Effects of a High-Monounsaturated Fat Diet on Glucose and Lipid Metabolisms in Normal and Diabetic Mice

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Summary The beneficial effects of high-monounsaturated fat (high-MUFA) diets on diabetic patients have been reported, whereas studies concerning the effects on animals have been few. Although experiments on animals should be useful in elucidating underlying mechanisms, it is not clear even whether there are benefits of a high-MUFA diet in animals. This study examined the short-term effects of a high-MUFA diet on normal and genetically diabetic mice. The high-MUFA diet supplied 38% of the total calories as fat (26% from MUFA), while a regular diet was 13% fat (3% from MUFA). Normal C57BL/6 and diabetic C57BL/KsJ-db/db mice were fed either the regular or the high-MUFA diet for 1 wk. Serum glucose and lipid levels were then measured. In normal mice, hepatic triglyceride production was also compared between the two dietary groups using the Triton WR1339 method. An oral glucose tolerance test was conducted on the diabetic mice. After 1 wk of feeding to normal mice, the high-MUFA diet was seen to lower serum triglyceride levels and reduce hepatic triglyceride production in comparison with the regular diet: It is suggested that the lowering of triglycerides consists of mechanisms including reduced hepatic triglyceride production. When diabetic mice were fed the high-MUFA diet with a controlled caloric intake, the serum glucose levels lowered without an accompanying deterioration in lipid metabolism and the impaired glucose tolerance was ameliorated. This study demonstrates that a high-MUFA diet can lower serum triglyceride levels in normal mice and improve disorders of glucose metabolism in diabetic mice.

Key Words high-monounsaturated fat diet, diabetes, mice, triglyceride, glucose tolerance

Nutritional management is essential in achieving optimal glycemic control and for reducing the risk of cardiovascular disease (CVD) in patients with diabetes mellitus. Dietary recommendations included restrictions in total fat intake, particularly saturated fats (1, 2). Such low-fat diets lower blood cholesterol levels, and are therefore expected to reduce the risk of CVD. However, this concept has recently become a controversial issue. Adverse effects of low-fat diets, i.e. increased blood triglyceride and decreased high-density lipoprotein (HDL) cholesterol levels, have been reported (3, 4).

On the other hand, high-monounsaturated fat (high-MUFA) diets have received much attention for the benefits they afford for CVD prevention, such as decreased blood triglyceride levels and modest increases in HDL cholesterol levels (5–7). High-polyunsaturated fat (high-PUFA) diets also possess similar effects, but it has been argued that high-MUFA diets are more appropriate in the prevention of CVD (6–9). Diets rich in MUFA, not PUFA, lead to favorable changes in the lipid profile of lipoproteins and can reduce the susceptibility of lipoproteins to oxidative modification, one of the initial steps in atherogenesis. Indeed, some dietary recommen-

dations for diabetic patients have recently changed in favor of higher consumptions of MUFA (10, 11).

In the past, Mediterranean regions have reported low mortality rates from CVD despite the consumption of diets high in total fat (12). A common feature of Mediterranean diets is the use of olive oil containing MUFA as the principal fat, suggesting that the consumption of MUFA is associated with reducing the CVD risk in this region. A number of studies have shown the effects of high-MUFA diets in relation to CVD prevention; high-MUFA diets lowered blood triglyceride (13–17) and very-low-density lipoprotein cholesterol (13–15) levels, and elevated HDL cholesterol levels (13, 14) in diabetic patients compared with low-fat diets. Furthermore, it has been suggested that high-MUFA diets may slow the progression of atherosclerotic lesions by reducing susceptibility to low-density lipoprotein oxidation (9, 18, 19). In addition, high-MUFA diets were seen to be more effective than low-fat diets for efficient glycemic control (13, 15–17) and improving insulin sensitivity (13, 17) in diabetic patients. However, the underlying mechanisms mediating the effects of high-MUFA diets remain to be established.

