Effect of soy protein supplementation in patients with chronic hepatitis C: A randomized clinical trial

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Abstract

AIM: To evaluate the effects of soy supplementation on insulin resistance, fatty liver and alanine aminotransferase (ALT) levels in non-diabetic patients with chronic hepatitis C (CHC).

METHODS: In a prospective, randomized and single-blinded clinical trial, we compared patients with CHC who had casein as a supplement (n = 80) (control group), with patients who consumed a soy supplement diet (n = 80) [intervention group (IG)]. Both groups received 32 g/d of protein for 12 wk.

RESULTS: Patients’ baseline features showed that 48.1% were overweight, 43.7% had abdominal fat accumulation, 34.7% had hepatic steatosis and 36.3% had a homeostasis model assessment index of insulin resistance (HOMA-IR) ≥ 3.0. Descriptive analysis showed that protein supplementation diet reduced hepatic steatosis in both groups; however, significant reductions in ALT levels occurred in the soy group. Multiple regression modeling indicated that in the presence of severe fibrosis (F3/F4), γ-glutamyl transferase elevation and high density lipoprotein (HDL) reduction, the intervention group had 75% less chance of developing hepatic steatosis (OR = 0.25; 95% CI: 0.06-0.82) and 55% less chance of presenting with an ALT level ≥ 1.5 × the upper limit of normal (ULN) (OR = 0.45, 95% CI: 0.22-0.89). Soy treatment did not have any effect on insulin resistance (OR = 1.92; 95% CI: 0.80-4.83), which might be attributed to the fact that the HOMA-IR values at baseline in most of our patients were in the normal range. Advanced hepatic fibrosis, an ALT level > 1.5 × ULN and visceral fat were predictors of an HOMA-IR ≥ 3. The IG group had a reduced risk of an ALT level > 1.5 × ULN. An HOMA-IR ≥ 3 and HDL < 35 mg/dL were also risk factors for increased ALT.

CONCLUSION: Soy supplementation decreased ALT levels.
levels and thus may improve liver inflammation in hepatitis C virus (HCV) patients; it also reduced hepatic steatosis in a subgroup of patients but did not change insulin resistance. It should be considered in the nutritional care of HCV patients.

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Key words: Chronic hepatitis C; Soy supplementation; Insulin resistance; Hepatic steatosis; Hepatitis C virus

Materials and Methods

Subjects

Non-diabetic patients with chronic hepatitis C were recruited from a reference ambulatory unit of the Federal University of Bahia’s Hospital between June 2008 and December 2009. The diagnosis of HCV infection was made by the presence of serum anti-HCV, which was confirmed by qualitative determination of HCV RNA. Inclusion criteria were the following: patients aged over 18 years, with or without liver cirrhosis; patients with ethanol consumption below 20 g/d; patients with normal liver function (Child-Pugh A); and patients who were not under antiviral therapy or who had discontinued antiviral therapy for at least three months.

Patients co-infected with HIV and/or HBV with renal failure as well as those with heart disease, decompensated cirrhosis, pregnancy, any malignancy, diabetes mellitus or obesity (BMI > 30 kg/m²) were excluded. The subjects gave written informed consent before participating in the study. The Ethics Committee of the Federal University of Bahia approved the study.

Study design

The study was a prospective, randomized and single-blinded clinical trial. Patients who were regularly followed in the Hepatology outpatient clinic were informed about the protocol and referred to the Nutrition clinic. Subjects who met the inclusion criteria of the study were randomly allocated into one of two study groups. The study was a prospective, randomized and single-blinded (only blinded for patients). The estimated sample size was 160 patients.

The 160 patients were equally divided into two groups (n = 80), and each group received isonitrogenous protein supplementation with 32 g of protein per day for twelve weeks. The control group (CG) was supplemented with animal protein (casein), and the intervention group (IG) was supplemented with vegetable protein (soy). The nutritional composition of the supplements used in this study is reported in Table 1.

