Fructose-Induced Fatty Liver Disease
Hepatic Effects of Blood Pressure and Plasma Triglyceride Reduction

Zvi Ackerman, Mor Oron-Herman, Maria Grozovski Talma Rosenthal, Orit Pappo, Gabriela Link, Ben-Ami Sela

Abstract—The most known risk factor for nonalcoholic fatty liver disease (NAFLD) is the metabolic syndrome. In this study, we characterized changes in liver pathology, hepatic lipid composition, and hepatic iron concentration (HIC) occurring in rats given fructose-enriched diet (FED), with and without therapeutic maneuvers to reduce blood pressure and plasma triglycerides. Rats were given FED or standard rat chow for 5 weeks. Rats on FED were divided into 4 groups: receiving amlodipine (15 mg/kg per day), captopril (90 mg/kg per day), bezafibrate (10 mg/kg per day) in the last 2 weeks, or a control group that received FED only. FED rats had hepatic macrovesicular and microvesicular fat deposits develop, with increase in hepatic triglycerides (+198%) and hepatic cholesterol (+89%), but a decrease in hepatic phospholipids (−36%), hypertriglyceridemia (+223%), and hypertension (+15%), without increase in HIC. Amlodipine reduced blood pressure (−18%), plasma triglycerides (−12%), but there was no change in hepatic triglycerides and phospholipids concentrations. Captopril reduced blood pressure (−24%), plasma triglycerides (−36%), hepatic triglycerides (−51%), and hepatic macrovesicular fat (−51%), but increased HIC (+23%), with a borderline increase in hepatic fibrosis. Bezafibrate reduced plasma triglycerides (−49%), hepatic triglycerides (−78%), hepatic macrovesicular fat (−90%), and blood pressure (−11%). We conclude that FED rats can be a suitable model for human NAFLD. Drugs administered to treat various aspects of the metabolic syndrome could have hepatic effects. An increase in HIC in rats with NAFLD could be associated with increased hepatic fibrosis. (Hypertension. 2005; 45:1012-1018.)

Key Words: amlodipine ■ bezafibrate ■ captopril ■ iron ■ nonalcoholic steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are increasingly recognized causes of liver disease and liver-related morbidity and mortality. The cause of NAFLD is multifactorial; however, the most known risk factor for NAFLD is the presence of the metabolic syndrome that includes insulin resistance, diabetes mellitus type II, obesity, dyslipidemia (mainly hypertriglyceridermia), and hypertension. Obesity and diabetes type II are considered risk factors for the development of the more severe manifestations of NAFLD, like NASH and cirrhosis. Recently, it has been suggested that to develop the more severe forms of NAFLD, 2 prerequisite conditions should exist: producing steatosis and a source of oxidative stress capable of initiating significant lipid peroxidation. In rats, moderate iron overload is known to enhance lipid peroxidation in the liver. Co-administration of iron and alcohol can facilitate the induction of significant liver injury and fibrosis. Hepatic iron overload is a relatively common finding in many patients with end-stage nontubular liver disease who do not have genetic hemochromatosis. However, it has been suggested that a mild increase in hepatic iron concentration in patients with NAFLD is associated with increased fibrosis. Moreover, it has also been suggested that the iron overload itself is responsible for the insulin resistance and iron depletion may even improve peripheral insulin sensitivity. Furthermore, it has been suggested that hyperinsulinemia seen in many patients with NASH may influence iron metabolism and may even increase iron pool that may again exacerbate liver injury. Improvement of glycemic control and other metabolic defects in patients with diabetes mellitus and NAFLD was reported to decrease hepatic iron concentration. Nevertheless, despite the ample presented evidence, there are a few groups of researchers that found no correlation between increased hepatic fibrosis and iron overload in patients with NAFLD.

NAFLD has no definite medical therapy. In the absence of treatment modalities of proven efficacy, it is recommended to correct the risk factors for NAFLD and especially for NASH. In our laboratory, we are presently experimenting with the fructose-enriched diet (FED) rat model that is charac-

Received November 16, 2004; first decision December 8, 2004; revision accepted March 21, 2005.
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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000164570.20420.67

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terized by many components of syndrome X, like insulin resistance, hypertriglyceridemia, hypertension, and hyperhomocysteinemia.24–27

The aims of the present work were to characterize liver pathology and function, hepatic lipid composition and hepatic iron concentration (HIC), and fasting plasma insulin changes that occur in rats as a result of FED, with and without therapeutic maneuvers to reduce blood pressure and plasma triglycerides.

