Management NAFLD and NASH in Patients with Type 2 Diabetes

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Disclosures

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

• **Consultant:** Allergan, AstraZeneca, BMS, Cirius, Coherus, Deutereplex, Janssen, Genentech, Gilead, Merck, Novo Nordisk, Pfizer, Poxel.

• **Stock/Shareholder:** None

• **Other:** None
The University de Florida (Gainesville, FL)
Want to do some research at the University of Florida?

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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
Fatty Liver identified

NAFLD

Steatosis but no inflammation, ballooning or fibrosis

NAFL

Progression and regression are possible

NASH

Steatosis with inflammation and hepatocyte injury (ballooning) +/- lobular fibrosis

Risk of cirrhosis

Risk of hepatocellular carcinoma

Absence alcohol abuse or competing causes

Budd & Cusi, American Journal of Medicine, 2020 (in press)
NAFLD in Type 2 Diabetes (T2DM)

1. Links between T2DM and NAFLD
   - Prevalence and risk factors
   - Mechanisms

2. Complications
   - Liver: risk of cirrhosis, hepatocellular carcinoma
   - Extra-hepatic: development of T2DM and of CVD

3. Management
   - Diagnosis
   - Treatment: a) Liver disease
     b) Extra-hepatic: T2DM prevention and CVD
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

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**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
# NASH in 2020 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 2020</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 in 2020</td>
</tr>
</tbody>
</table>
Prevalence of NAFLD using different diagnostic tools

- General Population
- T2DM

<table>
<thead>
<tr>
<th>Test</th>
<th>Plasma ALT</th>
<th>Computed tomography</th>
<th>Liver US</th>
<th>Controlled attenuation parameter (Fibroscan®)</th>
<th>(^1\text{H-MRS} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence (%)</td>
<td>10</td>
<td>30</td>
<td>50</td>
<td>70</td>
<td>60</td>
</tr>
</tbody>
</table>
The Prevalence of NAFLD* in T2DM: 55.5%

- NASH prevalence: 37.3% (10 studies)
- Fibrosis prevalence: 17% (7 studies)

*80 studies: 74 used liver ultrasound, 6 used magnetic resonance imaging

Younossi et al, J Hepatology 2019
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

The Prevalence of NAFLD* Increases with BMI in T2DM even when AST/ALT ≤40 IU/L

*Screened by magnetic resonance and spectroscopy

Portillo-Lopez et al, JCEM 2015
NAFLD in Type 2 Diabetes (T2DM)

1. Links between T2DM and NAFLD
   - Prevalence and risk factors
   - Mechanisms
From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH
   - Prevalence and risk factors
   - Mechanisms

2. Complications
   - Liver: risk of fibrosis/cirrhosis and hepatocellular carcinoma
By 2030, prevalence of NASH will increase by 63% to 27 million cases.

NASH-advanced fibrosis will increase by 160% to 8 million cases.

Liver deaths will increase 178% (78,300 deaths).
NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH
   - Prevalence and risk factors
   - Mechanisms

2. Complications
   - Liver: risk of cirrhosis, hepatocellular carcinoma
   - Extra-hepatic: development of T2DM and of CVD
Also shown in a meta-analysis of 19 observational studies with ~300,000 individuals.
Follow-up median of 5 years.
2-fold greater risk of diabetes in patients in NAFLD

Mantovani et al, Diabetes Care 2018;41:372–382
Potential mechanisms by which statins may favorably affect liver histology and hepatic complications in NAFLD

Mortality in Isolated Steatosis versus NASH

- No NAFLD: 14.5 y*
- Isolated steatosis: 13.3 y*
- NASH: 13.0 y*

- Liver related
- Cardiovascular
- Other

Bril & Cusi, Metabolic Clinics North America 2016
NAFLD in Type 2 Diabetes (T2DM)

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   - Liver: risk of cirrhosis, hepatocellular carcinoma
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3. Management
   - Diagnosis
Interpretation of FIB-4 and NFS for the Diagnosis of Advanced Fibrosis (stages 3-4)

**FIB-4**

- Risk of advanced fibrosis (stages 3-4)
  - Low: <1.3 (F0-F1)
  - Indeterminate: 1.3 – 2.67 (F1-F2)
  - High: >2.67 (F3-F4)

**Parameters**

- Age
- AST
- ALT
- Platelets
- BMI
- Serum Glucose (IGT or DM?)
- Albumin

**NFS**

- Risk of advanced fibrosis (stages 3-4)
  - Low: < -1.455
  - Indeterminate: 1.455 – 0.676
  - High: >0.676

FIB-4: Fibrosis-4 score; NFS: NAFLD fibrosis score.

