Management of Nonalcoholic Fatty Liver Disease (NAFLD) in Patients with Type 2 Diabetes: A Call to Action

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Disclosures

• Research support to the University of Florida: Cirius, Inventiva, Janssen, Lilly, Novartis, Novo Nordisk, Zydus.

• Consultant: Allergan, AstraZeneca, Deuterex, Gilead, Pfizer, Teva.

• Stock/Shareholder: None

• Other: None
The University de Florida (Gainesville, FL)
Grant support: Burroughs Wellcome Fund, American Diabetes Association; NIH; VA Research Fund; VA Merit Award
What is Non-Alcoholic Fatty Liver Disease?

• A chronic liver condition characterized by:
  – Hepatic fat accumulation (in the absence of ethanol abuse & other identifiable causes)
  – Insulin resistance
  – Frequently associated with impaired glucose intolerance or type 2 diabetes

• Steatosis may range from simple steatosis to steatohepatitis (NASH) with progressive liver damage with necrosis, inflammation and frequently fibrosis

• The natural history is poorly understood, no large long-term studies
The trouble with fat

By ANDREW FIERI

Diabetes or high blood pressure, or a combination of the two, are new frontiers in the battle against the health risks posed by obesity. And scientists are now seeing a growing concern about a liver disease that some experts believe could be the next big threat.

Fat accumulates in the liver and causes inflammation, leading to fatty liver disease. As the fat builds up, the liver can become scarred, and in severe cases, it can lead to cirrhosis or liver cancer.

The disease is particularly concerning because it is often asymptomatic in early stages, and by the time symptoms appear, the damage is usually irreversible. This makes it difficult to diagnose and treat early, which can lead to serious complications.

Scientists are working on new treatments and preventive measures to combat this growing threat. However, they emphasize the importance of maintaining a healthy lifestyle, including regular exercise and a balanced diet, as the best way to prevent obesity-related liver disease.

In conclusion, while obesity remains the top public health threat, the rise of liver disease linked to obesity is a cause for concern. Further research and public awareness are crucial in addressing this problem and protecting public health.
NAFLD: A Call to Action

1. Disease burden
   - Liver as a “barometer”/mirror of adipose tissue dysfunction
   - Increased risk of cirrhosis, hepatocellular carcinoma
   - Worse insulin resistance, dyslipidemia and CVD

2. Diagnosis
   - Plasma AST/ALT, fibrosis biomarkers, and diagnostic panels
   - Liver imaging and liver biopsy

3. Current and future treatments
   - Lifestyle and bariatric surgery, pioglitazone and GLP-1RA
   - Newer agents: “metabolic” + “antifibrotic” therapies
From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
Type 1 and 2 Diabetes: NAFLD Prevalence and Metabolic Associations

Post-hoc analysis of baseline data from 4 phase 3 trials (n=589):

Type 1 diabetes (IMAGINE 1 and 3); insulin-naïve type 2 diabetes (IMAGINE 2); insulin-experienced type 2 diabetes (IMAGINE 5)

Mean hepatic fat fraction: 3.2% versus 13.0% versus 10.2%, respectively

• NAFLD: hepatic fat fraction ≥6% by MRI

Adipose tissue and hepatic insulin sensitivity in patients with and without NASH and T2DM

B) Percentage suppression of plasma FFA concentration by low-dose insulin infusion; C) Hepatic insulin resistance index (HIR = fasting plasma insulin concentration × fasting endogenous [primarily hepatic] glucose production)

Lomonaco et al, Diabetes Care 2016
Diabetes and Fibrosis are Consistent Predictors of Poor Outcomes in Patients with NASH

Many longitudinal studies predict that fibrosis is associated with future cirrhosis and CVD:

- Angulo et al (Gastroenterology 2015, 149:389-97)
- Ekstedt et al (Hepatology 2015, 61:1547-54)
- Haflidadottir et al (BMC Gastroenterol, 2014, 14:166)
- Pais et al (J Hepatol 2013, 59:550-6)
- Stepanova et al (Dig Dis Sci 2013, 58:3017-23)
- Kim et al (Hepatology. 2013, 57:1357-65)