Methods

Forty-nine male Sprague-Dawley rats (Harlan Laboratories Limited; Jerusalem, Israel) weighing 200±20 grams were studied. Rats were housed in regular cages situated in an animal room at 22°C, with a 14-hour light/10-hour dark cycle. Rats were maintained on standard drinking water. Systolic blood pressure (BP) was measured in conscious rats by the indirect tail-cuff method using an electrosphygmomanometer and a pneumatic pulse transducer (Narco Biosystems, Houston, Tex). The animals were kept at 37°C for 30 minutes before measurements were taken. The mean of 5 consecutive readings was recorded as BP. Blood samples were taken from a retro-orbital sinus puncture under light ether anesthesia from all rats after 5 hours of fasting. Triglyceride concentration was measured with an automatic analyzer (Olympus AU2700; Hamburg, Germany). Additional biochemical parameters from the end of the study period, such as albumin, liver enzymes, cholesterol, and glucose, were measured by dry chemistry method (Kodak, Rochester, NY). Tumor necrosis factor-α and transforming growth factor β-1 were assayed by rat-specific RIA kits (R & D Systems). Insulin was assayed by a rat-specific RIA kit (Incstar, Stillwater, Minn). Insulin resistance was calculated by the Homeostasis Model Assessment score [fasting plasma insulin (μU/mL)×fasting plasma glucose (mmol/L)/22.5].28 Sections from the liver of each animal involved in the study were stained with hematoxylin & eosin for evaluation of necro-inflammatory grading. Masson trichrome stain for fibrosis and architectural changes, oil-red “O” for the evaluation of fatty droplets (macrovesicular or microvesicular steatosis), and with Perl’s Prussian blue for detection of iron. Histological changes were assessed by a modification of the scoring system for grading and staging for NASH described by Brunt et al29 (please see http://hyper.ahajournals.org). The histological evaluation of the liver sections was performed blindly.

Determination of Hepatic Lipids

Hepatic lipids (total lipids, phospholipids, triglycerides, and cholesterol) were measured as previously described.30–34

Determination of Hepatic Iron Concentration

Hepatic nonheme iron concentrations were measured by the method of Torrance and Bothwell.35

Statistical Evaluation

Results are expressed as mean±standard error. Comparisons between groups used 1-way analysis of variance with Tukey-Kramer multiple comparisons test. P<0.05 was considered statistically significant. The statistical analysis was performed using GraphPad Instant (Version 2.01; Mayo Foundation).

Results

Effects of FED

Baseline parameters did not differ between the rats that were scheduled for FED and the rats that were scheduled for further maintenance on SRCD. After 3 weeks, both groups...
had similar weight gain. However, the group on FED had 18% higher BP values, 188% higher plasma triglyceride levels, and 55% higher plasma insulin levels. After 5 weeks, the rats on FED again had similar weights but 15% higher BP, 223% higher plasma triglycerides, and 114% higher Homeostasis Model Assessment score than the SRCD rats (Tables 1 and 2). No change in liver enzymes was observed between both groups. However, the ratio of alanine to aspartate aminotransferase that was 1.2:1.0 in the SRCD group increased to 2.0:1.0 in the FED rats (Table 2). The livers of the FED rats had higher concentrations of total lipids (+43%) and hepatic cholesterol (+35%) was observed. This was accompanied with no significant histological changes (Figure and Tables 1 to 5). Insulin resistance improved.

In the group that received captopril, the alanine aminotransferase levels were the highest observed (Table 2). HIC, although insignificant, was increased (Table 4). Plasma triglyceride levels decreased (−36%) as well as hepatic triglycerides (−51%). Hepatic phospholipids concentrations increased (+37%) (Table 3). This was accompanied by a reduction of the macrovesicular fat score (−51%), but with no change in microvesicular fat score. Fibrosis, albeit minimal, was evident in 6 out of 8 rats that received captopril. (Figure and Tables 5 and 6)

Amlodipine and captopril administration caused an insignificant increase in transforming growth factor β-1 levels (Table 2).

Effects of Antihypertensive Medication
As expected, amlodipine and captopril caused a reduction in BP measurements in both groups of rats (−18% and −24%, respectively; Table 1). However, BP reduction was not the only effect observed in these rats. Amlodipine administration caused a reduction of plasma triglycerides (−12%) but no change in hepatic triglycerides and phospholipids. An increase in concentrations of hepatic total lipids (+43%) and hepatic cholesterol (+35%) was observed. This was accompanied with no significant histological changes (Figure and Tables 1 to 5). Insulin resistance improved.

### Effects of Pharmacologic Intervention
Baseline and week 3 parameters did not vary between the 4 groups of rats on FED (Table 1).

