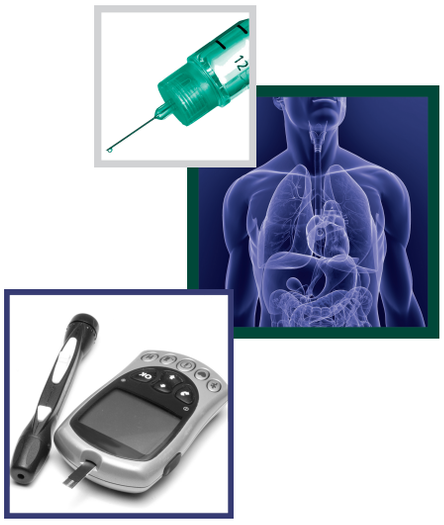
CLINICAL SNAPSHOT

Effect of pioglitazone in a patient with impaired glucose tolerance and nonalcoholic steatohepatitis



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Practice Points

- Physicians must be aware that nonalcoholic fatty liver disease, and its more severe form with steatohepatitis (nonalcoholic steatohepatitis [NASH]), occur frequently in patients with impaired glucose tolerance and Type 2 diabetes mellitus.
- NASH and Type 2 diabetes mellitus share a common pathophysiology characterized by dysfunctional adipose tissue and subclinical inflammation that lead to insulin resistance, abnormal glucose metabolism, hypertension and cardiovascular disease.
- Pioglitazone may be a safe and effective therapy to reverse the metabolic and histological abnormalities found in patients with NASH.

SUMMARY A man 55 years of age with impaired glucose tolerance, central obesity, atherogenic dyslipidemia and biopsy-proven nonalcoholic steatohepatitis was treated with the thiazolidinedione pioglitazone for 18 months in an attempt to reverse his severe steatohepatitis. Initial evaluation revealed marked insulin resistance, low plasma adiponectin and increased plasma biomarkers of subclinical inflammation (i.e., IL-6, TNF-α, TGF-β and hsCRP). After pioglitazone treatment insulin sensitivity was restored significantly, as well as plasma adiponectin and biomarkers of subclinical inflammation. Liver adiposity decreased together with a marked improvement of histological abnormalities. Histological markers of inflammation, hepatic stellate cell activation and apoptosis were reversed to near-normal levels. Practitioners should be aware that abnormal glucose metabolism is common in nonalcoholic steatohepatitis and thiazolidinediones may be valuble in the management of such patients.

A 55-year-old Hispanic male with a past medical history of impaired glucose tolerance, central obesity and atherogenic dyslipidemia was referred to us with a presumptive diagnosis of nonalcoholic steatohepatitis (NASH). This was based on a characteristic ultrasound with increased hepatic echogenicity and elevated plasma levels of alanine aminotransferase (69 IU/l), although aspartate aminotransferase was normal (33 IU/l). The past medical history was negative for identifiable causes of liver disease (such as alcohol consumption, viral hepatitis or others). Outpatient medications included only simvastatin and gemfibrozil. The physical examination was unremarkable. As part of a research protocol, insulin sensitivity, plasma biomarkers of nonalcoholic fatty liver disease and liver fat was measured by magnetic resonance

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imaging and spectroscopy. An ultrasound-guided liver biopsy confirmed the diagnosis of NASH.

The patient was treated with pioglitazone, 30 mg per day for 2 months, titrated-up to 45 mg per day for another 16 months. Statin and fibrate therapies were kept constant during the study. The aformentioned studies were repeated at 18 months. The results showed that liver fat by magnetic resonance imaging and spectroscopy improved from 11.4 to 2.3% (normal ≤5%), and hepatic and muscle insulin sensitivity were both markedly enhanced. Elevated plasma biomarkers of systemic inflammation were reduced (pre- vs post-treatment: IL-6: 2.6 to 1.4 pg/ml; TNF-α: 5.2 to 4.4 pg/ml; TGF-β: 3.6 to 1.3 ng/ml; hsCRP: 2.8 to 1.1 mg/l) and adiponectin levels increased from 3.0 to 27.3 µ/ml, the latter is an indication of improved adipose tissue biology. As shown in **Figures 1 & 2**, this metabolic improvement translated into a significant improvement in histology (including fibrosis [data not shown]).