Budd & Cusi, American Journal of Medicine, 2020 (in press)
Diagnosing **Advanced Liver Fibrosis with Biomarker Panels**

<table>
<thead>
<tr>
<th>Parameters and biomarkers</th>
<th>Cutoffs for advanced fibrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive biomarker detection methods</strong></td>
<td></td>
</tr>
<tr>
<td>NAFLD fibrosis score(^{50})</td>
<td></td>
</tr>
<tr>
<td>Age, BMI, IFG and diabetes, AST-to-ALT ratio, platelets, and albumin</td>
<td>( \leq 1.455 )</td>
</tr>
<tr>
<td>FIB-4 index(^{51})</td>
<td>( &lt;1.3 )</td>
</tr>
<tr>
<td>Age, AST, ALT, and platelet</td>
<td>( &gt;2.67 )</td>
</tr>
<tr>
<td>Enhanced liver fibrosis test(^{54})</td>
<td>( \geq 9.8 )</td>
</tr>
<tr>
<td>Age, hyaluronic acid, aminoterminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1</td>
<td></td>
</tr>
<tr>
<td>FibroTest ((\text{FibroSure})^{55})</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, ( \gamma )-glutamyltransferase, ( \alpha_2 )-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex</td>
<td>( &gt;0.30 ) ( &gt;0.70 )</td>
</tr>
</tbody>
</table>

Imaging Techniques Used to Assess Fibrosis in NAFLD

**Elastography**

- **Vibration-controlled transient elastography (FibroScan®)**
  - Accurate in detecting advanced fibrosis
  - Estimates hepatic fat
  - Predicts risk of decompensation and complications
  - Correlates well with portal pressure
  - Most reliable in ruling out advanced disease
  - Most widely used

- **Shear wave elastography (SWE)**
  - Uses acoustic radiation force impulse (ARFI) technology
  - Point quantification: SWE or 2-D supersonic shear imaging (SSI) SWE

- **MR elastography**
  - Most accurate of the imaging modalities
  - Costly, no point-of-care access

Diagnosis of Fibrosis in NASH with Elastography*

* Vibration controlled transient elastography (VCTE by Fibroscan® - Echosens)
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
Diagnostic Algorithm for NASH in the Primary Care Setting

Patient with prediabetes or T2DM

ALT or US abnormal

- ALT & US normal
  - Higher risk
    - Long-standing T2DM (>10 yrs)
    - Evidence of steatosis*
    - A1c ≥ 8.5%
    - Triglycerides ≥250 mg/dl
    - Genetic testing?

Rule out other causes of liver disease

Assessment of fibrosis
- MR elastography, or
- Transient elastography, or
- Fibrosis biomarker panels

NAFLD fibrosis score (NFS)
Fibrosis-4 index (FIB-4)

High risk of fibrosis
- Referral to hepatology and consider liver biopsy

Intermediate fibrosis risk
- Referral to hepatology

Low risk of fibrosis

Liver biopsy
- Definite NASH
- Absence of NASH
- Periodic evaluation; standard care

Lifestyle plus pioglitazone treatment

Bril & Cusi
Diabetes Care, March 2017 40:419-430
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   - Mechanisms

2. Complications
   - Liver: risk of cirrhosis, hepatocellular carcinoma
   - Extra-hepatic: development of T2DM and of CVD

3. Management
   - Diagnosis
   - Treatment of NASH, prevention of fibrosis and cirrhosis
“GOOD ON SO MANY LEVELS!”

AVAILABLE NOW, FOR A LIMITED TIME ONLY!
From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
The Future: “Combination Therapy” to Prevent Disease Progression

Potential Therapeutic Targets in NASH

Adapted from Rotman et al. Gut. 2017;66:180–90

ACC, acetyl-CoA carboxylase; DNL, de novo lipogenesis; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MPC, mitochondrial pyruvate carrier; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor.