Gupta et al, Hepatology 2010;51:1584-1592

Increased Risk of Mortality by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Mortality Rate Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.41 (0.17-11.95)</td>
</tr>
<tr>
<td></td>
<td>9.57 (1.67-54.93)</td>
</tr>
<tr>
<td></td>
<td>16.69 (2.92-95.36)</td>
</tr>
<tr>
<td></td>
<td>42.30 (3.51-510.34)</td>
</tr>
</tbody>
</table>

1,495 NAFLD patients with 17,452 patient years of follow-up
Predicting Future Burden of NASH and Adverse Outcomes

• By 2030, prevalence of NASH will increase 63% to 27 million cases
• NASH-advanced fibrosis will increase >160% to 8 million cases and will account for 29% of NASH cases
• Liver deaths will increase 178% (78,300 deaths)

From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
Cardiovascular Consequences of NAFLD

Cusi K, Gastroenterology, April 2012, 142:711-725
**Hepatic Steatosis and Insulin Resistance, But Not Steatohepatitis, Promote Atherogenic Dyslipidemia in NAFLD**  
Bril et al., JCEM 2016, 101:644-652.

![Graph A: Adipose tissue insulin resistance index (Adipo-IR)](image)

- For the effect of NAFLD: p=0.001, for obesity: p=0.17

![Graph B: LDL particle size](image)

- For the effect of NAFLD: p<0.00, for obesity: p=0.15

**Liver Safety of Statins in Prediabetes or T2DM and Nonalcoholic Steatohepatitis: *Post Hoc* Analysis of a Randomized Trial**  
J Clin Endocrinol Metab, August 2017, 102(8):2950–2961

Fernando Bril,1,2 Paola Portillo Sanchez,1,2 Romina Lomonaco,1,2 Beverly Orsak,3 Joan Hecht,4 Fermin Tio,3 and Kenneth Cusi1,2,3,4
Mortality in Isolated Steatosis versus NASH

![Bar chart showing mortality in different liver conditions: No NAFLD, Isolated steatosis, NASH. The chart indicates higher mortality in NASH compared to other conditions.](chart)

Bril & Cusi, Metabolic Clinics North America 2016
NAFLD: A Call to Action

1. Disease burden
   - Liver as a “barometer”/mirror of adipose tissue dysfunction
   - Increased risk of cirrhosis, hepatocellular carcinoma
   - Worse insulin resistance, dyslipidemia and CVD

2. Diagnosis
   - Plasma AST/ALT, fibrosis biomarkers, and diagnostic panels
   - Liver imaging and liver biopsy
Prevalence of NAFLD using different diagnostic tools

Bril & Cusi, Diabetes Care 2017 40:419-430
Relationship between Plasma ALT and Intrahepatic Triglyceride Accumulation

\[ (worse) \]

\[ (better) \]

\[ ALT \text{ IU/L} \]

\[ r = 0.48; p<0.001 \]

\[ n = 352 \]

\[ \text{IHTG measured by } ^1\text{H-MRS} \]

Bril/Cusi et al, Hepatology April 2017
Steatosis in NAFLD = insulin resistance, risk of steatohepatitis (NASH)

NASH = risk of cirrhosis and hepatocellular carcinoma
Liver biopsy remains the “suboptimal” gold standard to characterize liver histology in NAFLD/NASH

- Confirms the diagnosis and staging of disease
- Determines prognosis by severity of liver injury and fibrosis
- Limitations: high cost, potential complications, sampling/reader error
# Diagnosing Advanced Liver Fibrosis with Biomarker Panels

## Table 1—Biomarker panels for the diagnosis of advanced fibrosis (stages 3 and 4)

<table>
<thead>
<tr>
<th>Parameters included</th>
<th>n</th>
<th>PPV</th>
<th>NPV</th>
<th>Patients unable to be classified (&quot;gray zone&quot;)</th>
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<tbody>
<tr>
<td>FibroTest (215)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, sex</td>
<td>267</td>
<td>60%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT, α2-macroglobulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD fibrosis score (118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, BMI, Diabetes AST/ALT ratio Platelet, albumin</td>
<td>733</td>
<td>82%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>BARD score (117)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, Diabetes AST/ALT ratio</td>
<td>827</td>
<td>43%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>FIB-4 index (118)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, AST and ALT Platelet</td>
<td>541</td>
<td>80%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>NAFLC score (119)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin, Type IV collagen, Insulin</td>
<td>619</td>
<td>36%</td>
<td>99%</td>
<td></td>
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<tr>
<td>Hepascore (120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, sex, Total bilirubin, GGT, α2-macroglobulin, Haptoglobin</td>
<td>242</td>
<td>57%</td>
<td>92%</td>
<td></td>
</tr>
</tbody>
</table>