In contrast to numerous studies of diabetic patients, animal experiments reporting the beneficial effects of
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MUFA have been few: Rocca et al. demonstrated the benefit of a MUFA diet on glycemic tolerance in Zucker rats (20), while Peyron-Caso et al. reported that MUFA had no effect on plasma lipids and insulin resistance in sucrose-fed rats (21). On the contrary, it is known that high-MUFA diets extremely rich in total fat (about 60% fat on a caloric basis) induce hyperglycemia in C57BL/6J mice (22, 23). It has been suggested in human studies that high-MUFA diets improve insulin sensitivity without detrimental metabolic effects when total fat does not exceed 38% (24), but it is yet unknown as to whether this can also be seen in mice. Demonstrations with animal models, particularly diabetic animals, are needed in order to make clear the mechanisms. In this study, therefore, the effects of a high-MUFA diet containing 38% fat in normal C57BL/6J and diabetic C57BL/KsJ-db/db mice was investigated. First, it was determined whether a high-MUFA diet lowers blood triglyceride levels in mice. Second, the ability of a high-MUFA diet to improve metabolic abnormalities in diabetic mice was evaluated.

MATERIALS AND METHODS

Animals and Diets. Male C57BL/6J and C57BL/KsJ-db/db mice were purchased from CLEA Japan Inc. (Tokyo, Japan) and maintained in a temperature-controlled room with a 12 h light-dark cycle. They were given a regular, low-fat diet, MF (Oriental Yeast Co., Ltd., Tokyo, Japan) during an acclimation period of more than 5 d. Throughout the experimental period, the mice were housed in individual cages and had free access to their respective diets. Water was available ad libitum. This study was conducted in accordance with the Guidelines for Animal Care and Use in SSP. The composition of diets is shown in Table 1; the calories of the regular diet consisted of 13% fat (3% from MUFA), 60% as carbohydrate, and 27% as protein. In the high-MUFA diet (Nutrichem GmbH, Roth, Germany) as 38% fat (26% from MUFA), 47% as carbohydrate, and 15% as protein. Olive oil was used as the main source of fat in the high-MUFA diet.

Experimental design

Experiment I. Studies in C57BL/6J mice. Preliminary feeding trials were carried out. An increased caloric intake occurred when mice were switched from the regular diet to the high-MUFA diet and thus provided a solid formula. It was necessary to ensure that the mice took in constant calories without the food deprivation that is accompanied by changes in lipid metabolism (25). Accordingly, the high-MUFA diet was provided as a liquid formula, reducing caloric content of the diet to 94 kcal/100 g; although the effects of MUFA might have been attenuated to the fact that adding water to diets can be accompanied by increased blood triglyceride levels (26). The regular diet was provided as a regular solid-formula (357 kcal/100 g).

Experiment I-A: Serum glucose and lipid levels. C57BL/6J mice weighing 20 to 24 g (8 wk old) were divided into two groups (5 mice per group), regular diet and high-MUFA diet, of equivalent mean body weight. Body weight was 22.8 ± 0.5 g for the regular diet group and 22.4 ± 0.3 g for the high-MUFA diet group. Mice in both groups had nearly identical caloric intake. After 1 wk of feeding, blood samples were collected from the jugular vein in the non-fasted state between 10:00 a.m. and 11:00 a.m., after which the serum was obtained by centrifugation. The serum concentrations of glucose, triglyceride, free fatty acids and total cholesterol were enzymatically assayed using commercial kits (Wako Pure Chemical Industries Ltd., Osaka, Japan). Also, sera from individual mice were pooled in each group, and serum fatty acid composition was determined using gas chromatography as described elsewhere (27).