Patients were instructed to dissolve the protein supplement in water, juice, soup, porridge or to consume it with fruits. Additionally, considering their nutritional status and dietary habits, patients received dietary guidelines to promote healthy eating and weight control. Diet counseling aimed to promote the ingestion of a normocaloric, normoglycemic and high protein (1.5 g/kg per day) diet by both groups. Patients returned monthly to receive their supplements.
with an Elecsys 2010 device.

Plasma glucose, insulin, total cholesterol and cholesterol gamma glutamyl transferase (GGT) were determined aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, and beta-glucuronidase (B) were also measured in patients with a diagnosis of non-alcoholic fatty liver disease. The cutoff points adopted for the diagnosis of liver steatosis were as follows: AST > 40 U/L (male) or > 30 U/L (female), ALT > 35 U/L (male) or > 25 U/L (female), and GGT > 45 U/L (male) or > 28 U/L (female).

After a 12-h fast, a blood sample was collected for the determination of aspartate aminotransferase (AST), ALT, gamma-glutamyl transferase (γGT), alkaline phosphatase, plasma glucose, insulin, total cholesterol and cholesterol fractions. Analyses were performed on a Beckman Coulter LX-20 PRO and CX-9 equipment. Serum insulin was measured using an electrochemiluminescence method with an Elecsys 2010 device.

The characterization of the study population is presented in Table 2. Males (63.8%) were predominant. The prevalence of HCV genotype 1 infected patients was 83.5%.

### Table 1 Nutritional content per 100 g of supplement

<table>
<thead>
<tr>
<th></th>
<th>Whole soy powder</th>
<th>Calcium caseinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (Kcal)</td>
<td>392</td>
<td>371</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>40</td>
<td>97.4</td>
</tr>
<tr>
<td>Total fat (g)</td>
<td>18.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Alpha linoleic acid (mg)</td>
<td>1252</td>
<td>0</td>
</tr>
<tr>
<td>Linoleic acid (mg)</td>
<td>9332</td>
<td>0</td>
</tr>
<tr>
<td>Dietary fiber (g)</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Isoflavones (mg)</td>
<td>53.82</td>
<td>0</td>
</tr>
</tbody>
</table>

*Soyos<sup>®</sup> ingredients.

### Clinical parameters

Clinical survey data such as clinical diagnosis, viral genotyping, necroinflammatory activity index and fibrosis (METAVIR classification) were either collected from medical records or from patient examinations. Patients underwent ultrasonography of the upper abdomen with a team of three examiners using a single piece of equipment at the University Hospital’s radiology service. Hepatic steatosis was graded as mild, moderate or severe according to the classification of Saverumuttu et al<sup>[46]</sup>.

Measurement of waist circumference was performed according to the World Health Organization recommendations using an inelastic tape measure (TBW Import Ltd.) that was 0.5 cm wide and 200 cm in length. Waist circumference was measured at a level midway between the superior aspect of the iliac crests and the lower lateral margins of the ribs. The cutoff points adopted for classifying central obesity and increased risk of metabolic complications were above 80 cm for women and 94 cm for men<sup>[17]</sup>. Socio-demographic and lifestyle information was also collected using a structured questionnaire during the first appointment of follow-up (baseline).

Patients underwent follow-up visits once a month with registered dietitians to elucidate the adherence to the diet prescription and protein supplementation. Schedule monitoring also included weekly telephone calls in the first month and biweekly thereafter. After 12 wk of supplementation, physical, biochemical and anthropometric tests as well as a questionnaire were applied to evaluate possible changes during the intervention program. Ultrasound was also performed in patients with a diagnosis of hepatic steatosis at baseline. All procedures were performed within a maximum interval of ten days after the nutrition counseling.

### Laboratory measurement

After a 12-h fast, a blood sample was collected for the determination of aspartate aminotransferase (AST), ALT, gamma glutamyl transferase (γGT), alkaline phosphatase, plasma glucose, insulin, total cholesterol and cholesterol fractions. Analyses were performed on a Beckman Coulter LX-20 PRO and CX-9 equipment. Serum insulin was measured using an electrochemiluminescence method with an Elecsys 2010 device.