N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value. 1% independent validation cohort included in the study.
Diagnosis of Fibrosis in NASH with Elastography*

* Vibration controlled transient elastography (VCTE by Fibroscan® - Echosens)
Prevalence of Moderate to Severe Fibrosis Happens in 1 out of 6 Patients with Type 2 Diabetes

15-20% of unselected patients with T2DM with steatosis have MODERATE TO SEVERE liver fibrosis (!).

* Fibrosis stage F2-F4

Koehler et al, Hepatology 2016;63:138-147
Diagnosis of Fibrosis in NASH with Magnetic Resonance Elastography

Diagnostic Algorithm for NASH for PCPs and Endocrinologists
1. Disease burden
   - Liver as a “barometer”/mirror of adipose tissue dysfunction
   - Increased risk of cirrhosis, hepatocellular carcinoma
   - Worse insulin resistance, dyslipidemia and CVD

2. Diagnosis
   - Plasma AST/ALT, fibrosis biomarkers, and diagnostic panels
   - Liver imaging and liver biopsy

3. Current and future treatments
   - Lifestyle and bariatric surgery, pioglitazone and GLP-1RA
   - Newer agents: “metabolic” + “antifibrotic” therapies
"GOOD ON SO MANY LEVELS!"

AVAILABLE NOW, FOR A LIMITED TIME ONLY!
“Why diagnose NASH if there are no treatments…?”

Wrong!
Changes in Liver Fat with a VLCD (600 kcal/day)

30% decrease after 1st week

Liver fat content (%)

Week 0  Week 1  Week 4  Week 8

Lim et al, Diabetologia 2011
Changes in Liver Fat with a VLCD (600 kcal/day)*

36% liver fat (baseline)  
2% liver fat (4 weeks of VLCD)

*by $^1$H-MRS

(Courtesy of Dr. R. Taylor)
The Diagnosis and Management of NAFLD: Practice Guidance From the American Association for the Study of Liver Diseases (AASLD) 2018

Guidance statements – Weight Loss and Exercise

- **Weight loss (#21):** 3%-5% needed to improve steatosis, but 7%-10% minimal need to improve the majority of the histopathological features of NASH, including fibrosis.

- **Exercise (#22):** Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown

- **Bariatric surgery (#29-31):**
  - Can be considered in otherwise eligible obese individuals with NAFLD or NASH.
  - Premature to consider bariatric surgery as an established option to treat NASH.
  - The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD.
  - In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis.

Chalasani et al, Hepatology 2018
4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

**Recommendation**

**4.14** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. C

(page S40)
Increasing benefit of weight loss on fibrosis but with significant variability in response

Probability of improving NASH components under lifestyle intervention according to weight loss (N=293)

*At least one stage

Guidance statements – Pharmacological Agents

- **Metformin (#23):** Not recommended for treating NASH in adult patients.

- **Pioglitazone (#24-25):**
  - Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH.
  - Risks and benefits should be discussed with each patient.

- **GLP-1RAs (#26):** It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH.