Experiment I-B: Hepatic triglyceride production. Mice were fed the regular or high-MUFA diet as in Experiment I-A. Following the 1-wk feeding period, hepatic triglyceride production was compared between the two groups (12 mice per group) using the well-characterized Triton WR1339 method (28-31). Triton WR1339 blocks triglyceride removal from the bloodstream by inhibiting lipoprotein lipase activity (32). The serum triglyceride level increases linearly for at least 4 h following intravenous injection of Triton WR1339 (30, 31). In the fasting state, increasing serum triglyceride reflects a triglyceride secretion rate from the liver. In this study, after 4 h of fasting, the mice were treated intravenously with 500 mg/kg of Triton WR1339 (Sigma-Aldrich Co., St Louis, MO, USA) using a 15% solution in 0.9% NaCl. One hour after treatment, blood samples were collected from the jugular vein, and the serum triglyceride levels were measured as described above.

Experiment II. Studies in db/db mice. In the past db/db mice have been established as a spontaneous diabetes model, and display obesity, hyperglycemia and hypertriglyceridemia (33-36). This strain has a genetic mutation resulting in hyperphagia (37, 38). Preliminary experiments confirmed that the daily caloric intakes of db/db mice were higher than those of age-matched normal mice (C57BL/6J). Accordingly, when db/db mice are fed high-MUFA diets ad libitum, excess intakes with fat would be the result. An increased intake with fat should accelerate the development of

<table>
<thead>
<tr>
<th>Component</th>
<th>% of calories</th>
<th>Regular diet</th>
<th>High-MUFA diet</th>
</tr>
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<tbody>
<tr>
<td>Carbohydrate</td>
<td>60</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>27</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>13</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>1.9</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Oleic acid</td>
<td>2.8</td>
<td>26.1</td>
<td></td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>5.9</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>0.5</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1.9</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

MUFA: monounsaturated fat.
lipid abnormalities (36). Furthermore, the higher intake might worsen glycemic control; it has been reported that an excess intake with MUFA impaired glucose tolerance in mice (22, 23). Indeed, it is reasonable to assume that in hyperphagic db/db mice, overfeeding with high-MUFA diets would have undesirable consequences. In this study, if necessary, the daily caloric intake was adjusted to 450 kcal/kg, an amount comparable to that in normal C57BL/6J mice on a body weight basis, and the calorie-restricted groups were expressed as the controlled regular/high-MUFA diet group. We used the same diets as in Experiment I.

Experiment II-A: Serum glucose and lipid levels. Blood samples were obtained from the tail vein at 8 wk old in order to determine glucose concentrations using a GR-101 glucose analyzer (Terumo Corp., Tokyo, Japan). In the first study, the mice with non-fasting glucose levels of more than 400 mg/dL were divided into two groups (5 mice per group), regular diet and controlled high-MUFA diet, in which mean glucose levels and body weights were equivalent. The glucose level was 519.4±18.7 mg/dL for the regular diet group and 523.4±20.6 mg/dL for the controlled high-MUFA diet group. The body weights were 37.1±0.3 and 36.5±0.3 g, respectively. The regular diet group continued with the same diet with a usual caloric intake, while the controlled high-MUFA group was started with the high-MUFA diet with calorie restriction. Mice were allowed free access to their diets and water. The next study was a comparison between the two diets with identical calorie restriction; the mice were divided into two groups (5 mice per group), controlled regular diet and controlled high-MUFA diet, and fed the corresponding diets. After 1 wk of feeding, blood samples were collected from the jugular vein in the non-fasted state between 10:00 a.m. and 11:00 a.m., after which the serum parameters were assayed as described in Experiment I-A.

Experiment II-B: Oral glucose tolerance test. Following the 1-wk feeding period in Experiment II-A, an oral glucose tolerance test was conducted. Mice orally received 1.5 g/kg of glucose after a 17-h fast (7 mice per group). Blood samples were collected from the tail vein before (0 time) and at 30, 60, 90, 120 and 180 min after the glucose load. The glucose levels were determined using the glucose analyzer described above.