### Table 2. Week 5 Liver-Related Parameters, Plasma Biochemistry, and Cytokines

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Chow</th>
<th>FED Only</th>
<th>FED and Amlodipine</th>
<th>FED and Captopril</th>
<th>FED and Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Splenic weight, grams</td>
<td>0.7±0.03</td>
<td>0.6±0.02</td>
<td>0.6±0.02</td>
<td>0.6±0.03</td>
<td>0.6±0.03</td>
</tr>
<tr>
<td>Liver weight, grams</td>
<td>9.6±0.04</td>
<td>10.1±0.4</td>
<td>9.9±0.3</td>
<td>8.7±0.3</td>
<td>11.8±0.5*</td>
</tr>
<tr>
<td>Liver/body weight ratio</td>
<td>0.031±0.001</td>
<td>0.033±0.001</td>
<td>0.036±0.002</td>
<td>0.029±0.001</td>
<td>0.037±0.001</td>
</tr>
<tr>
<td>Albumin, gram/L</td>
<td>30.5±0.7</td>
<td>33.8±0.7</td>
<td>34.8±0.8</td>
<td>33.4±1.6</td>
<td>33.3±0.6</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>18.1±0.3</td>
<td>14.4±0.8</td>
<td>15.4±0.8</td>
<td>11.7±1.4</td>
<td>14.9±1.2</td>
</tr>
<tr>
<td>Alanine amino-transferase, IU/L</td>
<td>39.5±1.7</td>
<td>41.2±1.6</td>
<td>47.8±7.3</td>
<td>74±9.0*</td>
<td>42.7±1.7</td>
</tr>
<tr>
<td>Aspartate amino-transferase, IU/L</td>
<td>33.9±5.0</td>
<td>20.3±1.4</td>
<td>20.0±5.4</td>
<td>18.3±12.3</td>
<td>44.1±12.2</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>85.9±4.5</td>
<td>100.6±2.5</td>
<td>105.2±4.2</td>
<td>105.3±9.8</td>
<td>87.7±2.2</td>
</tr>
<tr>
<td>Lactic dehydrogenase, IU/L</td>
<td>357.6±24.9</td>
<td>715.4±96.8</td>
<td>766.4±167.8</td>
<td>1504±272.1</td>
<td>1006.0±289.0</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.9±0.3</td>
<td>9.0±0.4</td>
<td>8.3±0.3</td>
<td>8.7±0.3</td>
<td>7.2±0.4*</td>
</tr>
<tr>
<td>HOMA-IR score</td>
<td>8.1±0.6*</td>
<td>17.3±1.9</td>
<td>12.3±1.1*</td>
<td>13.1±1.2</td>
<td>9.2±0.5*</td>
</tr>
<tr>
<td>TGF-β1, pg/mL</td>
<td>23.1±5.1</td>
<td>19.5±4.7</td>
<td>27.1±6.4</td>
<td>28.4±7.7</td>
<td>15.0±1.7</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>&lt;12.5</td>
<td>&lt;12.5</td>
<td>&lt;12.5</td>
<td>&lt;12.5</td>
<td>&lt;12.5</td>
</tr>
</tbody>
</table>

HOMA-IR indicates homeostasis model assessment insulin resistance; TGF-β1, transforming growth factor β-1; TNF-α, tumor necrosis factor alpha.

*P<0.05 (vs FED).

### Table 3. Hepatic Lipids Composition

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Chow</th>
<th>FED Only</th>
<th>FED and Amlodipine</th>
<th>FED and Captopril</th>
<th>FED and Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Total lipids, mg/gram liver</td>
<td>23.1±0.4*</td>
<td>29.5±0.4</td>
<td>42.2±0.4*</td>
<td>32.5±0.5*</td>
<td>30.6±0.3</td>
</tr>
<tr>
<td>Phospholipids, mmol/gram liver</td>
<td>14.6±0.1*</td>
<td>9.3±0.2</td>
<td>9.6±0.1</td>
<td>12.7±0.1*</td>
<td>13.1±0.05*</td>
</tr>
<tr>
<td>Triglycerides, mmol/gram liver</td>
<td>4.1±0.2*</td>
<td>12.2±0.8</td>
<td>13.3±0.5</td>
<td>6.0±0.4*</td>
<td>2.7±0.1*</td>
</tr>
<tr>
<td>Cholesterol, mg/gram liver</td>
<td>0.9±0.05*</td>
<td>1.7±0.05</td>
<td>2.3±0.07*</td>
<td>1.8±0.06</td>
<td>1.4±0.06*</td>
</tr>
</tbody>
</table>

*P<0.01 (vs FED).
Effects of Bezafibrate

Bezafibrate administration caused a significant increase in the liver weight, as well as a modest increase in iron content (per total liver) but there was no change in HIC.

