr>
<td>Medium-chain fatty acids (g/d)</td>
<td>0.1±0.0</td>
<td>36.9±0.0</td>
</tr>
<tr>
<td>Cholesterol (mg/d)</td>
<td>266±32</td>
<td>265±30</td>
</tr>
</tbody>
</table>

* Values are the means ±SD of the data from the 11 men in each group. * Significantly different between the groups, P<0.05.

from 21:00 on the previous day. Serum cholesterol and triglycerol concentrations (very low density lipoprotein [VLDL], low density lipoprotein [LDL], and high density lipoprotein [HDL]) were assayed by agarose-gel (REP; Rapid Electrophoresis System, Helena Laboratories, Saitama, Japan). Hematological measurements were done with an SE-9000 (Sysmex, Kobe, Japan). Concentrations of ketone bodies, glucose, and lipid peroxide in serum were assayed on a JCA-BM12 automated system (JEOL, Tokyo) by enzymatic methods. Serum insulin concentrations were measured on an ARC950 (Alolka, Tokyo) by radio immunoassay. Other assays of blood samples were done on a 7170 automated system (Hitachi, Tokyo).

Quantitative assessment of liver fat. The hepatic fat content was assayed by ratio of the liver-to-spleen densities on computed tomography (CT) as described by Kato et al. Ricci et al. reported that the hepatic fat content is inversely correlated (r=-0.86, P<0.001) with the liver-to-spleen CT ratio. At the base line and 4 weeks, the subjects underwent CT scanning at Yokohama Red Cross Hospital (Yokohama, Japan) with a Pro Seed (GE Yokogawa Medical System, Tokyo).

Urinalyses. At the base line and 4 weeks, urine samples were collected just before blood sampling. Protein, glucose, ketone bodies, urobinogen, occult blood, and urine pH were assayed with URO PAPER sticks (Eiken Chemicals, Tokyo).

Statistical analyses. Values are expressed as means ±SD. The significance of differences between the groups was evaluated by the Mann-Whitney U test. Calculations were done with SPSS for Windows version 10.0J (SPSS Japan Inc., Tokyo). Differences at P<0.05 were considered significant.

Table 4. Mean Serum Cholesterol and Triglycerol Levels at the Base Line and after the 4-week Experiment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Long-chain triacylglycerol diet</th>
<th>Medium-chain triacylglycerol diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>193±38</td>
<td>206±30</td>
</tr>
<tr>
<td>4 weeks</td>
<td>165±43</td>
<td>187±30</td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>8.5±3.6</td>
<td>12.2±5.8</td>
</tr>
<tr>
<td>4 weeks</td>
<td>12.9±11.8</td>
<td>14.2±5.9</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>115.0±34.5</td>
<td>126.9±29.6</td>
</tr>
<tr>
<td>4 weeks</td>
<td>93.1±33.0</td>
<td>112.5±30.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
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<tr>
<td>Base line</td>
<td>68.7±13.7</td>
<td>66.5±16.7</td>
</tr>
<tr>
<td>4 weeks</td>
<td>58.0±7.4</td>
<td>58.4±13.2</td>
</tr>
<tr>
<td>Total triglycerol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>65±25</td>
<td>92±48</td>
</tr>
<tr>
<td>4 weeks</td>
<td>69±31</td>
<td>90±44</td>
</tr>
<tr>
<td>VLDL triglycerol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>27.7±19.4</td>
<td>48.9±48.9</td>
</tr>
<tr>
<td>4 weeks</td>
<td>32.5±20.7</td>
<td>49.4±23.4</td>
</tr>
<tr>
<td>LDL triglycerol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>23.5±7.1</td>
<td>28.3±12.3</td>
</tr>
<tr>
<td>4 weeks</td>
<td>20.8±10.6</td>
<td>23.4±14.8</td>
</tr>
<tr>
<td>HDL triglycerol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>11.7±3.2</td>
<td>13.3±4.3</td>
</tr>
<tr>
<td>4 weeks</td>
<td>13.0±6.6</td>
<td>14.7±6.4</td>
</tr>
</tbody>
</table>

* Values are the means ±SD of the data from the 11 men in each group.
* VLDL, very low density lipoprotein.
* LDL, low density lipoprotein.
* HDL, high density lipoprotein.

Results

Energy and nutrient intakes

During the study, there were no significant differences between the MCT and LCT groups in energy, fat, protein, carbohydrate, or cholesterol intake (Table 3). The amount of medium-chain fatty acids consumed was higher in the MCT group than in the LCT group.

Serum cholesterol and triglycerol concentrations

There were no significant differences between the two groups in their serum total, VLDL, LDL, or HDL cholesterol or triglycerol levels at the base line or at 4 weeks (Table 4).