Daily caloric intake. Diets were provided to each of the mice. The food intake per day was estimated by subtracting the weight of any remaining food from the initial food weight. In each group, the caloric intake was calculated and expressed as kcal per mouse per day.

Statistics. The results were expressed as means±SE. Student's t-test or Welch's t-test was used to evaluate differences between two groups. All statistical analyses were performed using the StatLight series software version 1.0 (Yukms Co., Ltd., Tokyo, Japan). p-values of less than 0.05 were considered statistically significant.

RESULTS

Experiment I. Studies in C57BL/6J mice

Experiment I-A: Serum glucose and lipid levels. C57BL/6J mice were fed either the regular or the high-MUFA diet for 1 wk. As shown in Table 2, the caloric intakes were similar in both groups. The body weight gain was somewhat higher in the high-MUFA diet than the regular diet group (2.1±0.2 and 1.4±0.2 g, respectively), but the difference was not statistically significant. The serum triglyceride levels in the high-MUFA diet group were significantly lower compared with the regular diet group (101.5±13.2 and 136.5±5.7 mg/dL, respectively). The serum free fatty acid levels were also significantly lower in the high-MUFA diet than in the regular diet group (0.59±0.06 and 0.92±0.04 mEq/L, respectively). There were no significant differences between the dietary groups in the serum glucose or total cholesterol levels (data not shown). Serum fatty acid composition was also different between the groups, with the high-MUFA diet group having a lower proportion of saturated fatty acids and a higher proportion of monounsaturated and polyunsaturated fatty acids.
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Experiment II. Studies in db/db mice

Experiment II-A: Serum glucose and lipid levels. When db/db mice were fed the high-MUFA diet on an approximately 25% lower calorie intake compared to those on the regular diet (17.0±0.6 and 23.2±0.6 kcal/mouse/d, respectively), serum glucose levels lowered (464.4±57.4 and 623.5±25.9 mg/dL, respectively. Study 1 in Table 4). Serum triglyceride levels and free fatty acid levels were also low in the controlled high-MUFA diet group. The body weight gain and serum total cholesterol levels were not significantly different between the two groups. On the other hand, when mice were fed the regular or the high-MUFA diet with an identical calorie restriction, serum triglyceride, free fatty acids and total cholesterol levels did not significantly differ between the two groups (Study 2 in Table 4). Serum glucose levels in the controlled high-MUFA diet group were, however, significantly lower compared with the controlled regular diet group (433.8±32.1 and 561.1±15.8 mg/dL, respectively). The body weight gain was greater in the controlled high-MUFA diet than in the controlled regular diet group (3.1±0.5 and 1.4±0.2 g, respectively). Serum fatty acid composition in the latter study is shown in Table 5. The percentages of 18:1n-9 and 18:3n-3 were greater and 16:0 and 18:2n-6 were lesser in the controlled high-MUFA diet, similar to the results seen in normal mice (Experiment I-A).

Experiment II-B: Oral glucose tolerance test. The feeding conditions were the same as in Experiment II-A. When caloric intake in the controlled high-MUFA diet and the regular diet group was 17.6±0.8 and 23.3±0.7 kcal/mouse/d, respectively (p<0.01), the raised glucose levels after glucose load were lower and the following decline was faster in the controlled high-MUFA diet than in the regular diet group (Fig. 2A). Moreover, as shown in Fig. 2B, the raised glucose levels showed a small but significantly lower value in the controlled high-MUFA diet than in the controlled regular diet group even when caloric intakes of both dietary groups were nearly identical (16.9±0.5 and 16.8±0.0 kcal/mouse/d, respectively), but the following decline was

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Table 4. Body weight gain and serum glucose and lipid levels in db/db mice fed a regular or a high-monounsaturated fat diet for 1 wk.

