Soy protein retards the progression of non-alcoholic steatohepatitis via improvement of insulin resistance and steatosis

Hsin-Yi Yang Ph.D. a, Ya-Hui Tzeng M.S. b, Chiah-Yang Chai M.S. c, An-Tsz Hsieh M.D. d, Jiun-Rong Chen Ph.D. b, *, Le-Shin Chang Ph.D. e, Sien-Sing Yang Ph.D. f

a Department of Medical Nutrition, I-Shou University, Kaohsiung, Taiwan
b School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan
c General Surgery, Taipei Medical University Hospital, Taipei, Taiwan
d Division of Endocrinology and Metabolism, Department of Internal Medicine, Shuang Ho Hospital, Taipei, Taiwan
e Department of Nutrition and Health Sciences, Kainan University, Taoyuan, Taiwan
f Liver Unit, Cathay General Hospital, Taipei, Taiwan

Keywords:
Soy protein
Non-alcoholic fatty liver disease
Insulin resistance
Steatosis

A B S T R A C T

Objective: Non-alcoholic steatohepatitis (NASH) is a common cause of liver disease, and it may progress to fibrosis or cirrhosis. The aim of this study was to investigate the effects of soy protein on hepatic steatosis and insulin resistance in NASH.

Methods: Forty male Sprague-Dawley rats were fed a high-fat diet for 4 wk to induce NASH and then were allocated to one of four diets: a NASH-inducing diet, a standard diet, a NASH-inducing diet plus soy protein, and a standard diet plus soy protein.

Results: After the 10-wk experimental period, the results showed that soy protein significantly lowered plasma cholesterol concentrations and body fat accumulation. Soy protein intake also decreased the hepatic lipid depots of triacylglycerols and cholesterol and decreased the concentrations of lipid peroxides. In an analysis of antioxidative status, rats fed the soy protein diet showed improved antioxidative potential due to increases in superoxide dismutase and catalase activities and a decrease in the protein expression of cytochrome P450 2E1.

Conclusion: Soy protein may improve the liver function in patients with NASH by lowering lipid levels in the blood and liver, increasing the antioxidative capacity, and improving insulin resistance.

Introduction

Non-alcoholic fatty liver disease is one of the most common liver diseases with increasing prevalence in the developed world. At one end of the non-alcoholic fatty liver disease continuum is non-alcoholic steatohepatitis (NASH) with or without cirrhosis [1]. The term non-alcoholic steatohepatitis was introduced in 1980, and liver biopsies from patients with alcoholic hepatitis [2]. Clinical characteristics associated with NASH include obesity, hyperlipidemia, diabetes mellitus, and hypertension, which have been associated with underlying insulin resistance [3,4]. Imbalanced metabolism induced by insulin resistance increases levels of circulating free fatty acids and results in liver fat accumulation, which then leads to liver inflammation and fibrosis [5]. Furthermore, high levels of free fatty acids induce the overexpression of cytochrome P450 (CYP) 2E1 and increase oxidative stress by the process of lipid peroxidation, which may also lead to liver injury [6].

Epidemiologic studies have shown that the morbidity of NASH in Japan (14%) is lower than that in the United States (23%) [7] and this might be associated with the consumption of soy products. Soy protein has long been an important protein source in traditional Oriental diets. Although studies have found that soy protein shows benefits in decreasing liver lipid accumulation [8,9], increasing antioxidation ability [10], and improving insulin resistance [11], no study has reported the relation between NASH and soy protein consumption. Recently, a NASH animal model was reported, which has facilitated research to the relations between diet components and NASH. The aim of this study was to
investigate the effects of soy protein on lipid metabolism, insulin resistance, and antioxidative status in the NASH animal model.

