NASH and Diabetes Linkage: Where do we go from here?

NASH Leadership Forum
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Disclosures

• Research support to the University of Florida:
  – National Institute of Health
  – Pharmaceutical company grants: Cirius, Echosens, Inventiva, Janssen, Lilly, Novartis, Novo Nordisk, Poxel, Zydus.

• Consultant:
  – Allergan, AstraZeneca, BMS, Pfizer, Poxel, Genentech, Gilead, Merck, Novo Nordisk, Prosciento, Zydus.

• Stock/Shareholder: None
Global prevalence of NAFLD among T2DM patients 55.5% (95% confidence interval: 47.3-63.7)

Interaction between T2DM and NASH

Type 2 Diabetes ⇔ NASH
NASH and Diabetes Linkage: Closing the knowledge gap

1. Potential mechanisms
   - What is the role of hyperglycemia (glucotoxicity)?

2. The diagnostic challenge of NASH-fibrosis in T2DM
   - Value of diagnostic panels and novel biomarkers

3. The treatment opportunity of T2DM
   - Brief overview of the potential of SGLT2i, GLP-1RAs, PIO
   - Can combination therapy change the natural history of NASH?
Glucotoxicity Promotes Steatohepatitis and Fibrosis in Animal Models

Lo et al, J Hepatol 2011;55:435–444
Potential Mechanisms for Hyperglycemia to Promote Steatohepatitis or Fibrosis\textsuperscript{1-3}

• **Chronically high glucose concentration can have toxic effects on a broad spectrum of cells ("glucotoxicity").**
  - Microvascular diabetic complications
  - Glucose regulates the transcription of genes encoding key lipogenic/glycolytic pathways (i.e., transcription factor carbohydrate responsive element-binding protein or ChREBP; stimulation of liver-pyruvate kinase or L-PK).

• **Advanced glycosylation end-products (AGEs).**
  - Both Kupffer and hepatic stellate cells have RAGE receptors that are associated with the development of inflammation.

• **High fructose-based diets and DNL.**
  - Could promote de novo lipogenesis and activate inflammatory pathways (i.e., c-jun N-terminal kinase [JUN]-signaling pathway).

• **Hepatic inflammation and oxidative stress.**
  - Formation of hydrogen peroxide/hydroxyl radicals leading to hepatocyte lipid peroxidation.

Studies Needed to Establish the Role of Hyperglycemia in NASH

Two approaches for future studies:

• Prospective, parallel, well-controlled studies examining the progression of disease in patients with vs. without T2DM
  - Establish the severity of NASH on biopsies at baseline and over time (paired biopsy studies)
  - Assess at baseline and during the study macro- and microvascular diabetic complications (progression worsened by severity of steatohepatitis and/or fibrosis?)
  - Close control of confounding factors

• A RCT to assess the role of controlling hyperglycemia on liver histology, independent of treating insulin resistance
  - Using insulin and other agents that do not promote weight loss
  - Avoiding use of an insulin-sensitizer
  - Prospectively controlling for confounding factors
NASH and Diabetes Linkage:
Closing the knowledge gap

1. Potential mechanisms
   - What is the role of hyperglycemia (glucotoxicity)?

2. The diagnostic challenge of NASH-fibrosis in T2DM
   - Value of diagnostic panels and novel biomarkers
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
Fibrosis Scores for Clinical Practice

**NAFLD Fibrosis Score (NFS)**

- **Parameter**
  - Age, years
  - AST
  - ALT
  - Platelet count, cells $\times 10^9$
  - BMI
  - Albumin, g/L
  - Impaired fasting glucose/DM?

**FIB-4 Cutoff Value**

<table>
<thead>
<tr>
<th>NFS Cutoff Value $^1$</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;-1.455$</td>
<td>F0–F2</td>
</tr>
<tr>
<td>$1.455$ to $0.676$</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>$&gt;0.676$</td>
<td>F3–F4</td>
</tr>
</tbody>
</table>


Do you order an HbA1c in all NASH patients?
Use of a metabolomic approach to non-invasively diagnose non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus

Metabolomics still needs further validation in patients with diabetes

Diabetes Obes Metab. 2018;20:1702–1709.
Diagnosing Advanced Liver Fibrosis with Plasma Propeptide of type III (PRO-C3) Procollagen

Use of Plasma Fragments of Propeptides of Type III, V, and VI Procollagen for the Detection of Liver Fibrosis in Type 2 Diabetes

Diabetes Care 2019;42:1348-1351.