Bezafibrate administration caused a reduction in plasma (−49%) and hepatic (−78%) triglycerides concentrations and an increase in hepatic phospholipids (+41%). This was accompanied by a significant reduction in the hepatic macrovesicular steatosis (−90%) but no change in the microvesicular steatosis, inflammatory, or fibrosis score. A reduction in BP (−11%) and insulin resistance (−47%) was observed, too (Figure and Tables 1 to 6).

Liver pathology in the various study groups. Photomicrographs of liver samples stained with hematoxylin & eosin and oil-red “O,” respectively, in rats given standard rat chow diet (SRCD) (A, B), in rats on fructose-enriched diet (FED) (C, D), in rats on FED and amlodipine (E, F), in rats on FED and captopril (G, H), and in rats on FED and bezafibrate (I, J).

TABLE 4. Hepatic Iron Content and Stain

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Chow</th>
<th>FED Only</th>
<th>FED and Amlodipine</th>
<th>FED and Captopril</th>
<th>FED and Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Iron, µg/gram liver</td>
<td>49.9±8.0</td>
<td>51.6±3.0</td>
<td>46.3±2.9</td>
<td>66.8±4.5</td>
<td>60.6±4.6</td>
</tr>
<tr>
<td>Iron, µg/total liver</td>
<td>472.2±73.8</td>
<td>525.0±42.1</td>
<td>451.5±27.3</td>
<td>577.1±41.7</td>
<td>712.1±60.7*</td>
</tr>
<tr>
<td>N of rats with positive iron stain†</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Distribution of iron stain</td>
<td>Hepatocytes</td>
<td>NA</td>
<td>Hepatocytes and macrophages</td>
<td>Hepatocytes</td>
<td>Hepatocytes and Kupffer cells</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

*P<0.05 (vs FED).

†In most rats with ‘positive iron stain’ the number of stainable liver cells was not >2%. The number of rats with positive iron stain was the highest in the FED and bezafibrate group (P=0.03 by Fisher exact test vs FED only rats).
Discussion

In the present study, we demonstrated that Sprague-Dawley rats given FED are a suitable model for nonobese rats with NAFLD that present some aspects of the metabolic syndrome, such as hypertension, insulin resistance, and hypertriglyceridemia.1–7,27 To date there are no published controlled trials of effective treatment modalities for NAFLD. Treatment modalities have been directed toward reduction of weight, improvement of insulin resistance, lipid-lowering agents, and hepatoprotective drugs.1,2 In the present study, we investigated the hepatic effects of medications with known beneficial effects on few of the manifestations of the metabolic syndrome, like hypertension and hypertriglyceridemia.

Amlodipine, a calcium channel blocker, in addition to its antihypertensive effects, has known favorable metabolic effects, like improvement of insulin resistance and decreasing low-density lipoprotein cholesterol levels.36,37 Furthermore, amlodipine has been found to have potent antioxidant activities38 and hepatoprotective effects.39 In the present study, we were not able to observe any hepatic beneficial effects. No favorable effects for amlodipine in patients with acute alcoholic hepatitis have been reported.40

Captopril, an angiotensin-converting enzyme inhibitor, has also reported metabolic effects. Captopril improves insulin sensitivity,41 has antioxidant properties,42 and is able to scavengen reactive oxygen species43 and to attenuate the progression of hepatic fibrosis in rats.44 In our study, captopril did not significantly improve insulin resistance; however, there was a significant reduction in plasma and hepatic triglycerides, which was accompanied by a significant reduction in macrovesicular steatosis score. Surprisingly, there was a mild increase in HIC, which was accompanied by an increase in the fibrosis score. Plasma transforming growth factor β-1 levels, a marker of hepatic fibrosis,45 were also increased. Although we did not directly examine the mechanisms responsible for the increased HIC in the rats treated with captopril, data from previous studies suggested that the change was not caused by increased absorption of iron from the gut46 but was probably attributable to increased hemolysis caused by captopril administration with deposition of iron in the liver.47 We may speculate that in the presence of iron, captopril is not able to inhibit iron ion-dependent generation of hydroxyl radicals from hydrogen peroxide48 and may even be a pro-oxidant.49 The presence of both increased HIC and the pro-oxidant properties of captopril could act together to increase the liver collagen synthesis in these rats.49 Our finding are supported the report of George et al that a mild increase in HIC is associated with increased fibrosis.15 Our finding that rats given FED and FED plus amlodipine had “normal” HIC indicates that increased HIC is not needed for the development of uncomplicated steatosis and hyperinsulinemia. Moreover, hyperinsulinemia itself may not cause an increase in HIC.