Materials and methods

Animals and diets

Forty male Sprague-Dawley rats weighing approximately 150 to 200 g were purchased from the National Laboratory Animal Breeding and Research Center (Taipei, Taiwan). Animals were housed in individual cages in a room maintained at 23 ± 2°C with 55 ± 5% humidity and a 12-h light–dark cycle. Animals were fed a standard rat chow diet (Rodent Laboratory Chow 5001, LabDiet, Richmond, IN, USA) for 1 wk to allow acclimation and then were fed a high-fat liquid diet for 4 wk to induce NASH [12]. After the induction period, animals were randomly assigned to four groups and fed the different experimental diets for 6 wk. As presented in Table 1, the four experiment groups included an N group (NASH diet), an S group (standard diet), an NS group (NASH diet + soy protein isolate), and an SS group (standard diet + soy protein isolate). In the NS and SS groups, rats were fed diets containing soy protein isolate (Fuji Oil Co. Ltd., Osaka, Japan) as 50% of the dietary protein source substituted for casein. During the experimental period, food intake was recorded daily, and the animals were weighed each week. All animals were treated in accordance with the National Institutes of Health’s Guide for the Care and Use of Laboratory Animals (National Research Council, 1985).

Sample collection and analysis

Blood

During the last week of the experiment, an oral glucose tolerance test with 5-g/kg glucose intake was performed in rats starved for 12 h. Changes in blood glucose and plasma insulin levels were measured before and 30, 60, 90, 120, and 180 min after glucose intake. Blood glucose was determined using a commercial kit (Randox, Antrim, UK), and plasma insulin levels were determined using an enzyme-linked immunosorbent assay kit (Mercodia Rat Insulin ELISA, Uppsala, Sweden). All experiments were carried out on a Hitachi 7170 Autoanalyser (Tokyo, Japan) or with commercial kits (Randox).

Liver

After perfusing the livers with saline, these were collected and stored at −80°C. Liver lipids were extracted according to the method of Folch et al. [13].

Sample collection and analysis

Liver

After perfusing the livers with saline, these were collected and stored at −80°C. Liver lipids were extracted according to the method of Folch et al. [13].

Table 1 Composition of the experimental diets

<table>
<thead>
<tr>
<th>Ingredients/group (g/L)</th>
<th>N</th>
<th>S</th>
<th>NS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>84</td>
<td>84</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Soy protein isolate</td>
<td>—</td>
<td>—</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Corn oil</td>
<td>97</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Olive oil</td>
<td>56.8</td>
<td>56.8</td>
<td>56.8</td>
<td>56.8</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Dextrin</td>
<td>51.2</td>
<td>230.4</td>
<td>51.2</td>
<td>230.4</td>
</tr>
<tr>
<td>Choline</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
</tr>
<tr>
<td>Xanthan</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Vitamins</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Minerals</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

N, non-alcoholic steatohepatitis–inducing diet; NS, non-alcoholic steatohepatitis–inducing diet plus soy protein; S, standard diet; SS, standard diet plus soy protein

The liver triacylglycerol and total cholesterol concentrations were determined by commercial kits (Randox). Hepatic peroxide (malondialdehyde and 4-hydroxyalkenals) and antioxidative enzymes (catalase and superoxide dismutase) were also determined by commercial kits (Randox SD 125 Kit). For the measurement of CYP2E1 protein expression, microsome proteins (40 μg) were prepared as previously described by Funae and Imaoka [14]. The western blots were reacted with rabbit anti-hamster P450 2E1 immunoglobulin G and immunostained using goat anti-rabbit immunoglobulin G conjugated with alkaline phosphatase. The bands were quantified by densitometry using Image-Pro Plus 4.5 (Media Cybernetic, Bethesda, MD, USA). For quantification of the liver tumor necrosis factor-α (TNF-α) level, liver tissues were homogenized in extraction buffer (50 mmol/L of Tris, 150 mmol/L of NaCl, 13 Triton-X 100, and a protease inhibitor cocktail). The homogenate was shaken on ice for 90 min and then centrifuged at 3000 × g at 4°C for 15 min, and the precipitate was discarded. TNF-α levels were detected using a commercial enzyme-linked immunosorbent assay kit (Quantikine M TNF-α, Abingdon, UK) according to the manufacturer’s guidelines.

Abdominal fat

Epididymal and retroperitoneal fat tissues were collected and weighed.

Feces

At the end of the experiment, 24-h feces were collected, and the wet weight was recorded. The feces was then dried and ground for analysis. Bile acids and steroids were extracted from the feces according to the method of Folch et al. [13] and were measured with commercial kits (Randox).