- **Vitamin E (#27-28) for non-diabetics:**
  - At 800 IU/day improves liver histology in nondiabetic adults with NASH.
  - Risks and benefits should be discussed with each patient.
  - Not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

Chalasani et al, Hepatology 2018
Approach #1: The “Antifibrotic Approach” to Prevent NASH-Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
Approach #2: The “Insulin-Sensitizer Approach” to Prevent NASH-Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
Direct and Indirect effects of GLP-1 RA in Humans

Dhir G and Cusi K. Journal Invest Med September 2017
NAFLD Activity Score (NAS):
Steatosis + inflammation + ballooning (max score = 8)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Extent</th>
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</thead>
<tbody>
<tr>
<td><strong>Steatosis</strong></td>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5-33%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt;33-66%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;66%</td>
</tr>
<tr>
<td><strong>Lobular Inflammation</strong></td>
<td>0</td>
<td>No foci</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt;2 foci/200x</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2-4 foci/200x</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;4 foci/200x</td>
</tr>
<tr>
<td><strong>Hepatocyte Ballooning</strong></td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Few balloon cells</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Many cells/prominent balloon</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td>0 - 4</td>
<td></td>
</tr>
</tbody>
</table>

Kleiner DE. *Hepatology*. 2005
LEAN Study:
Changes in Histologic Features at Week 48

Patients With Improvement

- NASH Resolution (Primary Outcome): 39% Liraglutide, 9% Placebo (P=0.02)
- NAFLD Activity Score: 74% Liraglutide, 64% Placebo (P=0.5)
- Fibrosis: 26% Liraglutide, 14% Placebo (P=0.5)
- Hepatocellular Ballooning: 61% Liraglutide, 32% Placebo (P=0.05)
- Steatosis: 83% Liraglutide, 45% Placebo (P=0.009)
- Lobular Inflammation: 48% Liraglutide, 55% Placebo (P=0.7)

LEAN: Liraglutide Efficacy and Action in NASH.

Effect of Dulaglutide in Patients with T2DM: Changes in Plasma ALT, AST and GGT at 24 weeks

*p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. placebo.

Treatment difference [LSM difference (SE)].

Note: Integrated data from AWARD-1, AWARD-5, AWARD-8 and AWARD-9.

Jun 5. doi: 10.1111/dme.13697. [Epub ahead of print]
Effect of Canagliflozin on Intrahepatic Triglycerides in Patients with Type 2 Diabetes

Effect of Canagliflozin on Intrahepatic Triglycerides in Patients with Type 2 Diabetes

Rationale for Pioglitazone in NASH

Cusi K. Gastroenterology 2012, 142:711-25
A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Joan Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.

ABSTRACT

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, a peroxisome proliferator-activated receptor-gamma agonist, has been shown to improve hepatic insulin resistance and inflammation in a randomized, placebo-controlled trial of patients with type 2 diabetes. This trial was designed to determine whether pioglitazone would improve steatohepatitis.

METHODS

In a randomized, placebo-controlled trial, we included 125 subjects with biopsy-proven nonalcoholic steatohepatitis, of whom 70 were randomly assigned to receive placebo and 55 were randomly assigned to receive 45 mg of pioglitazone per day. Subjects were followed for 1 year, after which time they were switched to open-label treatment with pioglitazone. The primary outcome was improvement in the histologic activity index, as determined by a blinded pathologist. All other outcomes were summarized descriptively.

RESULTS

The median baseline values for the histologic activity index were 10 (interquartile range, 7 to 12) in the placebo group and 11 (interquartile range, 8 to 13) in the pioglitazone group (P = 0.49). Of the 55 subjects who received pioglitazone, 47 (85%) improved in histologic activity index, compared with 20 (57%) of the 35 subjects who received placebo (P = 0.01). Pioglitazone treatment was well tolerated, with no significant adverse events.
Effect of Pioglitazone in NASH

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>64 y.o. CF (IGT)</td>
<td></td>
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<tr>
<td>BMI (kg/m²)</td>
<td>30.9</td>
<td>32.4</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>109</td>
<td>87</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>NASH activity score / Fibrosis</td>
<td>5</td>
<td>0 (normal)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0 (normal)</td>
</tr>
</tbody>
</table>

Before treatment biopsy

After treatment biopsy
Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus
A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orenak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fernin Tri, MD; Joan Hardies, PhD; Celia Durian, RD; Nicolas Musi, MD; Amy Webb, MD; and Paolo Portillo-Sanchez, MD

Background: The metabolic defects of nonalcoholic steatohepatitis (NASH) and prediabetes or type 2 diabetes mellitus (T2DM) seem to be specifically targeted by pioglitazone. However, information about its long-term use in this population is limited.