Fernando Bril,1,2 Diana Julie Leeming,3 Morten Asser Karsdal,3 Sriram Kevulapalli,1 Diana Barb,2 Jinping Lai,4 Matthew Rabe,1 and Kenneth Cusi1,2

n = 191

A. Moderate Fibrosis (stages 2-4)

B. Advanced Fibrosis (stages 3-4)

Plasma PRO-C3 Levels

Plasma PRO-C5 Levels

Plasma PRO-C6 Levels

Diagnosing **Advanced Liver Fibrosis with Plasma Propeptide of type III (PRO-C3) Procollagen**


<table>
<thead>
<tr>
<th>Diagnosis of moderate-to-advanced fibrosis (stages 2, 3, or 4)</th>
<th>AUROC (CI 95%)</th>
<th>Optimum cutoff point</th>
<th>Sensitivity, % (CI 95%)</th>
<th>Specificity, % (CI 95%)</th>
<th>PPV, % (CI 95%)</th>
<th>NPV, % (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma PRO-C3</td>
<td>0.81 (0.74–0.88)</td>
<td>—</td>
<td>9.70 ng/mL</td>
<td>86 (74–94)</td>
<td>68 (59–75)</td>
<td>50 (39–61)</td>
</tr>
<tr>
<td>APRI</td>
<td>0.83 (0.76–0.90)</td>
<td>0.73</td>
<td>0.46</td>
<td>72 (58–84)</td>
<td>86 (79–91)</td>
<td>66 (51–78)</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.73 (0.65–0.81)</td>
<td>0.10</td>
<td>1.30</td>
<td>70 (55–82)</td>
<td>87 (81–92)</td>
<td>67 (53–80)</td>
</tr>
<tr>
<td>ADAPT</td>
<td>0.77 (0.69–0.84)</td>
<td>0.06</td>
<td>6.20</td>
<td>72 (58–84)</td>
<td>71 (63–79)</td>
<td>49 (37–60)</td>
</tr>
<tr>
<td>Plasma PRO-C3 plus clinical parameters#</td>
<td>0.87 (0.81–0.94)</td>
<td>0.10</td>
<td>—</td>
<td>71 (57–83)</td>
<td>94 (88–97)</td>
<td>81 (67–92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of advanced fibrosis (stages 3 or 4)</th>
<th>AUROC (CI 95%)</th>
<th>Optimum cutoff point</th>
<th>Sensitivity, % (CI 95%)</th>
<th>Specificity, % (CI 95%)</th>
<th>PPV, % (CI 95%)</th>
<th>NPV, % (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma PRO-C3</td>
<td>0.88 (0.80–0.95)</td>
<td>—</td>
<td>13.2 ng/mL</td>
<td>82 (62–94)</td>
<td>82 (76–88)</td>
<td>43 (29–58)</td>
</tr>
<tr>
<td>APRI</td>
<td>0.87 (0.81–0.93)</td>
<td>0.98</td>
<td>0.42</td>
<td>89 (71–98)</td>
<td>75 (67–81)</td>
<td>38 (26–50)</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.83 (0.75–0.92)</td>
<td>0.43</td>
<td>1.76</td>
<td>74 (54–89)</td>
<td>79 (72–85)</td>
<td>38 (25–52)</td>
</tr>
<tr>
<td>ADAPT</td>
<td>0.86 (0.77–0.94)</td>
<td>0.56</td>
<td>6.58</td>
<td>82 (62–94)</td>
<td>81 (74–87)</td>
<td>42 (29–57)</td>
</tr>
<tr>
<td>Plasma PRO-C3 plus clinical parameters*</td>
<td>0.91 (0.86–0.96)</td>
<td>0.23</td>
<td>−1.40</td>
<td>82 (62–94)</td>
<td>85 (78–90)</td>
<td>50 (35–65)</td>
</tr>
</tbody>
</table>

#Only AST, HOMA-IR (fasting glucose [in mg/dl] * fasting insulin [in μU/mL]/405), sex, and weight remained independently associated with moderate-advanced fibrosis in the multiple logistic regression model (model: 0.11 × PRO-C3 + 0.05 × AST + 0.17 × HOMA-IR + 2.16 × sex [1 = male; 0 = female] − 0.03 × weight [in kg] − 4.021109; pseudo-R² = 0.39). *Only AST, HOMA-IR, and platelets remained independently associated with advanced fibrosis in the multiple logistic regression model (model: 0.14 × PRO-C3 + 0.03 × AST + 0.14 × HOMA-IR − 0.01 × platelets − 2.807115; pseudo-R² = 0.41).
Performance of Clinical Models or Plasma Biomarkers for the Diagnosis of Steatohepatitis in T2DM