This case offers important lessons to clinicians. NASH is common in patients with Type 2 diabetes mellitus (T2DM) affecting at least two out of three patients with T2DM, although it is frequently unrecognized by healthcare providers [1]. It is likely that the development of NASH precedes the onset of T2DM, as seen in this case, in which the patient had impaired glucose tolerance but had not yet developed full-blown diabetes. The majority of subjects with NASH (as well as their physicians) are unaware that NASH is a 'prediabetic state' in which the metabolic abnormalities promoting the development of NASH also predispose the development of impaired glucose tolerance or T2DM. This was a finding recently reported by our group [2]. New diagnostic and treatment approaches are likely to lead to increased awareness and treatment of such patients [3]. In NASH and T2DM, dysfunctional adipose tissue leads to ectopic fat deposition ('lipotoxicity') and subclinical inflammation [1,2]. Thiazolidinediones in patients with NASH may restore adipose tissue to a more normal biology and normalize plasma adiponectin levels, ameliorate subclinical inflammation and reverse adipose tissue insulin resistance (as well as hepatic and muscle insulin resistance)[4–6]. It is noteworthy that, treatment in this case led to the same metabolic improvements reported in clinical trials and to a reduction in hepatic lymphocyte infiltration and inflammation, HSC activation and apoptosis. Recent randomized controlled trials using pioglitazone (Actos®) in patients with NASH have proven that thiazolidinedione therapy is overall safe and effective in improving metabolic and histological abnormalities (i.e., reduction of steatosis, inflammation and ballooning necrosis) [4,7]. These studies, together with examples, such as the one reported here, suggest that thiazolidinediones may play a larger role in the future, either as monotherapy or combined with other emerging approaches under investigation, such as vitamin E [7] and others [1,3].

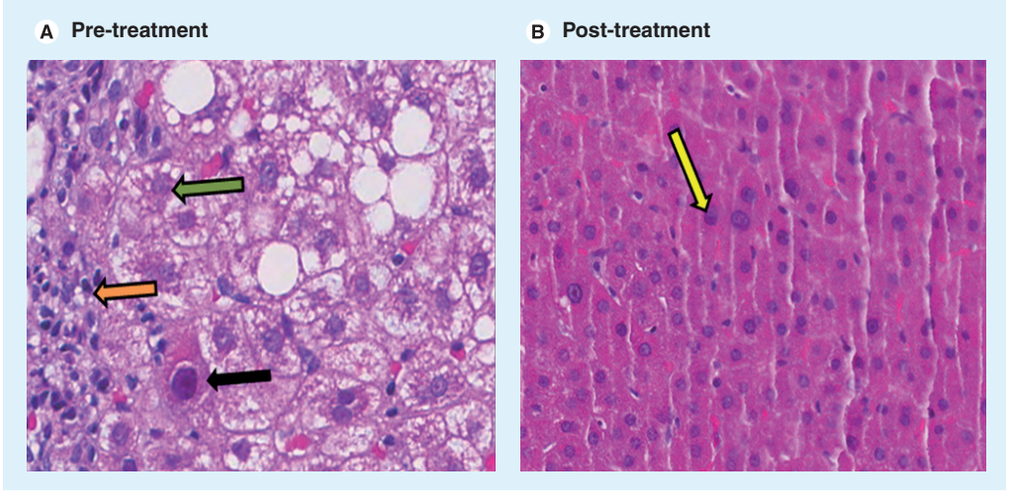

Figure 1. Hematoxylin and eosin stain. (A) Liver biopsy pretreatment shows steatosis, inflammatory activity, portal inflammation (orange arrow), ballooning degeneration of hepatocytes (green arrow) and acidophil body (black arrow). **(B)** Post-treatment biopsy showing restitution of the normal hepatic architecture with no steatosis or inflammation (yellow arrow).