Objective: To determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: University hospital.

Participants: Patients (n = 101) with prediabetes or T2DM and biopsy-proved NASH were recruited from the general population and outpatient clinics.

Intervention: All patients were prescribed a hypocaloric diet (500–1,000 kcal/day deficit from weight-maintaining caloric intake) and then randomly assigned to pioglitazone, 45 mg/day, or placebo for 16 months, followed by an 18-month open-label phase with pioglitazone treatment.

Measurements: The primary outcome was a reduction of at least 2 points in the nonalcoholic fatty liver disease activity score (NASH) (n = 2 histologic categories) without worsening of fibrosis. Secondary outcomes included other histologic outcomes, hepatic triglyceride content measured by magnetic resonance and proton spectroscopy, and metabolic parameters.

Results: Among patients randomly assigned to pioglitazone, 58% achieved the primary outcome (treatment difference, 41 percentage points [95% CI, 23 to 59 percentage points]) and 51% had resolution of NASH (treatment difference, 32 percentage points [CI, 13 to 51 percentage points] [P < 0.001 for each]). Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, −0.5 [CI, −0.9 to 0.0]; P = 0.039); reduced hepatic triglyceride content from 19% to 7% (treatment difference, −12 percentage points [CI, −10 to −4 percentage points]; P < 0.001); and improved adipose tissue, hepatic, and muscle insulin sensitivity (P < 0.001 vs. placebo for all). All 18-month metabolic and histologic improvements persisted over 36 months of therapy. The overall rate of adverse events did not differ between groups, although weight gain was greater with pioglitazone (2.5 kg vs. placebo).

Limitation: Single-center study.

Conclusion: Long-term pioglitazone treatment is safe and effective in patients with prediabetes or T2DM and NASH.

Primary Funding Source: Barraques Wellcome Fund and American Diabetes Association.

Plasma ALT Concentration after 18 months of Pioglitazone or Placebo, and after 18 or 36 Months of Pioglitazone

Long-term Effect of Pioglitazone in NASH

Primary endpoint

- ~50% response rate vs. placebo

Why is Pioglitazone not Used More in NASH?

The 3 common “barriers”:  
• Unaware of efficacy (2 out of 3 have NASH resolution)  
• Lack of familiarity with prescribing the drug  
  “It is a diabetes drug and I am not an endocrinologist”  
• Misperception about weight gain or the risk of other side effects
Piohlazone profile: pros and cons

The “good”

– Liver:
  • Resolution of NASH in ~ 2 out of 3 patients
  • Prevention of fibrosis progression

– Extra-hepatic
  • Reversal of IR, systemic inflammation, ectopic fat deposition and lipotoxicity
  • Improved lipid panel (lower TG; higher HDL-C)
  • Reduction of cardiovascular disease
  • Prevention of type 2 DM and durable metabolic effects in diabetes

The “bad”

– Weight gain: 2.0 to 4.5 kg (although metabolically healthy fat…)
– Edema: 5-8% (more if combined w/insulin)
– Osteoporosis: greatest issue
– Bladder cancer? Unclear, likely very small

By Kenneth Cusi, MD, FACP, FACE
Cohort Studies of the Association of Bladder Cancer and Pioglitazone Exposure (dependent variable)

Most (18 out of 23) Published Studies are Negative

<table>
<thead>
<tr>
<th>Author</th>
<th>PIO Bladder Cancer, %</th>
<th>Control Bladder Cancer, %</th>
<th>HR*</th>
</tr>
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<tbody>
<tr>
<td>Lewis et al, 2011</td>
<td>0.30†</td>
<td>0.48</td>
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<td>Neumann et al, 2012</td>
<td>0.11</td>
<td>0.14</td>
<td>1.22*</td>
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<td>We L, 2012</td>
<td>0.28</td>
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<td>Tseng C-H, 2012</td>
<td>0.39‡</td>
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<td>Mamtani et al, 2012</td>
<td>0.32</td>
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<td>0.23</td>
<td>1.03</td>
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<td>Levin et al, 2015</td>
<td>0.33</td>
<td>0.34</td>
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</tr>
<tr>
<td>Lewis et al, 2015</td>
<td>0.62**</td>
<td>0.66</td>
<td>1.06</td>
</tr>
<tr>
<td>Korhonen et al, 2015</td>
<td>0.23</td>
<td>0.27</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*P <0.05; †HR = 1.4*; **HR = 1.16 for exposure > 4 years; ‡HR = 0.82 for exposure > 1 year, no trend with > 2 years.