Bril/Cusi et al, Diabetes Care 2019 (in press)

<table>
<thead>
<tr>
<th>Table 1—Demographic and clinical characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NAFLD (n = 51)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Sex, male %</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Total body fat, %</td>
</tr>
<tr>
<td>Hemoglobin A₁₀₀</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/mL</td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/mL</td>
</tr>
<tr>
<td>Diabetes medications, %</td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Intrahepatic triglyceride content, %</td>
</tr>
<tr>
<td>AST, units/L</td>
</tr>
<tr>
<td>ALT, units/L</td>
</tr>
<tr>
<td>NAFLD activity score</td>
</tr>
<tr>
<td>Steatosis grade</td>
</tr>
<tr>
<td>Inflammation grade</td>
</tr>
<tr>
<td>Ballooning grade</td>
</tr>
<tr>
<td>Fibrosis stage</td>
</tr>
</tbody>
</table>

Data are mean ± SDs or n (%). P values represent comparison among the three groups with ANOVA.
Performance of Clinical Models or Plasma Biomarkers for the Diagnosis of Advanced Fibrosis in T2DM

Bril/Cusi et al, Diabetes Care 2019 (in press)
Performance of Clinical Models or Plasma Biomarkers for the Diagnosis of Advanced Fibrosis in T2DM

n = 213

<table>
<thead>
<tr>
<th>Test</th>
<th>Predefined Cutoff Points</th>
<th>Cohort-specific Cutoff Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>PRO-C3</td>
<td>20.0 ng/mL</td>
<td>50 (29–71)</td>
</tr>
<tr>
<td>Cohort-specific model†</td>
<td>&lt;−2.613 &gt;−1.015</td>
<td>88 (68–97)</td>
</tr>
<tr>
<td>APRI</td>
<td>&lt;0.500 &gt;1.500</td>
<td>31 (9–61)</td>
</tr>
<tr>
<td>AST</td>
<td>40 units/L</td>
<td>77 (59–90)</td>
</tr>
<tr>
<td>FIB-4</td>
<td>&lt;1.450 &gt;3.250</td>
<td>33 (10–65)</td>
</tr>
<tr>
<td>FibroTest</td>
<td>&lt;0.300 &gt;0.700</td>
<td>17 (2–48)</td>
</tr>
<tr>
<td>NFS</td>
<td>&lt;−1.455 &gt;0.676</td>
<td>91 (59–100)</td>
</tr>
</tbody>
</table>

*144 not classified. †48 not classified. #84 not classified. ¥83 not classified. ‡68 not classified. ††Model was = 0.0034 × (CK-18) + 0.0588 × (fasting insulin) − 0.0116 × (platelets) − 1.3336 × (sex) + 0.4469 × (HbA1c) − 3.82 (where sex: 1 = male and 0 = female).

Bril/Cusi et al, Diabetes Care 2019 (in press)
Performance of Clinical Models or Plasma Biomarkers for the Diagnosis of Advanced Fibrosis in T2DM

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   - Can combination therapy change the natural history of NASH?
Approach #1: The “Downstream Approach” in NASH

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

Direct and Indirect effects of GLP-1RAs in Humans

**Heart**
- ↑ Cardiac Function
- ↑ LV Ejection fraction
- ↑ Coronary Flow
- ↓ Infract size

**Stomach**
- ↓ Gastric emptying

**Pancreas**
- ↑ Insulin secretion
- ↓ Glucagon secretion
- ↑ β cell proliferation
- ↓ β cell Apoptosis

**Kidneys**
- ↑ Natriuresis
- ↓ Blood Volume

**Adipocytes**
- ↓ White adipocyte
- ↑ Brown adipocyte

**Liver**
- ↓ Steatosis
- ↓ Glucose output

**GLP-1R Agonist**
- Immune cells
  - ↓ Inflammation
- Brain
  - Early Satiety
  - Food intake
  - Neuroprotection
- Hypothalamic Nuclei
  - Weight loss
  - Indirect effect of GLP-1RAs in Humans