Pathologic analysis

At the end of the experimental period, livers were rapidly fixed in a 19% buffered formaldehyde solution. Sections were stained with hematoxylin and eosin for routine histology or with silver for evaluation of fibrosis. The results were interpreted by a pathologist.

Statistical analysis

Data are reported as mean ± standard error of the mean. Statistical analyses were performed using the SAS 8.2 (SAS Institute, Cary, NC, USA). Data were analyzed by one-way analysis of variance, least significant difference, and Tukey’s honest significant difference. Results are expressed as mean ± standard deviation. Differences were considered statistically significant at P < 0.05.

Results

Body weight, food intake, and tissue weight

The initial average body weight of animals was 165.9 ± 2.2 g. After the 4-wk induction period, the average body weight of animals was 386.5 ± 3.5 g. At the end of the study, final body weights of the rats showed no significant differences among groups (P > 0.05), and soy protein had no effect on food intake or body weight gain (Table 2). In addition, the liver and fat tissues were significantly higher in the N group compared with the other three groups (Table 3).

Plasma lipid profiles, AST, and ALT

Plasma cholesterol of the N group was higher than that of the S group, and there was no significant difference between the NS and S groups. Although the concentrations of low-density lipoprotein cholesterol showed no significant differences among groups (P > 0.05), soy protein intake significantly improved the high-density lipoprotein cholesterol/low-density lipoprotein cholesterol ratio (Table 2). In addition, the plasma free fatty acid level, AST, and ALT were higher in the N group than in the S group, and there was no significant difference between the NS and S groups.

Liver lipid profiles, antioxidative capacity, and inflammation

Liver cholesterol and triacylglycerol levels were lower in the S group than in the N group, and there was no difference
between the S and NS groups. Results showed that soy protein intake improved the liver lipid profiles (Table 3). Concentrations of lipid peroxides, malondialdehyde, and 4-hydroxyalkenals were significantly lower in the NS and SS groups than in the N group. Activities of the antioxidant enzymes, superoxide dismutase and catalase, were higher in the NS and SS groups than in the N group. Hepatic CYP2E1 protein expression was significantly higher in group N than in the other three groups (Fig. 1). The level of TNF-α in the liver, used as an indicator of inflammation, in group N was higher than that in group S, and there was no significant difference between groups S and NS (Fig. 2).

Feces

At the end of the study, we found no difference in fecal cholesterol and bile acid excretion between rats consuming casein and those consuming a soy protein diet (data not show).

**Oral glucose tolerance test**

Results of the oral glucose tolerance test are shown in Figure 3. Thirty minutes after ingestion of the glucose solution, the plasma glucose level had reached a peak and showed no significant difference among groups (Fig. 3A). Plasma insulin levels in all groups also reached the maximum levels 30 min after ingestion of the oral glucose solution. However, plasma insulin levels in the N group were significantly higher than those of the other three groups at 30 and 60 min (Fig. 3B).

**Hepatic pathology**

Compared with the other three groups, the N group had significant hepatic lipid accumulation in zones 3 and 2. Moreover, there were inflammatory cell congestion and hepatic fibrosis in zone 3 in the N group (Fig. 4).

**Discussion**

The results of this study show that soy protein ameliorated liver function and lowered plasma lipids and liver fat accumulation in rats consuming a NASH diet. In the experimental period, the soy protein diet was as effective in achieving these improvements as the standard diet. The combination of the standard diet and soy protein showed additional benefits by improving plasma free fatty acid levels and liver fat levels. We fed rats with a liquid NASH diet containing lipids for about 70% of their energy intake. Substituting soy protein isolate for casein as a portion of dietary protein source did not affect food intake and there was no significant difference in weight change or feeding efficiency between the casein and soy groups. This indicates that soy protein in the diet did not affect the normal growth of rats. The beneficial effects of soy protein may be due to its constituents, such as amino acid profile, peptides, or isoflavones.