The insulin resistance index was predicted according to the homeostasis model assessment index of insulin resistance (HOMA-IR). The formula was as follows: insulin resistance (HOMA-IR) = (fasting insulinemia (microU/mL) × fasting glycemia (mmol/L))/22.5<sup>[18]</sup>. We considered ≥ 3.0 as the cutoff point to define insulin resistance.

### Virolological tests

An enzyme linked immunosorbent assay was performed on all serum samples to detect the presence of anti-HCV using third generation commercial kits (anti-HCV Hepatitis C<sup>®</sup> Wiener Lab.) following the manufacturer’s instructions. Reverse transcription-polymerase chain reaction (RT-PCR) was performed on all samples for qualitative determination of HCV RNA. The method used was the nested PCR (HCV-RNA detectable using the COBAS<sup>®</sup> AMPlicor HCV Test, v2.0, Roche). HCV genotyping was performed using the technique of restriction fragment polymorphism (RFLP-PCR).

### Histological analysis

The stages of fibrosis and inflammation were determined according to the METAVIR scoring system: F0 = no fibrosis, F1 = expansion of fibrosis in portal areas without septa, F2 = fibrous portal expansion with septa, F3 = numerous septa or fibers with nodular transformation, and F4 = cirrhosis<sup>[19]</sup>.

### Statistical analysis

Descriptive analysis was performed to characterize the population. Mann-Whitney U and Wilcoxon’s rank sum tests were used to compare the biochemical values in the intervention and control groups and to evaluate the differences obtained at baseline and after intervention. Logistic regression analysis was used to evaluate risk predictor factors for hepatic steatosis, insulin resistance (HOMA-IR ≥ 3.0) and changes in ALT levels (1.5 above the upper limit of normal). Confounding and interaction analyses were performed to select the final models. Multiple regression analysis was performed after the intervention considering the groups had similar demographic, clinical and laboratory features before protein supplementation.

The sample size was calculated using an estimated 20% loss to follow-up, a confidence level of 95% and 80% power. A statistical significance was inferred at P < 0.05. In some biochemical analyses, the Bonferroni method was applied to adjust the multiple comparisons P-value between the groups at the significance level of 0.007. Statistical analysis was performed with the statistical package R version 2.12<sup>[20]</sup>.

### RESULTS

### Characteristics of patients

The characterization of the study population is presented in Table 2. Males (63.8%) were predominant. The prevalence of HCV genotype 1 infected patients was 83.5%.
Advanced fibrosis (Metavir F3/F4) was detected in 40.5% of patients. The average age was 52.2 (± 10.5) years, 48.1% were overweight and 51.9% had a BMI < 25 kg/m²; 43.7% individuals had abdominal fat accumulation. It was also observed that 34.7% of the patients had hepatic steatosis, and 36.3% had an HOMA-IR ≥ 3.0 at baseline.

Biochemical data presented in Table 2 show that glucose and lipid profiles were not altered; however, high transaminase levels were observed in both groups. It is also observed that the median value for γGT is greater in the CG than in the IG (102.0 U/L vs 87.0 U/L); however, no significant difference was detected between the groups. Median alkaline phosphatase was in the normal range for both groups. Baseline demographic, anthropometric, clinical and laboratory data show that the study population had a homogeneous distribution between the groups.

Table 3 shows the comparison of the prevalence of hepatic steatosis before and after the intervention in the IG and CG. The prevalence of hepatic steatosis was different between the groups at baseline (29.7% vs 40.0%) and remained different after the interventions (15.6% vs 26.7%), but without statistical significance in both instances (Figure 1).