Mayer, J Diabetes & Complications 2016; 30:981-985
Effect of Pioglitazone or Placebo for 18 Months on Liver Triglycerides (¹H-MRS) and Insulin Sensitivity*
Prolonged Durability of Glycemic Control with Thiazolidinediones – but Weight Gain

TZD weight gain range: from 2.3 to 4.8 kg
Insulin weight gain range: from 3 to 10 kg

Weight Gain and Poor Durability with Sulfonylurea Treatment in T2DM

Weight gain range: from 1.1 to 4.2 kg

Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Metabolism in Patients With Well-Controlled Type 2 Diabetes Mellitus

Rutger W. van der Meer, MD, PhD*; Luuk J. Rijzewijk, MD*; Hugo W.A.M. de Jong, PhD;
Hildo J. Lamb, MD, PhD; Mark Lubberink, PhD; Johannes A. Romijn, MD, PhD;
Jeroen J. Bax, MD, PhD; Albert de Roos, MD, PhD; Otto Kamp, MD, PhD;
Walter J. Paulus, MD, PhD; Robert J. Heine, MD, PhD; Adriaan A. Lammertse, PhD;
Johannes W.A. Smit, MD, PhD; Michaela Diamant, MD, PhD

Pioglitazone Improves Left Ventricular Diastolic Function in Subjects With Diabetes

Diabetes Care 2017;40:1530–1536 | https://doi.org/10.2337/dc17-0078

Geoffrey D. Clarke,1,2
Carolina Safis-Herrera,1
Marjorie Molina-Wilkins,1
Sandra Martinez,1 Aurora Merovci,1
Eugenio Cersosimo,1 Robert J. Chilton,
Patricia Izzo,6 Amalia Gastaldelli,1,5
Muhammad Abdul-Ghani,1 and
Ralph A. DeFranzo1,4,6
How to Use Pioglitazone in Patients with NASH?

❖ Get at baseline:
  ❖ Labs: AST/ALT, urinalysis (bladder cancer?)
  ❖ Imaging: liver ultrasound, CAP [liver fat] /VCTE [fibrosis])
  ❖ Osteoporosis? Order bone density (DXA)
  ❖ CHF/"diastolic dysfunction" (HFP EF)? LE edema, “fatigue”, long-standing DM or CAD. Order BNP, echocardiogram, consult cardiology

❖ Poor candidates: BMI ≥40 kg/m², high-insulin or amlodipine use

❖ Start pioglitazone at 15 or 30 mg/day

❖ Follow patient every 2-3 months:
  ❖ ALT, A1c, if good tolerance (>85-90%), increase from 15 to 30 mg/day

❖ Continue to monitor for AEs (most in first 6 months)
  ❖ Check for fluid retention: ankle swelling (~5-8%), rarely shortness of breath or easy fatigability (~1%); repeat urinalysis and DXA q12 months.
NAFLD: A Call to Action

1. Disease burden
   - Liver as a “barometer”/mirror of adipose tissue dysfunction
   - Increased risk of cirrhosis, hepatocellular carcinoma
   - Worse insulin resistance, dyslipidemia and CVD

2. Diagnosis
   - Plasma AST/ALT, fibrosis biomarkers, and diagnostic panels
   - Liver imaging and liver biopsy

3. Current and future treatments
   - Lifestyle and bariatric surgery, pioglitazone and GLP-1 RA
   - Newer agents: “metabolic” + “antifibrotic” therapies
Euglycemic Insulin Clamp with Glucose Turnover and Indirect Calorimetry
Current and Potential Therapeutic Targets in NASH


Fat Deposition & Metabolic Stress
- Bile Acids
- Dietary Fat

Injury
- Apoptosis

Inflammation

Oxidative Stress

Fibrosis

- Thyroid hormone receptor (THR) β-selective agonist
  - BMS-986066 (FGF-21)
  - GC35947 (FGF21)
  - NGM-282 (FGF-19)