Previous research has shown that plasma free fatty acid plays an important role in the progression of NASH [15]. High free fatty acid levels may induce the expression of liver CYP2E1, the production of reactive oxygen species, the peroxidation of phospholipids on cell membranes, and result in cell damage or

### Table 2

Body weight, food intake, and plasma lipid profiles of rats fed different diets

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>S</th>
<th>NS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>535.9 ± 18.5</td>
<td>529.6 ± 10.0</td>
<td>530.3 ± 8.8</td>
<td>523.1 ± 9.0</td>
</tr>
<tr>
<td>Food intake (g/d)</td>
<td>59.3 ± 3.2</td>
<td>60.0 ± 3.3</td>
<td>58.1 ± 3.2</td>
<td>58.1 ± 3.1</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>0.29 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.37 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.21 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.37 ± 0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>1.89 ± 0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.56 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.56 ± 0.07&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.60 ± 0.07&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.48 ± 0.03</td>
<td>1.42 ± 0.04</td>
<td>1.44 ± 0.05</td>
<td>1.42 ± 0.06</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>0.23 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.06 ± 0.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.19 ± 0.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.14 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>HD L-C/LDL-C ratio</td>
<td>6.46 ± 0.92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.09 ± 1.76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.30 ± 1.33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.64 ± 1.39&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Free fatty acid (mmol/L)</td>
<td>1.43 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.85 ± 0.13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.46 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.54 ± 0.06&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GOT (IU/L)</td>
<td>171.8 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>130.3 ± 4.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>130.0 ± 8.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>107.7 ± 2.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GPT (IU/L)</td>
<td>38.4 ± 1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.1 ± 0.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.3 ± 1.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27.4 ± 0.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>1.48 ± 0.08</td>
<td>1.25 ± 0.09</td>
<td>1.25 ± 0.05</td>
<td>1.42 ± 0.08</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, non-alcoholic steatohepatitis inducing diet; NS, non-alcoholic steatohepatitis-inducing diet plus soy protein; S, standard diet; SS, standard diet plus soy protein

Values are presented as mean ± SEM (n = 10).<sup>a,b</sup> Values in a row with different superscript letters indicate significant differences (P < 0.05).

### Table 3

Analytical data of liver and fat tissue<sup>1</sup>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>S</th>
<th>NS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat weight (g)</td>
<td>30.2 ± 3.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.6 ± 1.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22.5 ± 1.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>23.6 ± 0.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>15.8 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.1 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.7 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.0 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepatosomatic index&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.03 ± 0.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.02 ± 0.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.02 ± 0.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.02 ± 0.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cholesterol (mmol/liver)</td>
<td>1042.4 ± 4.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>910.1 ± 1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>833.5 ± 3.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>603.1 ± 1.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/liver)</td>
<td>171.8 ± 16.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1330.6 ± 6.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1168.8 ± 8.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>792.5 ± 5.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDA + 4-HNE (mmol/mg protein)</td>
<td>1313.5 ± 73.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11487.1 ± 4.38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1070.0 ± 58.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1033.9 ± 29.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOD (U/mg protein)</td>
<td>343.0 ± 20.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>461.2 ± 24.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>530.1 ± 34.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>748.5 ± 31.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Catalase (U/mg protein)</td>
<td>434.3 ± 45.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>499.2 ± 16.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>508.6 ± 17.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>509.6 ± 32.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N, non-alcoholic steatohepatitis inducing diet; NS, non-alcoholic steatohepatitis-inducing diet plus soy protein; S, standard diet; SS, standard diet plus soy protein

Values in a row with different superscript letters indicate significant differences (P < 0.05).

<sup>1</sup> Liver weight per body weight.
an inflammatory response. Studies also have shown the over-expression of the CYP2E1 gene in animals with NASH, and that this is one of the factors causing liver damage [16]. In the present study, plasma free fatty acids in the S group were lower than those in the N group, and plasma free fatty acid levels in the NS and SS groups were lower than in the S group. Liver CYP2E1 expression was also lower in rats fed soy protein. Remarkable increases in the liver function index and liver dysfunction, mainly caused by lipid accumulation and free radicals, appeared in subjects with NASH [2]. Levels of AST and ALT were lower in the N group compared with the NS group. Concentrations of malondialdehyde and 4-hydroxyalkenals, products of lipid peroxidation, were also lower in rats consuming soy protein. In addition, superoxide dismutase and catalase activities were higher in the soy protein groups. Soy protein may prevent oxidative damage in the liver by lowering plasma free fatty acids and decreasing CYP2E1 expression.

