

N Engl J Med. 2006 Nov 30;355(22):2297-307. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis.

Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K.

University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900, USA.

BACKGROUND: No pharmacologic therapy has conclusively proved to be effective for the treatment of nonalcoholic steatohepatitis, which is characterized by insulin resistance, steatosis, and necroinflammation with or without centrilobular fibrosis. Pioglitazone is a thiazolidinedione that ameliorates insulin resistance and improves glucose and lipid metabolism in type 2 diabetes mellitus. **METHODS:** We randomly assigned 55 patients with impaired glucose tolerance or type 2 diabetes and liver biopsy-confirmed nonalcoholic steatohepatitis to 6 months of treatment with a hypocaloric diet (a reduction of 500 kcal per day in relation to the calculated daily intake required to maintain body weight) plus pioglitazone (45 mg daily) or a hypocaloric diet plus placebo. Before and after treatment, we assessed hepatic histologic features, hepatic fat content by means of magnetic resonance spectroscopy, and glucose turnover during an oral glucose tolerance test ([¹⁴C]glucose given with the oral glucose load and [³H]glucose given by intravenous infusion).

RESULTS: Diet plus pioglitazone, as compared with diet plus placebo, improved glycemic control and glucose tolerance ($P < 0.001$), normalized liver aminotransferase levels as it decreased plasma aspartate aminotransferase levels (by 40% vs. 21%, $P = 0.04$), decreased alanine aminotransferase levels (by 58% vs. 34%, $P < 0.001$), decreased hepatic fat content (by 54% vs. 0%, $P < 0.001$), and increased hepatic insulin sensitivity (by 48% vs. 14%, $P = 0.008$). Administration of pioglitazone, as compared with placebo, was associated with improvement in histologic findings with regard to steatosis ($P = 0.003$), ballooning necrosis ($P = 0.02$), and inflammation ($P = 0.008$). Subjects in the pioglitazone group had a greater reduction in necroinflammation (85% vs. 38%, $P = 0.001$), but the reduction in fibrosis did not differ significantly from that in the placebo group ($P = 0.08$). Fatigue and mild lower-extremity edema developed in one subject who received pioglitazone; no other adverse events were observed.

CONCLUSIONS: In this proof-of-concept study, the administration of pioglitazone led to metabolic and histologic improvement in subjects with nonalcoholic steatohepatitis. Larger controlled trials of longer duration are warranted to assess the long-term clinical benefit of pioglitazone. (ClinicalTrials.gov number, NCT00227110 [ClinicalTrials.gov]). Copyright 2006 Massachusetts Medical Society.

Related Links

- A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naïve patients with type 2 diabetes mellitus. [Clin Ther. 2003] PMID:12809958
- Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial. [Clin Ther. 2004] PMID:15220012
- Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. [Diabetes. 2003] PMID:12765945
- Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. [J Clin Endocrinol Metab. 2004] PMID:14715850
- Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. [Clin Ther. 2004] PMID:15220018