Liver function tests and fatty liver

The liver function tests are done, and their results, given in Table 5. The only significant difference found was that the mean serum alanine aminotransferase activity in the MCT group was significantly lower than that in the LCT group at 4 weeks. The two groups had no significant difference in the mean liver-to-spleen CT ratios at either time measured. The diagnosis of fatty liver is made when this ratio is less than 0.85. Both at the base line and at 4 weeks,
all subjects had a liver-to-spleen CT ratio that was 0.85 or more.

Hematological and biochemical results
Results of hematological and biochemical tests are given in Table 6. There were no significant differences found between the groups.

Urinalyses
None of the test subjects had abnormal results for urine tests at 4 weeks.

Discussion
Tsai et al. reported that when 30 g/day of MCTs were given to healthy subjects for 4 weeks, their mean serum cholesterol levels were lower than those who received triacylglycerol composed of long-chain saturated fatty acids (trilaurin).\(^6\) Their and our results suggest that the effects of MCTs on the serum cholesterol levels in healthy subjects resemble the effects of vegetable oil with a large amount of unsaturated fatty acids more than the effects of long-chain saturated fatty acids.

The reasons for the different effects of medium- and long-chain saturated fatty acids on serum cholesterol are not known in detail. The activity of 3-hydroxy-3-methylglutaral-CoA (HMG-CoA) reductase, a key enzyme in cholesterol synthesis, is reduced in rats treated with MCTs.\(^7\) The LDL receptor activity of mononuclear cells from healthy subjects who have been consuming MCTs is higher than that of
those who have been consuming trilaurin.\(^{19}\) Hepatic cholesterol synthesis and LDL receptor activity may have a role in the different effects.

The results of experiments in which MCTs were administered for a short time are not all concordant. Hill et al. added about 40 g of MCT to a diet for 6 days and found that the addition raised the plasma cholesterol levels in comparison with the addition of soybean oil.\(^{18}\) In their study, the calories consumed were 150% of the required amount; and the fat accounted for 40% of intake. Hasegawa et al. gave 20 g/day of MCTs for 7 days and compared the effects of this diet on the plasma total cholesterol concentrations to those of coconut oil, which contains a large amount of long-chain saturated fatty acids.\(^{20}\) They found that the cholesterol levels decreased compared with coconut oil but increased compared with rapeseed oil. In their experiment, the fat energy was 40% of intake.

MCTs differ greatly from LCTs, not only in how they are digested and absorbed but also in they are metabolized in the liver. A fatty acid must be first metabolized to form acyl-CoA before it can be incorporated into triglycerides.\(^{21}\) However, medium-chain acyl-CoA synthetase does not exist in the cytoplasm.\(^{22}\) Medium-chain fatty acids, on the other hand, can pass through the mitochondrial membrane without binding with carnitine, and when transported to the liver, they are rapidly \(\beta\)-oxidized.\(^{23}\) Scheig and Klatskin did an experiment on liver slices from rats and found that medium-chain fatty acids are broken down to carbon dioxide 10 times faster than long-chain fatty acids, but that only 1/20 of the former is used for lipid synthesis.\(^{24}\) However, in a report in which a 12-year-old epileptic boy had been on a high-MCT diet (the amount of MCTs were not specified) for 3 years, hepatic fat accumulation was detected by ultrasound but liver dysfunction did not appear.\(^{25}\) A diet high in MCTs content (as high as 60%) may be given for the treatment of refractory epilepsy.\(^{26}\) In this study, no difference was noted in the MCT and LCT groups in the liver-to-spleen CT ratio, an index for liver fat content. Fatty liver that could be attributed to the LCT or MCT diet was not found. Except for the serum alanine aminotransferase activity, significant differences were not found between the two groups in the results of liver function tests. The serum alanine aminotransferase activity was lower in the MCT group. The results of this study suggest that even long-term dietary intake of MCTs at the rate of 40 g/day does not cause liver dysfunction or liver lipid accumulation.

Baldermann et al. administered a mixed emulsion containing MCTs for 7 days to patients receiving total parenteral nutrition and concluded that an emulsion containing about 35 g/day of MCTs is less likely than an emulsion containing LCTs to cause liver disorders, such as fatty liver and cholestasis.\(^{27}\) Ball also administered an emulsion containing MCTs to patients undergoing total parenteral nutrition for 6 to 14 days.\(^{28}\) He found that an emulsion containing 50 g/day of MCTs had no adverse effects on hematological and biochemical indices, the results of liver function tests, or nitrogen balance. In our study, no adverse effects of MCTs ingestion for 4 weeks were found in 11 liver function tests, 8 hematological tests, and 16 biochemical measurements. There was no sign of fatty liver at 4 weeks that may have been caused by MCTs intake. In order to assure the safety of dietary MCTs more certainly, further long-term study would be required.

In conclusion, the results of our study suggest that the long-term effects of dietary MCTs on the serum cholesterol level were similar to those of unsaturated fatty acids found abundantly in vegetable oil, and that consumption of MCTs at 40 g/day for 4 weeks does not cause liver fat accumulation or liver dysfunction.

Acknowledgments

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