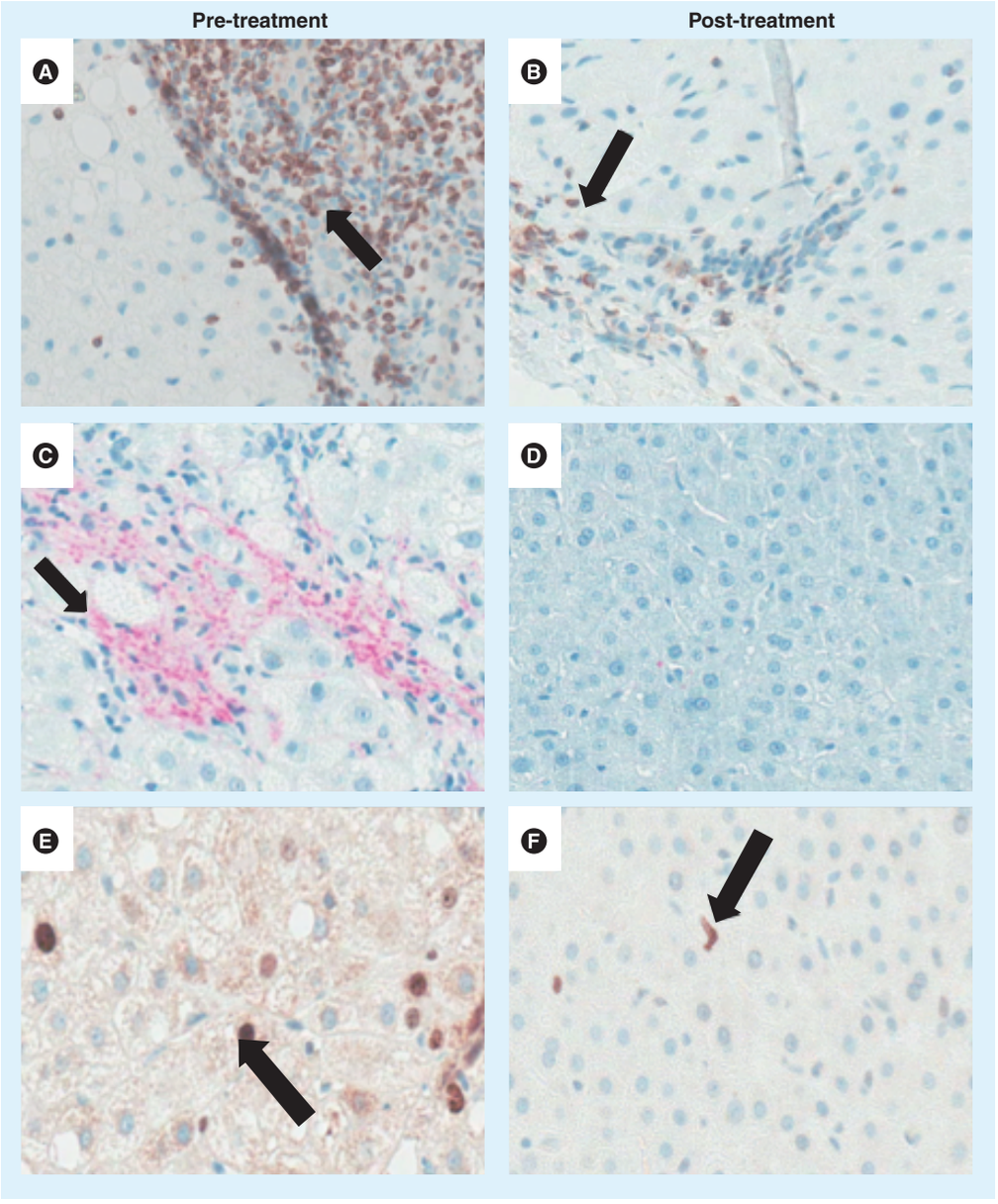

Figure 2. Immunoperoxidase stains. (A) BCL2 (an apoptotic marker) immunostaining in many T lymphocytes (black arrow) in the portal and lobular area. No BCL2 staining is observed in the hepatocytes. **(B)** Fewer BCL2-positive T lymphocytes in the portal tract (black arrow) after treatment. **(C)** Presence of smooth muscle actin, a tissue marker of activation of hepatic stellate cells. Hepatic stellate cells mediate liver fibrosis (black arrow). **(D)** Absence of smooth muscle actin suggesting reversal of HSC activation. **(E)** Increased hepatocyte nuclear staining indicative of proliferation and apoptosis using apoptosis marker Ki-67 (black arrow). **(F)** Decreased hepatocyte nuclear staining by marker Ki-67.

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