<table>
<thead>
<tr>
<th>Study</th>
<th>Caloric intake (kcal/mouse/d)</th>
<th>Body weight gain (g)</th>
<th>Glucose (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
<th>Free fatty acids (mEq/L)</th>
<th>Total cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular diet</td>
<td>23.2±0.6</td>
<td>3.0±0.1</td>
<td>623.5±25.9</td>
<td>545.5±33.3</td>
<td>1.64±0.07</td>
<td>188.9±1.3</td>
</tr>
<tr>
<td>Controlled high-MUFA diet</td>
<td>17.0±0.6**</td>
<td>4.0±0.4</td>
<td>464.4±57.4*</td>
<td>290.4±69.0*</td>
<td>1.20±0.09**</td>
<td>170.5±2.5</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled regular diet</td>
<td>16.9±0.1</td>
<td>1.4±0.2</td>
<td>561.1±15.8</td>
<td>280.7±37.4</td>
<td>1.02±0.07</td>
<td>157.4±5.1</td>
</tr>
<tr>
<td>Controlled high-MUFA diet</td>
<td>17.6±0.5</td>
<td>3.1±0.5*</td>
<td>433.8±32.1**</td>
<td>299.7±21.4</td>
<td>1.19±0.09</td>
<td>168.9±3.8</td>
</tr>
</tbody>
</table>

In Study 1, male db/db mice were fed a regular diet with a usual calorie (regular diet) or a high-monounsaturated fat diet with calorie restriction (controlled high-MUFA diet) for 1 wk. In Study 2, male db/db mice were fed the regular or the high-monounsaturated fat diet with calorie restriction for 1 wk (controlled regular diet and controlled high-MUFA diet group, respectively). Each value represents the mean±SE of 5 animals. *p<0.05 and **p<0.01. significantly different from the group fed the regular diet.

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Fig. 1. Effect of a high-monounsaturated fat diet on hepatic triglyceride production. Male C57BL/6J mice were fed ad libitum a regular or a high-monounsaturated fat (high-MUFA) diet for 1 wk. After 4 h of fasting, the mice were treated intravenously with 500 mg/kg of Triton WR1339. Serum triglyceride levels were measured at 1 h after the Triton WR1339 treatment. Each column represents the mean±SE of 12 animals.
Table 5. Effects of a high-monounsaturated fat diet on serum fatty acid composition in db/db mice.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Controlled regular diet</th>
<th>Controlled high-MUFA diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>16:0 Palmitic acid</td>
<td>22.8</td>
<td>17.2</td>
</tr>
<tr>
<td>18:0 Stearic acid</td>
<td>8.4</td>
<td>10.1</td>
</tr>
<tr>
<td>18:1n-9 Oleic acid</td>
<td>17.0</td>
<td>31.1</td>
</tr>
<tr>
<td>18:2n-6 Linoleic acid</td>
<td>33.1</td>
<td>24.2</td>
</tr>
<tr>
<td>18:3n-3 Linolenic acid</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>20:4n-6 Arachidonic acid</td>
<td>3.2</td>
<td>3.4</td>
</tr>
<tr>
<td>20:5n-3 Eicosapentaenoic acid</td>
<td>4.0</td>
<td>3.3</td>
</tr>
<tr>
<td>22:5n-3 Docosapentaenoic acid</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>22:6n-3 Docosahexaenoic acid</td>
<td>5.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Male db/db mice were fed a regular or a high-monounsaturated fat diet with calorie restriction for 1 wk (controlled regular diet and controlled high-MUFA diet group, respectively). The sera from individual mice were pooled in each group and fatty acid composition was determined.

Fig. 2. Effect of a high-monounsaturated fat diet on glucose tolerance in db/db mice. A: Male db/db mice were fed ad libitum a regular diet with a usual calorie (regular diet group) or a high-monounsaturated fat diet with calorie restriction (controlled high-MUFA group) for 1 wk. B: Male db/db mice were fed the regular or the high-monounsaturated fat diet with calorie restriction for 1 wk (controlled regular diet and controlled high-MUFA diet group, respectively). Then, after 17 h of fasting, 1.5 g/kg of glucose was orally administered. Each symbol represents the mean±SE of 7 animals. *p<0.05, significantly different from the group fed the regular diet. ○, regular diet; ▲, controlled high-MUFA diet; ●, controlled regular diet.