Dhir G and Cusi K. Journal Invest Med September 2017
Table 2. Effect of liraglutide in NAFLD

<table>
<thead>
<tr>
<th>Author †</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>Comparator</th>
<th>Weight</th>
<th>ALT</th>
<th>Liver fat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open label studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohki et al, Sci World J 2012</td>
<td>82</td>
<td>74</td>
<td>Sitagliptin, pioglitazone</td>
<td>↓</td>
<td>↓</td>
<td>n/a</td>
</tr>
<tr>
<td>Eguchi, Hepatol Res 2015</td>
<td>19</td>
<td>24</td>
<td>Lifestyle</td>
<td>↓</td>
<td>↓</td>
<td>↓*</td>
</tr>
<tr>
<td>Tang et al, 2015</td>
<td>35</td>
<td>12</td>
<td>Insulin</td>
<td>↓</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Feng et al, 2017</td>
<td>87</td>
<td>24</td>
<td>Gliclazide, metformin</td>
<td>↓</td>
<td>↓</td>
<td>↓**</td>
</tr>
<tr>
<td>Bouchi et al, 2017§</td>
<td>17</td>
<td>24</td>
<td>Insulin alone</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Petit et al, 2017</td>
<td>68</td>
<td>24</td>
<td>Insulin alone</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Matikainen et al, 2018</td>
<td>22</td>
<td>16</td>
<td>Lifestyle</td>
<td>↓</td>
<td>not reported</td>
<td>↓</td>
</tr>
<tr>
<td><strong>RCTs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smits et al, 2016</td>
<td>18</td>
<td>12</td>
<td>Sitagliptin or placebo</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Armstrong et al, 2016</td>
<td>52</td>
<td>48</td>
<td>placebo</td>
<td>↓</td>
<td>↓</td>
<td>↓***</td>
</tr>
<tr>
<td>Vanderheiden et al, 2016 §</td>
<td>71</td>
<td>24</td>
<td>Insulin alone</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Frossing et al, 2018</td>
<td>72</td>
<td>26</td>
<td>placebo</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Statistically significant changes vs. comparison(s) indicated by arrows
§ Liraglutide plus insulin vs. insulin alone
* 10 of 19 had a repeat liver biopsy; NAS score improved in 6.
** Reduced more versus gliclazide (but not metformin)
*** Improvement on histology (NAS score) greater with liraglutide on paired liver biopsies.
Effect of Semaglutide vs. Liraglutide in T2DM

B

Mean at baseline (kg):

93.4  92.4  98.1  94.8  92.3  92.7  96.7  93.4  95.3  94.0

Overall average at baseline: 94.3 kg

Body weight

Semaglutide 0.05 mg  Semaglutide 0.1 mg  Semaglutide 0.2 mg  Semaglutide 0.3 mg  Liraglutide 0.3 mg  Liraglutide 0.6 mg  Liraglutide 1.2 mg  Liraglutide 1.8 mg  Semaglutide flexible dose  Placebo

-2.8  -4.3  -6.7  -8.2  -1.5  -1.7  -1.7  -3.7  -6.4  -1.2

Change from baseline at week 26 (kg)

Mean at baseline (%):

7.9  7.9  8.0  8.2  8.1  8.1  8.1  8.1  8.1  8.1

Overall average at baseline: 8.1%

HbA$_{1c}$

Semaglutide 0.05 mg  Semaglutide 0.1 mg  Semaglutide 0.2 mg  Semaglutide 0.3 mg  Liraglutide 0.3 mg  Liraglutide 0.6 mg  Liraglutide 1.2 mg  Liraglutide 1.8 mg  Semaglutide flexible dose  Placebo

-1.1  -1.4  -1.7  -1.9  -0.5  -0.9  -0.8  -1.3  -1.7  -0.02

Change from baseline at week 26 (%)