Paired analysis, within groups (before and after protein supplementation), showed the reduction in hepatic steatosis was significant for both groups. The IG showed a reduction from 19 to 10 cases (47.4% reduction, \( P = \))

in the CG than in the IG (102.0 U/L vs 87.0 U/L); however, no significant difference was detected between the groups. Median alkaline phosphatase was in the normal range for both groups. Baseline demographic, anthropometric, clinical and laboratory data show that the study population had a homogeneous distribution between the groups.

### Table 2 Characterization of the study population \( n (\%) \)

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>CG-casein</th>
<th>IG-soy</th>
<th>Total</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (61.2)</td>
<td>31 (38.8)</td>
<td>80 (63.8)</td>
<td>0.024²</td>
</tr>
<tr>
<td>Female</td>
<td>31 (38.8)</td>
<td>53 (61.2)</td>
<td>84 (66.2)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>37 (46.7)</td>
<td>30 (37.1)</td>
<td>67 (52.9)</td>
<td>0.0077²</td>
</tr>
<tr>
<td>Single, widowed or divorced</td>
<td>23 (28.8)</td>
<td>35 (42.2)</td>
<td>58 (47.1)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Comparison of the distribution of hepatic steatosis before and after intervention between groups of patients with hepatitis C virus

<table>
<thead>
<tr>
<th>Hepatic Steatosis</th>
<th>( n )</th>
<th>Yes</th>
<th>No</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>64</td>
<td>19</td>
<td>45</td>
<td>0.2604²</td>
</tr>
<tr>
<td>CG-casein</td>
<td>60</td>
<td>24</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>64</td>
<td>10</td>
<td>54</td>
<td>0.1850²</td>
</tr>
<tr>
<td>IG-soy</td>
<td>60</td>
<td>16</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>IG-soy: before vs after</td>
<td>0.0077²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hepatic steatosis</td>
<td>19</td>
<td>10</td>
<td>9</td>
<td>(47.4%)</td>
</tr>
<tr>
<td>Without hepatic steatosis</td>
<td>45</td>
<td>0</td>
<td>45</td>
<td>(100.00)</td>
</tr>
<tr>
<td>GC-casein: before vs after</td>
<td>0.0133²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hepatic steatosis</td>
<td>24</td>
<td>16</td>
<td>8</td>
<td>(33.3%)</td>
</tr>
<tr>
<td>Without hepatic steatosis</td>
<td>36</td>
<td>0</td>
<td>36</td>
<td>(100.00)</td>
</tr>
</tbody>
</table>

1 Fishers exact test: Comparison between groups before and after intervention; ²Paired analysis: McNemar’s test: Comparison in each group. CG-casein: Control group-casein; IG-soy: Intervention group-soy.

**Figure 1** Hepatic estatosis before and after intervention between groups of patients with hepatitis C virus.
0.0076) and the CG decreased from 24 to 16 cases (33.3% reduction, \( P = 0.0133 \)) (Figure 2 and Table 3).

### Biochemical data before and after intervention

After protein supplementation, a significant reduction was observed in the transaminase levels of the IG vs the CG (AST \( \leq 49.5 \) U/L \( vs \) 61.5 U/L, \( P = 0.02 \); ALT \( \leq 64.0 \) U/L \( vs \) 73.0 U/L, \( P = 0.007 \)). A reduction in the levels of γGT was observed in the IG compared to the CG (84.0 U/L \( vs \) 108.0 U/L, \( P = 0.09 \)) but without statistical significance (Table 4).

The IG had a significant reduction in ALT levels (73.5 U/L \( vs \) 64.0 U/L; 12.92% change, \( P = 0.006 \)) (Figure 3) and γGT levels (87.0 U/L \( vs \) 84.0 U/L; 3.45% change, \( P = 0.007 \)) after 12 wk of intervention. Reductions were also observed in total cholesterol (160.0 mg/dL \( vs \) 153.0 mg/dL; 4.37% change), but without statistical significance (Table 5). It is noteworthy that the CG did not present improvements in these biochemical tests.