DISCUSSION

Diabetic patients have a high frequency of dyslipidemia such as hypertriglyceridemia. It is generally accepted that hypertriglyceridemia is strongly related to the prevalence of CVD and is an independent risk factor for CVD in diabetic patients (39–41). Recently, it has been proposed that high-MUFA diets are beneficial for CVD prevention in diabetic patients, since such diets lower blood triglyceride levels more effectively in comparison with low-fat diets (5–7). In this study, C57BL/6J mice fed a high-MUFA diet had lower serum triglyceride levels compared with those fed a regular diet. We also measured serum triglyceride levels following Triton WR1339 treatment. During fasting, liver-derived triglyceride progressively accumulates in the blood after Triton WR1339 treatment (30, 31). The mean triglyceride level in the regular diet group (as control) increased to 562.3 mg/dL after 1 h of treatment. In contrast, the value in the high-MUFA diet group was 411.6 mg/dL, indicating that the high-MUFA diet caused a reduction in hepatic triglyceride production. This is supported by previous reports that high-fat diets of corn oil, lard or fish oil reduced hepatic triglyceride production (42–44). Willumsen et al. suggested that the triglyceride lowering property of n-3 PUFA in fish oil, eicosapentaenoic acid, may be due in part to a reduced supply of fatty acids for hepatic triglyceride synthesis because fatty acid oxidation maximally increased after 2 d of feeding (45). As with n-3 PUFA, reduced triglyceride production following a high-MUFA diet may be one factor contributing to the lowering in serum triglyceride.

Additionally, it is a possibility that the triglyceride-lowering effect of the high-MUFA diet was mediated by several factors. The high-MUFA diet clearly lowered serum free fatty acid levels in C57BL/6J mice; decreased mobilization of free fatty acids from adipose tissue might occur. It has been reported that oleic acid inhibits hormone-sensitive lipase, that is the enzyme regulating the release of lipids from adipose tissues into the bloodstream as free fatty acids, and has a major role in determining circulating levels (46, 47). It seems that triglyceride lowering occurred as a consequence of a decrease in free fatty acid levels at least in part because free fatty acids are delivered to the liver and stimulate hepatic triglyceride production (48, 49). Another possibility is that the fatty acid composition was associated with triglyceride levels (49, 50). In the high-MUFA diet group, the percentages of oleic acid (18:1n-9), linoleic acid (18:3n-3) and arachidonic acid (20:4n-6) seem to have risen, which coincided with falls in those of nearly all other fatty acids. These changes might reflect dietary fatty acid composition and be based on the competitive inhibition between linoleate, linolenate, and oleate metabolisms; previous studies have reported the effects of MUFA consumption on fatty acid composition and desaturase activities, which are related to fatty acid
metabolism (51–53). Accordingly, it is considered that serum triglyceride lowering might be attributed to the effects of diet on serum fatty acid composition. On the other hand, the increase in arachidonic acid may be an adverse effect increasing thrombosis tendency (54). However, current studies have reported that olive oil reduces the conversion of arachidonic acid to proinflammatory eicosanoid (55) and shows antithrombotic effects (56). Indeed, it is possible that the increments of arachidonic acid resulted from inhibition of eicosanoid synthesis and this may be not disadvantageous. Further research is required in order to obtain a better understanding of the effects of MUFA on lipid metabolism.