### TABLE 1. Effect of Sitagliptin in NAFLD

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Duration (Weeks)</th>
<th>Comparator</th>
<th>Main Study Results</th>
<th>Liver Fat (IHTG*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label studies</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Iwasaki et al. (2011)</td>
<td>30</td>
<td>16</td>
<td>None</td>
<td>Not reported</td>
<td>n/a</td>
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<tr>
<td>Ohki et al. (2012)</td>
<td>82</td>
<td>74</td>
<td>Liraglutide, pioglitazone</td>
<td>Unchanged</td>
<td>n/a</td>
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<tr>
<td>Fukuhara et al. (2014)</td>
<td>44</td>
<td>52</td>
<td>None</td>
<td>Not reported</td>
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<tr>
<td>Asakawa et al. (2015)</td>
<td>62</td>
<td>57</td>
<td>None</td>
<td>Not reported</td>
<td>Unchanged</td>
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<tr>
<td>Kato et al. (2015)</td>
<td>20</td>
<td>24</td>
<td>Glimepiride</td>
<td>↓</td>
<td>Not reported</td>
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<tr>
<td>Alam et al. (2018)</td>
<td>40</td>
<td>52</td>
<td>Lifestyle</td>
<td>Unchanged</td>
<td>↓</td>
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<tr>
<td>Sayari et al. (2018)</td>
<td>138</td>
<td>16</td>
<td>Sitagliptin + symbiotic</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Smits et al. (2016)</td>
<td>18</td>
<td>12</td>
<td>Liraglutide or placebo</td>
<td>Unchanged</td>
<td>Unchanged</td>
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<td>Cui et al. (2016)</td>
<td>50</td>
<td>24</td>
<td>Placebo</td>
<td>Unchanged</td>
<td>Unchanged</td>
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<tr>
<td>Joy et al. (2017)</td>
<td>12</td>
<td>24</td>
<td>Placebo</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

Statistically significant changes vs. comparison indicated by arrows.
*Liver fat measured with MRI-based imaging.
†Improvement on histology (NAFLD activity score) greater with sitagliptin on paired liver biopsies.
‡No significant improvement in liver histology on paired liver biopsies.
Abbreviations: ALT, alanine aminotransferase; n/a, not applicable.
SGLT2 Inhibitors: Mechanism of Action

Glucose renal filtration >180 gr/day*

*SGLT2 inhibitor

SGLT1

*Loss of ~ 80 g of glucose/day = 320 calories/day.

Effects of SGLT2i on the Heart, Kidney and Liver in T2DM

SGLT2 inhibition

- Glucosuria
  - Weight
  - Lipolysis
  - Gluconeogenesis
- NHE1↓
- Tubuloglomerular feedback activation
- Total body Na⁺ and H₂O↓

Ketone bodies

- Steatosis, NALD/NASH
- Blood pressure
- Angiotosingenin, Endothelein, TGFβ
- NHE3

- Steatosis

- Hypertension
- Intraglomerular pressure
- Albuminuria

- Heart failure

Sympathetic nerve activity

- Fibrosis
- DKD/CKD progression

Verma & McMurray; Diabetologia 2018;61:2108–2117

Wanner & Marx; Diabetologia 2018;61:2134–2139.
Clinical Studies: Effect of SGLT2i on Steatosis

a) Negative controlled studies:
  ✓ Dapagliflozin (Bolinder et al, JCEM 2012)

b) Positive observational studies with reduction in ALT:
  ✓ Dapagliflozin (Bailey et al, Lancet 2009; Tobita, Therapeutic Research 2017)
  ✓ Canagliflozin (Leiter, Diabetes Metab 2016; Seko, J Gastroenterol 2017)

c) Positive studies reporting a decrease in liver fat:
  ✓ Luseogliflozin (Shibuya et al, Diabetes Obes Metab 2017)
  ✓ Ipragliflozin (Ito et al, D. Care 2017; Ohta et al, Expert Opin Pharm 2017)
  ✓ Empagliflozin (Kuchay et al, Diabetes Care 2018; Shimizu et al, DOM 2019; Kahl et al, Diabetes Care 2019)
  ✓ Canagliflozin (Cusi et al, DOM 2019)
  ✓ Dapagliflozin (Latva-Rasku et al, Diabetes Care 2019)
Effect of Canagliflozin on Intrahepatic Triglycerides in Patients with Type 2 Diabetes