Hypertriglyceridemia was a prominent feature in the rats given FED. Hypertriglyceridemia is also a frequent finding in patients with NAFLD. Nevertheless, there is an ongoing debate as to whether reduction of high triglyceride may improve liver function or histology.46 In our study, bezafibrate reduced plasma and hepatic triglycerides, which was accompanied by a significant reduction in macrovesicular steatosis score, without a significant increase in microvesicular steatosis score. Moreover, a decrease in BP and insulin resistance was also observed. Administration of bezafibrate to humans with the metabolic syndrome and fenofibrate to rats given FED caused amelioration of many aspects of the metabolic syndrome.50,51 It has been demonstrated that fenofibrate, which, like bezafibrate, is a ligand to peroxisomal proliferator-activated receptor-α, induces enzyme expression related to β-oxidation and the enhancement of mitochondrial gene expression.51 Other peroxisomal proliferator-activated receptor-α agonists may enhance lipid turnover and prevent the development of steatohepatitis.52

### TABLE 5. Liver Histology: Grading and Staging

<table>
<thead>
<tr>
<th></th>
<th>Chow</th>
<th>FED Only</th>
<th>FED and Amlodipine</th>
<th>FED and Captopril</th>
<th>FED and Bezafibrate</th>
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<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Macrovesicular steatosis</td>
<td>0.0±0.0*</td>
<td>1.41±0.13</td>
<td>0.8±0.2</td>
<td>0.69±0.23*</td>
<td>0.15±0.10*</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
<td>0.29±0.10*</td>
<td>1.41±0.23</td>
<td>0.80±0.07</td>
<td>1.12±0.23</td>
<td>1.65±0.21</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td>0.5±0.19</td>
<td>0.82±0.17</td>
<td>0.54±0.119</td>
<td>0.56±0.18</td>
<td>0.65±0.13</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td>0.43±0.2</td>
<td>0.32±0.14</td>
<td>0.42±0.12</td>
<td>0.63±0.08</td>
<td>0.20±0.13</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.0±0.0</td>
<td>0.23±0.12</td>
<td>0.08±0.06</td>
<td>0.625±0.16</td>
<td>0.35±0.13</td>
</tr>
<tr>
<td>n of rats with acidophil bodies</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*P<0.05 (vs FED).

### TABLE 6. Distribution of Fibrosis among the Treatment Groups

<table>
<thead>
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<th></th>
<th>Chow</th>
<th>FED Only</th>
<th>FED and Amlodipine</th>
<th>FED and Captopril</th>
<th>FED and Bezafibrate</th>
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<tr>
<td>n</td>
<td>7</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Total n of rats with any degree of fibrosis</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>N of rats with sinusoidal fibrosis</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>N of rats with portal fibrosis</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
A lesser known metabolic effect of fibrates is their role in iron homeostasis and metabolism. Fibrates may suppress transferrin expression, reduction of hepatic iron efflux, and cause an increase of free iron pool within the liver. These effects are probably needed to conserve iron for the synthesis of a variety of iron-containing enzymes that are upregulated by the fibrates. In our study, the increase in iron liver content in the bezafibrate-treated rats was not accompanied by an increase in hepatic fibrosis. It may be suggested that because in these rats the increase in the total hepatic iron content was not accompanied by an increase in the HIC, no increased toxicity from the iron excess was noted.

The levels of plasma tumor necrosis factor-α were low in all rats, including those given FED. It may be speculated that the levels of this cytokine were low because that the rats were all rats, including those given FED. It may be speculated that because in these rats the increase in the total hepatic iron content was not accompanied by an increase in the HIC, no increased toxicity from the iron excess was noted.

Perspectives
This study demonstrates that the model of fructose-treated rats can be a suitable model for studying various aspects of human NAFLD. An increase in hepatic iron concentration in rats with NAFLD may be associated with increased hepatic fibrosis.

Drugs administered to subjects to treat the various aspects of the metabolic syndrome associated with NAFLD may have additional unexpected metabolic and hepatic effects. Physicians taking care of patients with the metabolic syndrome should be aware that such events may occur and monitor their patients appropriately. Human data that such events are possible are emerging.45

References
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Hypertension. 2005;45:1012-1018; originally published online April 11, 2005;
doi: 10.1161/01.HYP.0000164570.20420.67
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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