Tumor necrosis factor-α and other TNF-induced cytokines such as interleukin-6 and interleukin-8 levels were higher in animals with NASH. This is likely related to the progression of NASH in liver cirrhosis [4]. Soy protein ingestion significantly lowered TNF-α levels in the livers of rats. One of the mechanisms for lowering TNF-α levels may have been the anti-inflammatory properties of soy protein. Previous studies have indicated that the isoflavones in soy protein may regulate the inflammatory response and immune function [17]. For example, soy protein was found to regulate bronchial contractions caused by allergens as a tyrosine kinase inhibitor [18]. Another mechanism for regulating the inflammatory response and immune function may be the decrease of liver fat and oxidative stress, which indirectly decreases the damage of hepatocytes and lowers TNF-α level. These results suggest that soy protein may inhibit the inflammatory response in NASH and further decrease damage to the liver.

In subjects with NASH, insulin resistance may cause abnormal lipid metabolism, increase hepatic steatosis, and result in liver inflammation and necrosis [5,19]. The oral glucose tolerance test performed in this study revealed no difference in glucose levels among groups, but the insulin level was lower in the soy
protein-consuming groups. Soy protein consumption may affect hormone excretion in vivo, such as an increase of glucagons and a decrease in insulin levels [11]. Recent studies have shown that replacing casein with soy protein may ameliorate insulin resistance by increasing tissue insulin sensitivity and decrease post-prandial glucose and insulin concentrations [20]. Soy isoflavones may also improve lipid profiles and glucose tolerances by activating peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor-γ [21]. These results indicate that soy protein may have beneficial effects on insulin resistance and may retard the pathologic progression of NASH.

Several studies in humans and animals have indicated that ingesting soy protein can improve lipid profiles. Moreover, consuming soy protein may decrease hepatic fat and the incidence of fatty liver [22,23]. In this study, diets containing soy protein significantly lowered plasma and liver cholesterol levels and decreased liver triacylglycerol accumulation caused by the NASH diet, although the liver weights of the soy protein groups were also lower than those in the casein groups. The mechanism by which soy protein decreases serum and hepatic lipids is not yet fully established. A possible mechanism of this decrease is the enhancement of bile acid excretion, by which soy protein acts as dietary fiber to promote bile acid excretion and increase the rate of cholesterol resynthesis in the liver [24]. However, fecal cholesterol and bile acid excretion were not different in the casein and soy protein groups in this study. Recent reports have shown that soy protein may improve hyperlipidemia due to its effects on the transcription factors, called sterol regulatory element binding proteins, which are important in the regulation of enzymes involved in lipid metabolism in vivo [25]. Tovar et al. [26] found that soy protein lowered sterol regulatory element binding protein-1 expression in adipocytes, which also helped prevent the development of hepatic lipotoxicity. Consistent with these findings, the present study shows that soy protein decreased the weight of fat tissue and reduced the accumulation of lipids in the liver induced by NASH.

Dietary habit modification is an important factor in the treatment of NASH and may help decrease the accumulation of hepatic lipids and improve insulin resistance. After a 4-wk NASH-inducing diet, a 6-wk standard diet decreased hepatic steatosis, improved insulin resistance, and decreased oxidative injury in rats. A soy protein–containing high-fat diet had the same result. Although the effects of the standard diet and soy protein combination (the SS group) for rats with NASH on plasma lipids and hepatic steatosis showed no significant difference from the S group, the SS group had the lowest hepatic CYP2E1 protein expression and liver TNF-α levels.

Soy protein may improve the liver function of rats with NASH by lowering the lipid levels in the blood and liver, increasing the antioxidative capacity, and improving insulin resistance. The results of this study may be useful in considering dietary modification in patients with NASH. Further research is necessary to clarify the mechanisms explaining soy protein’s beneficial effects on NASH.

References