\[ r = 0.69, p < 0.001 \]
A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial
Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Table 2—Primary and secondary histological outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 32)</th>
<th>Vitamin E (n = 36)</th>
<th>P value vs. placebo</th>
<th>Vitamin E + pioglitazone (n = 37)</th>
<th>P value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: reduction of ≥2 points in NAS (from two different parameters), without worsening of fibrosis</td>
<td></td>
<td></td>
<td>0.26</td>
<td>20 (54)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prespecified analysis (noncompleters considered as failures)</td>
<td>6 (19)</td>
<td>11 (31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation of missing data</td>
<td>7 (22)</td>
<td>13 (36)</td>
<td>0.18</td>
<td>24 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resolution of NASH without worsening of fibrosis</td>
<td>4 (12)</td>
<td>12 (33)</td>
<td>0.04</td>
<td>16 (43)</td>
<td>0.005</td>
</tr>
<tr>
<td>Prespecified analysis (noncompleters considered as failures)</td>
<td>5 (17)</td>
<td>14 (40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation of missing data</td>
<td>5 (17)</td>
<td>14 (40)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of Vitamin E or Pioglitazone + Vitamin E versus Placebo in Patients with T2DM and NASH
Comparison to earlier trials on resolution of NASH

Cusi et al (unpublished)
Resolution of NASH with Pioglitazone is not Correlated to the Decrease of Intrahepatic Triglycerides (IHTG)

B.

Pioglitazone

$n = 63; p = 0.71$

Resolution of NASH* (%)

<table>
<thead>
<tr>
<th>Relative Change in IHTG Content</th>
<th>Resolution of NASH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\uparrow$IHTG (n=NA)</td>
<td>0</td>
</tr>
<tr>
<td>$\downarrow$1-30% (n=6)</td>
<td>20</td>
</tr>
<tr>
<td>$\downarrow$31-50% (n=12)</td>
<td>40</td>
</tr>
<tr>
<td>$\downarrow$51-70% (n=20)</td>
<td>60</td>
</tr>
<tr>
<td>$\downarrow$&gt;70% (n=25)</td>
<td>80</td>
</tr>
</tbody>
</table>

Relationship between PRO-C3 and Histological Change in Fibrosis Stage after Treatment

Changes After 18 Months of Therapy

$p=0.02$

<table>
<thead>
<tr>
<th>Change in PRO-C3 (ng/ml)</th>
<th>≥2 stages</th>
<th>1 stage</th>
<th>≥1 stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>-4</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>No Change</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Worsening</td>
<td></td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Fibrosis Over Time
Pioglitazone profile: pros and cons in diabetes

Hepatic and extra-hepatic effects

- Liver:
  - Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  - Prevention of fibrosis progression
- Extra-hepatic:
  - Reversal of insulin resistance, ectopic fat deposition and lipotoxicity
  - Improved CV profile: inflammation/lipid panel (lowers TG; increases HDL-C)

Caution

- Dose-dependent weight gain: 1% with 15 mg/day and 3 to 4% with 45 mg/day
- Edema: 5-8% (more if combined with insulin or amlodipine)
- Risk of bone loss: should be monitored
- Bladder cancer? Unclear, likely very small (18 out of 23 studies negative)

Khan, Bril, Cusi and Newsome, Hepatology 2019
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” (HFpEF)? 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.
NASH and Diabetes Linkage:
Closing the knowledge gap

1. Potential mechanisms
   - What is the role of hyperglycemia (glucotoxicity)?

2. The diagnostic challenge of NASH-fibrosis in T2DM
   - Value of diagnostic panels and novel biomarkers

3. The treatment opportunity of T2DM
   - Brief overview of the potential of SGLT2i, GLP-1RAs, PIO
   - Can (early) combination therapy change the natural hx of NASH?
Current and Potential Therapeutic Targets in NASH

The Future: Combination Therapy Early on for NASH in Patients with T2DM
Future Combination Therapies in NASH

• Use FXR plus another agent:
  – FXR + elafibranor
  – Tropifexor (FXR) + cenicriviroc (chemokine receptor type 2/5 antagonist)
  – Cilofexor (FXR) + firsocostat (ACCi) + semaglutide

• Use diabetes medications alone or combined plus + anti-inflammatory or antifibrotic (“downstream” agent) to increase efficacy in NASH:
  – “Upstream” agent that promotes weight loss (GLP-1RA or SGLT2i) + “downstream” agent
  – Insulin-sensitizer (PIO or novel one) + “downstream” agent
  – Any combination of the above
NASH and Diabetes Linkage: Closing the knowledge gap

1. Potential mechanisms
   - There is a need to more carefully establish the role of hyperglycemia (glucotoxicity) in NASH

2. The diagnostic challenge of NASH-fibrosis in T2DM
   - Need for more work in diagnostic panels and novel biomarkers

3. The treatment opportunity of T2DM
   - Combination of available plus novel agents will change the natural history of NASH in the near future
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