### Predictors of hepatic steatosis after intervention

Table 6 presents the logistic regression analysis for predictive factors of hepatic steatosis. Multiple regression modeling indicates that, in the presence of severe fibrosis (F3/F4), γGT elevation and HDL reduction, the IG had a 75% less chance of developing hepatic steatosis (OR = 0.25; 95% CI 0.06-0.82). Nevertheless, in the IG, those with an HOMA-IR ≥ 3 were three times more likely to develop hepatic steatosis (OR = 3.49; 95% CI 1.10-11.90) (Table 6). The bivariate analysis also revealed that an age ≥ 60 years (crude OR = 3.81; 95% CI 1.50-9.70), abdominal fat accumulation (crude OR = 3.87; 95% CI 1.57-10.29) and BMI ≥ 25.0 kg/m² (crude OR = 1.32; 95% CI 1.12-1.61) were independent risk factors for hepatic steatosis (data not shown).

### Predictors of insulin resistance (HOMA-IR ≥ 3.0) after intervention

Soy treatment did not have any effect on insulin resistance (OR = 1.92; 95% CI 0.80-4.83). In patients with advanced fibrosis, an ALT level ≥ 1.5 times upper limit of normal (ULN) and increased abdominal fat accumulation were independent risk factors for insulin resistance.
Logistic regression analysis showed that the presence of severe fibrosis promoted a five-fold increase in the chance (OR = 5.25; 95% CI: 2.17-13.67) for an HOMA-IR ≥ 3.0 as well as accumulation of abdominal fat (OR = 5.57; 95% CI: 2.23-15.27). Those with an ALT level ≥ 1.5 × ULN had a three times greater chance of developing insulin resistance. Being single, widowed or divorced was a protective factor (OR = 0.24; 95% CI: 0.08-0.65) for an HOMA-IR ≥ 3.0 (Table 7).

**Predictors of elevated an ALT level after intervention**

The independent predictive factors for changes in ALT levels (≥ 1.5 × ULN) were an HOMA-IR ≥ 3.0, HDL < 35 mg/dL and being a male subject (Table 8). Severe fibrosis and alterations in AST and γGT levels were also independent predictors of an increased ALT level (≥ 1.5 × ULN). Multivariate analysis showed that supplementation with soy protein per se represents a protective factor; the IG had a 55% less chance of presenting with an ALT level ≥ 1.5 × ULN (OR = 0.45, 95% CI: 0.22-0.89), and subjects with an HOMA-IR ≥ 3.0 were three times more likely to have an increased ALT level (OR = 3.16, 95% CI: 1.51-6.93). However, females had 72% less chance to have an increased ALT level (OR = 0.28, 95% CI: 0.12-0.60) (Table 8).

**DISCUSSION**

Our population was predominantly male, infected with HCV genotype 1, overweight and presented abdominal
fat accumulation. Both studied groups had similar characteristics. These clinical conditions increase the chances of developing insulin resistance and hepatic steatosis, which have a negative impact in patients with chronic hepatitis C [21]. In patients infected with HCV genotype 1, steatosis is frequently associated with metabolic syndrome and insulin resistance and is also called “metabolic steatosis” [8,21].

A large proportion of our patients had increased liver enzymes (i.e., ALT, AST, γGT) and had not yet been subjected to antiviral treatment. In our population, at baseline, there was a 34.7% prevalence of hepatic steatosis and a 36.3% prevalence of an HOMA-IR ≥ 3.0. The prevalence of hepatic steatosis associated with HCV varies widely in the literature [22,23], and may differ depending on the population profiles [24].

In this study, protein supplementation caused a significant reduction of hepatic steatosis in both groups; however, this reduction was not significant between the groups. The probable mechanism is not associated with the quality of protein supplementation (animal or vegetable) but likely the nutritional care offered to both groups, which promoted changes in eating habits and consequently improved the overall quality of the diet. Of note, there was no change in body mass index (BMI) or in the pattern of physical activity of these patients.