Diabetic db/db mice have hyperphagic characteristics (33, 35), and overfeeding with fat can increase serum lipid levels and intensify the development of diabetes (22, 23, 36). Indeed, overfeeding with high-MUFA diets probably has adverse effects on glucose and lipid metabolisms. It should be noted that caloric control would be required in conjunction with high-MUFA diet feeding. Therefore, the caloric intake of mice given the high-MUFA diet was controlled (the controlled high-MUFA diet group) to the same level as that of normal C57BL/6J mice on a per body weight basis (450 kcal/kg/d). However, owing to obese mice, caloric intake was greater for C57BL/6J mice in absolute amounts (17.0 kcal/mouse/d in Table 4 and approximate 11 kcal/mouse/d in Table 2, respectively), meaning that the caloric restriction was moderate. The body weight gain was maintained and was similar to that seen in the regular diet group with the usual caloric intake. The high-MUFA diet under such conditions lowered serum glucose and lipid levels, and ameliorated the impaired glucose tolerance of diabetic mice. Furthermore, these effects on glucose metabolism were observed in the comparisons between the two diet groups under conditions of identical caloric restriction, suggesting that a high-MUFA diet containing 38% fat on a caloric basis acted favorably on glucose metabolism in diabetic mice. This is in agreement with the results from human studies (24). These actions may largely result from the low carbohydrate content of the high-MUFA diet; which must be helpful in the avoidance of hyperglycemia. Nevertheless, we cannot rule out another possibility: the changes of fatty acid composition following a high-MUFA diet might modulate insulin action. It has been suggested that insulin sensitivity is associated with low proportions of saturated fat and n-6 PUFA and with higher proportions of MUFA and n-3 PUFA in blood and tissue fatty acid composition (57, 58). There was a tendency towards an increase in oleic and linolenic acid and a decrease in palmitic and linoleic acid following the high-MUFA diet, thus these changes might prevent the development of diabetes in db/db mice. In contrast to the effect on glucose metabolism, when identical caloric restriction was carried out, serum triglyceride and free fatty acid levels did not differ between the two dietary groups since lipid levels were also low in the controlled regular diet group. However, this result suggests that the high-MUFA diet used did not have a detrimental effect on lipid metabolism despite being a diet rich in fats; which may be connected to the lipid-lowering effect observed in normal mice. Further studies are needed in order to know for certain whether the hypoglycemic effect of the high-MUFA diet is at least partially associated with the changes in lipid profiles.

It is acknowledged that the dietary periods in this study were of a relatively short duration, and the possibility that these results were not in a steady state cannot be excluded. For example, although the body weight gain in C57BL/6J mice did not significantly differ between the two dietary groups, acceleration of body weight gain in the mice may be a phenomena occurring over several weeks, which has been reported previously (22, 23). Undoubtedly, a longer-term study would be necessary in gaining a better understanding of the effects of a high-MUFA diet. However, it is of interest that the consumption of MUFA changed serum lipid profiles and contributed to favorable effects on glucose metabolism in a feeding period of 1 wk. Girón et al. reported that the effects of dietary supplementation on the lipid composition and desaturase activity in tissue phospholipid were observed within 2 d (52). Furthermore, Williamsen et al. reported that triglyceride lowering of n-3 PUFA was established within 1 to 2 d of feeding (45). It has also been reported that a diet rich in olive oil modified low-density lipoprotein lipid composition even after 1 wk (19). Accordingly, the short-term effects of MUFA feeding should also be noted as a benefit of MUFA.

In conclusion, this study has shown that a high-MUFA diet lowers serum triglyceride levels in normal C57BL/6J mice within a short period of time in comparison with a regular diet. It also shows that the mechanisms controlling the reduction of hepatic triglyceride production and possible other factors might be associated. Furthermore, in diabetic db/db mice, the high-MUFA diet ameliorated abnormalities in serum glucose levels, as well as impaired glucose tolerance, suggesting that the high-MUFA diet improved disorders associated with glucose metabolism in diabetic mice, as seen in human studies. The underlying mechanisms mediating the reported effects of a high-MUFA diet remain to be established and hence these results should be helpful in further investigation.

Acknowledgments

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