**Therapeutics**

**Pioglitazone reduced liver injury and improved fasting glucose in nonalcoholic steatohepatitis without diabetes**

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**Clinical impact rating:** ★★★★★✩

**Question**

In patients who have nonalcoholic steatohepatitis (NASH) without diabetes, is pioglitazone therapy effective?

**Methods**

**Design:** Randomized placebo-controlled trial. National Research Register N0192119052; ISRCTN 10319160.

**Allocation:** Concealed.*

**Blinding:** Blinded (patients, clinicians, outcome assessors, safety committee); †, data collectors, and pathologist). *

**Follow-up period:** 1 year.

**Setting:** Queen’s Medical Centre, Nottingham, and Derby City General Hospital, Derby, England, UK.

**Patients:** 74 patients 27 to 73 years of age (mean age 54 y, 61% men) who had NASH without diabetes. Exclusion criteria were history of alcohol excess, use of weight-reduction drugs or drugs associated with fatty liver, current or previous heart failure, renal impairment, and pregnancy or lactation.

**Intervention:** Standard diet and exercise with pioglitazone, 30 mg/d (n = 37), or matching placebo (n = 37) for 1 year.

**Outcomes:** Reduction in liver injury and fibrosis, and change in biochemical parameters (included body weight, blood pressure, and hemoglobin [Hb] A1c, fasting glucose, cholesterol, triglyceride, C-peptide, and fasting insulin levels).

**Patient follow-up:** 82%.

**Main results**

The pioglitazone group had greater reduction in liver injury, higher body weight, and lower HbA1c, fasting glucose, and insulin C-peptide levels than did the placebo group (Table). Groups did not differ for fibrosis or blood pressure, cholesterol, triglyceride, or fasting insulin levels.

### Pioglitazone vs placebo in nonalcoholic steatohepatitis without diabetes†

<table>
<thead>
<tr>
<th>Outcomes at 1 y</th>
<th>Pioglitazone</th>
<th>Placebo</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in liver injury</td>
<td>32%</td>
<td>10%</td>
<td>223% (8 to 920)</td>
<td>5 (3 to 61)</td>
</tr>
<tr>
<td>Reduction in fibrosis</td>
<td>25%</td>
<td>20%</td>
<td>45% (−39 to 254)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>2.6</td>
<td>−3.5</td>
<td>6.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>−0.2%</td>
<td>0.1%</td>
<td>−0.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>−0.4</td>
<td>0.4</td>
<td>−0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Insulin C-peptide (pmol/L)</td>
<td>−97</td>
<td>0</td>
<td>−97</td>
<td>0.02</td>
</tr>
</tbody>
</table>

†Information provided by author.

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**Conclusion**

Pioglitazone reduced liver injury and improved fasting glucose levels in nonalcoholic steatohepatitis without diabetes.

**Commentary**

Nonalcoholic fatty liver disease (NAFLD) affects about one third of the US population (1); some patients with NAFLD develop NASH (characterized by hepatic necroinflammation, hepatocyte injury, and fibrosis) (2). NAFLD was associated with progression to cirrhosis in approximately 5% of cases and a 34% increase in mortality in 1 study (3). Therefore, treatments to reduce this risk for progression are urgently needed.

Because insulin resistance is central to the pathogenesis of NASH, thiazolidinediones have been studied and offer some promise. An uncontrolled pilot study in 18 patients who had NASH without diabetes showed histologic benefit with pioglitazone after 48 weeks, but liver tests indicated relapse when treatment was withdrawn (4). A randomized placebo-controlled study in 55 patients with impaired glucose tolerance or diabetes also showed histologic improvement with pioglitazone after 6 months (5). The study by Aithal and colleagues showed histologic improvement with pioglitazone in patients who had NASH without diabetes.

The major strength of the study is its double-blind, randomized, placebo-controlled design. Limitations include reliance on fasting glucose rather than an oral glucose tolerance test for diagnosis of diabetes and a high drop-out rate (17%), although this was similar between groups. Of 269 patients screened, only 74 were randomized. Therefore, the results may not be applicable to many patients with NASH.

Pioglitazone has been associated with adverse effects, including weight gain, congestive heart failure, edema, and increased risk for fracture. In the study by Aithal and colleagues, weight increased by a mean 2.6 kg in the pioglitazone group and decreased by a mean 3.5 kg in the placebo group.

In summary, pioglitazone is a promising therapeutic option for NASH, particularly in patients with type 2 diabetes. Longer-term studies are needed to assess safety and efficacy in patients without diabetes.

**References**


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