It is controversial whether insulin resistance is a cause or consequence of steatosis, however the literature suggests that it seems to work more like a cause than a consequence of steatosis in patients infected with HCV genotype 1 [2]. In the present study, the regression model showed that an HOMA-IR ≥ 3 increased the chances of hepatic steatosis more than three-fold. The regression model also revealed that advanced age (≥ 60 years) and a higher waist circumference and BMI were independent predictor factors for hepatic steatosis. These results are in agreement with other studies which have observed a direct correlation between BMI, visceral obesity and liver steatosis [25-27].

Clinical and experimental studies suggest that soy protein and isoflavones can synergistically act to promote a greater benefit in controlling hypercholesterolemia, hypertriglyceridemia, insulin resistance and steatosis [3,12,26,29]. We observed that consumption of soy protein had a protective effect and was associated with 75% less chance of having hepatic steatosis.

In an experimental study with obese Zucker rats, a diet with isolated soy protein favored reduced triglycerides in the liver. The proportions of AST/ALT, alkaline phosphatase, bile acids in plasma and pro-inflammatory cytokines (TNF-α and II.1) were also reduced. The authors suggested that soy protein enriched with isoflavones has a favorable effect on the inflammatory status of obese mice, which may promote a favorable outcome in NAFLD patients [30]. It is known that oxidative stress is a decisive factor in the progression of steatosis [30,31]; thus, if isoflavones can act as an antioxidant, then they may minimize the negative progression of steatosis [32,33].

The morbidity of hepatic steatosis is increasing and has been recognized as a liver component of the metabolic syndrome, which also has a negative effect on HCV treatment [26,29,34-36].

Our data revealed a significant decrease in ALT values after supplementation with soy protein compared to the control patients who consumed casein. These findings agree with experimental studies, which have found that soy protein enriched with isoflavones reduces plasma aminotransferase levels [33] and the proportion of AST/ALT [28]. However, a reduction in HOMA-IR levels after supplementation with soy was not observed in our study, which can be attributed to the fact that the HOMA-IR values at baseline in most of our patients were in the normal range. In contrast, Jayagopal et al. [31] in a study conducted with diabetic women in which the mean value of the HOMA-IR was 5.54 in the intervention group and 5.14 in the control group, supplementation with soy protein enriched with isoflavones significantly reduced serum insulin and the HOMA-IR.

We found that insulin resistance (HOMA-IR ≥ 3.0) and lower HDL values were predictors for increased ALT. Soy protein intervention in female subjects presented per se as a protective factor for increased ALT levels. Our data are in agreement with a recent study that showed higher levels of ALT were significantly associated with gender, a low HDL level and a high HOMA-IR [29]. When evaluating patients with HCV with and without changes of ALT levels and healthy controls, Addel-Azziz et al. [31] found a higher value of HOMA-IR in patients with abnormal ALT levels compared with those with no change in ALT levels and healthy controls (3.98 vs 2.69 vs 1.92, respectively), with a significant difference between those with abnormal ALT levels and controls (3.98 vs 1.92).

In our study, abdominal fat concentration, an ALT level ≥ 1.5 the upper limit of normal and the presence of advanced fibrosis were independent predictors of insulin resistance, and even in a multivariate model, they
remained significant. Addel-Azziz et al. also detected a positive correlation between the HOMA-IR and fibrosis. We detected that marital status was a predictor for insulin resistance as well; single, widowed or divorced patients were less susceptible to inadequacy of the HOMA-IR. This could be associated with the fact that a higher prevalence of overweight and abdominal fat accumulation has been described among married subjects.

In patients with hepatitis C, the presence of a high BMI, insulin resistance and high cholesterol are important predictors for mortality. Multivariate analysis has shown increased mortality associated with metabolic disorders such as diabetes, hypertension and a higher BMI]. Mehta et al. found that individuals with HCV and an age above 40 years had a three-fold higher chance of presenting with type 2 diabetes. Therefore, it is recommended that all patients with chronic hepatitis C avoid excess weight and maintain blood glucose, cholesterol levels and blood pressure within normal ranges.