- Vitamin E
  - Pentoxifylline

- Simtuzumab
  - GR-MD-02

- Sevelamer
  - Volixibat

- Orlistat

- Emricasan
  - Selonsertib
  - Cenicriviroc

- Simtuzumab
  - GR-MD-02

- Fecal Microbiota Transplantation

- Solithromycin

- Orlistat
  - Sevelamer

- Volixibat

- Orlistat

- Emricasan
  - Selonsertib
  - Cenicriviroc

- Simtuzumab
  - GR-MD-02

- Fecal Microbiota Transplantation

- Solithromycin

- “Pioglitazone-like”
  - DRX-065
  - MSD0602

- Obeticholic Acid
  - GS-8674
  - EDP305
  - LMB763
  - LJN452

- Aramchol (inhibitor of SCD-1)
  - GS-9976 (inhibitor ACC)

- PPAR agonists
  - Pioglitazone
  - Elafibranor
  - Lanifibranor
  - Saroglitazar
  - Seladelpar
  - CHS-131

- Liraglutide (daily GLP-1)
  - Semaglutide (daily GLP-1)

- Thyroid hormone receptor (THR) β-selective agonist
  - BMS-986066 (FGF-21)
  - GC35947 (FGF21)
  - NGM-282 (FGF-19)

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- Solithromycin

- “Pioglitazone-like”
  - DRX-065
  - MSD0602
# NASH in 2019 as a Public Health Problem

<table>
<thead>
<tr>
<th></th>
<th>DM nephropathy in the 80s</th>
<th>Osteoporosis in the 90s</th>
<th>NASH in 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long natural history</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High prevalence?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Major cause of morbidity?</td>
<td>Yes</td>
<td>Yes</td>
<td>Cirrhosis, HCC, + CVD</td>
</tr>
<tr>
<td>Increased mortality?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Microalbuminuria</td>
<td>Bone mineral density</td>
<td>No simple, “great” test yet for fibrosis</td>
</tr>
<tr>
<td>Adequate treatments?</td>
<td>Not initially, but yes today</td>
<td>Not initially, but yes today</td>
<td>Pioglitazone GLP-1RA? vitamin E? others ≥ 2019</td>
</tr>
</tbody>
</table>
Diagnostic Algorithm
for NASH in the
Primary Care
Setting

Bril & Cusi
Diabetes Care, March 2017 40:419-430
Treatment of NASH

Patient with prediabetes or T2DM and definite NASH

Treatments of NASH:
- Pharmacological treatment: Pioglitazone as first-line therapy
- Lifestyle intervention: Weight reduction of 8-10%

If no response or not achieved:
- Second-line therapies
- Pharmacological treatment or metabolic surgery

Control of other CV risk factors:
- Glucose control: Metformin as first-line therapy
- Blood pressure control: ARB or ACEI as first-line therapy
- Lipid-lowering therapy: Statins as first-line therapy

If elevated A1c:
- Add pioglitazone
- Add GLP-1RA or SGLT-2 inhibitors

If elevated BP:
- Second-line therapies

If elevated TG and low HDL:
- Add fibrates to statins

Bril & Cusi, Diabetes Care 2017 40:419-430
Summary: A Call to Action

1. **NAFLD**: high disease burden
   - Liver fat is a “barometer” of adipose tissue dysfunction/insulin resistance
   - **High risk populations for NASH**: obese, T2DM, higher AST/ALT
   - **Watch for CVD** (use of statins overall safe in NASH)

2. **NASH**: LFTs and imaging (ultrasound, elastography)
   - **Fibrosis stage**: strongest predictor for mortality in NASH
   - **Liver biopsy**: remains the gold standard for diagnosis

3. **Treatment**: focus on patients with T2DM that have fibrosis
   - **AASLD guidelines**: Lifestyle, if biopsy-proven NASH, pioglitazone
   - **Pioglitazone** will be to NASH what metformin has been to treat T2DM
   - Many new drugs under development
   - **ADA**: incorporated in 2019 NASH as a medical problem in T2DM