Soy supplementation decreased ALT levels and thus may improve liver inflammation in HCV patients. It also reduced hepatic steatosis in a subgroup of individuals with advanced fibrosis, insulin resistance, increased γGT levels and low HDL. On the other hand, soy supplementation did not change insulin resistance, which might be attributed to the fact that the HOMA-IR values at baseline in most of our patients were in the normal range. To our knowledge, this is the first study to show that soy protein supplementation reduces hepatic steatosis and decreases ALT levels in chronic hepatitis C patients. Control of insulin resistance, hepatic steatosis, abdominal obesity and body weight seems to play an essential role in nonpharmacological therapies for chronic hepatitis C treatment. These practices should therefore be encouraged by a multidisciplinary team. Supplementation with soy protein should be considered as an important choice of nutritional management of patients with chronic hepatitis C.

**COMMENTS**

**Background**

Hepatitis C virus (HCV) infection is an important public health problem and is the leading cause of liver transplantation in the Western world. Chronic HCV infection increases the risk for hepatic steatosis, insulin resistance, glucose intolerance and type 2 diabetes. The improvement of these comorbidities may benefit the clinical course of the patients.

**Research frontiers**

Several studies have shown that soy protein may stimulate peroxisome proliferator-activated receptors-α and thus might increase liver fatty oxidation and decrease hepatic steatosis. It also may inhibit sterol regulatory element-binding transcription factor 1 and decrease hepatic lipogenesis. Clinical studies have previously demonstrated that soy consumption may reduce plasma lipid levels, promote insulin resistance reduction and maintain normal glucose levels. HCV infection may be associated with hepatic steatosis and increased insulin resistance. The morbidity of hepatic steatosis is increasing and it has been recognized as a liver component of the metabolic syndrome, which also has a negative effect on HCV treatment. The role of soy supplementation in the improvement of liver diseases is still a matter of debate and there are no studies that have evaluated its effect on insulin resistance, liver fat content and alanine transaminase (ALT) levels in non-diabetic patients with chronic hepatitis C.

**Innovations and breakthroughs**

Our work is characterized by its originality since it evaluated the impact of soy nutritional intervention in a population of patients infected with hepatitis C. To our knowledge, this is the first study to show that soy protein supplementation decreases ALT levels and reduces hepatic steatosis in a subgroup of individuals with advanced fibrosis, insulin resistance, increased γGT levels and low HDL in chronic hepatitis C. In an experimental study with obese Zucker rats, a diet with isolated soy protein favored reduced triglycerides in the liver. The AST/ALT ratio, alkaline phosphatase, bile acids in plasma and pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-1) were also reduced. However, there are no clinical studies that have evaluated the role of soy supplementation on liver enzymes levels, insulin resistance and hepatic steatosis of patients with chronic HCV infection. The authors emphasize the need for further clinical trials to confirm the soy effects on ALT levels and hepatic steatosis of patients with chronic HCV infection.

**Applications**

This study showed that soy supplementation may improve liver inflammation (decrease ALT level), and may improve steatosis in a subgroup of patients with HCV. Therefore, supplementation with soy protein should be considered in the nutritional management of patients with chronic hepatitis C. However, further clinical trials are necessary to confirm our results.

**Terminology**

HOMA-IR: Homeostasis model assessment index of insulin resistance; PPARs: Peroxisome proliferator-activated receptors. These are nuclear receptors that function as transcription factors regulating the expression of genes. PPARs play essential roles in the regulation of cellular differentiation and metabolism (carbohydrate, lipid, protein); SREBP-1: Sterol regulatory element-binding tran-
scription factor 1 is a transcription factor involved in sterol biosynthesis.

**Peer review**

The topic of the study is interesting and based on rational logic. The design of the study is appropriate, but to be sure of that we need to know some more information about the recruitment, randomization and blinding method. In a clinical trial design the conclusions are based only in the analysis performed for the main objectives of the study, otherwise the conclusion from sub-analysis must be biased.

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