Insulin sensitizers
- Pioglitazone
- Elafibranor
- MSD0602
- Lanifibranor
- CHS-131
- Saroglitazar
- Seladelpar
- PXL-065

GLP-1RA agonists
- Liraglutide
- Semaglutide (daily injection formulation)

Thyroid hormone receptor (THR)-β-selective agonists
- NGM-282 (FGF-19 agonist)
- Vitamin E
- Pentoxifylline
- VK2809
- MGL-3196

FGF21 agonists
- Pegbelfermin
- AKR-001
- MK-3655
- NNC0194-9499
- BFKB8848A
- BIO89-100
- LY-3025876

FXR agonists
- Obeticholic Acid
- INT-767
- Tropifexor
- LMB-763
- Cilofexor
- EDP305
- EY_001
- MET409

Aramchol
- (inhibitor of SCD-1)
- GS-0976
- (inhibitor ACC)

FXR agonists
- Obeticholic Acid
- INT-767
- Tropifexor
- LMB-763
- Cilofexor
- EDP305
- EY_001
- MET409

Dietary Fat
- Sevelamer
- Volibixat

Bile Acids
- Simtuzumab
- GR-MD-02

Bacterial Products
- IMM-124e
- Fecal microbiota transplantation
- Solithromycin

Fecal microbiota transplantation
- SIM-124e
- Solithromycin

Obeticholic Acid
- INT-767
- Tropifexor
- LMB-763
- Cilofexor
- EDP305
- EY_001
- MET409

Insulin sensitizers
- Pioglitazone
- Elafibranor
- MSD0602
- Lanifibranor
- CHS-131
- Saroglitazar
- Seladelpar
- PXL-065

Intestine
Physicians ask:

“Why diagnose NASH if there are no treatments...?”

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

36% liver fat (baseline)

2% liver fat (4 weeks of VLCD)

(Courtesy of Dr. R. Taylor)
Increasing Benefit of Weight Loss on Fibrosis

Probability of Improving NASH Components According to Weight Loss\(^1,2\)

\(^a\)At least one stage.

N=293 patients with NASH were encouraged to adopt lifestyle changes for weight loss over 52 weeks.


Rho=0.13, \(P=0.02\)

Large variability in response

Mean weight loss, %

% Weight Loss 5% 7% 10%

52 weeks of lifestyle intervention

Fibrosis status\(^2\)

Worsened Stabilized Regressed
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
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.
Pioglitazone is not approved for treatment of NAFLD or NASH.
Rationale for Pioglitazone in NASH

Liver

- Hepatocytes
  - Steatosis
  - Fibrosis
  - Inflammation

Activated immune response

- Activated stellate cell
- Cytokines (systemic effects)

Adipose tissue

- Adipose tissue insulin resistance
- Inflammation

FFA

- Glucose
- Triglycerides

Activated macrophage

- Cytokines (systemic effects?)

B cell

T cell

Cytokines

B cell

T cell

Cusi K. Gastroenterology 2012, 142:711-25
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

- Patients With Improvement, %
  - ≥2-point reduction in NAS (No worsening of fibrosis): 19% vs. 65% (P < 0.001)
  - Resolution of NASH: 21% vs. 58% (P = 0.001)
  - Completers With Definite NASH at Baseline: 17% vs. 67% (P < 0.001)

~50% response rate vs. placebo

Pioglitazone profile: pros and cons in diabetes

The “good”

- Liver:
  - Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  - 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

Khan, Bril, Cusi and Newsome, Hepatology 2019
Cardiovascular Consequences of NAFLD

Pioglitazone Reduces CVD, Prevents Progression of Atherosclerosis and Improves LV Function

- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007)
- PERISCOPE (JAMA 2008)
- IRIS Study (NEJM 2016; Circulation 2017; JAMA 2019)
# Pioglitazone Therapy in Patients With Stroke and Prediabetes

A Post Hoc Analysis of the IRIS Randomized Clinical Clinical Trial


Table 2. Hazard Ratios in Cox Regression for On-Treatment and Intention-to-Treat Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence ≥80%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/MI</td>
<td>0.57 (0.39-0.84)</td>
<td>.004</td>
<td>24</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.64 (0.42-0.99)</td>
<td>.04</td>
<td>39</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0.47 (0.26-0.85)</td>
<td>.01</td>
<td>40</td>
</tr>
<tr>
<td>Stroke/MI/HF hospitalization</td>
<td>0.61 (0.42-0.88)</td>
<td>.008</td>
<td>26</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>0.18 (0.10-0.33)</td>
<td>&lt;.001</td>
<td>12</td>
</tr>
<tr>
<td><strong>Intention to treat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/MI</td>
<td>0.70 (0.56-0.88)</td>
<td>.002</td>
<td>28</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.72 (0.56-0.93)</td>
<td>.01</td>
<td>39</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0.72 (0.52-1.00)</td>
<td>.052</td>
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<tr>
<td>Stroke/MI/HF hospitalization</td>
<td>0.78 (0.63-0.96)</td>
<td>.02</td>
<td>34</td>
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<tr>
<td>New-onset diabetes</td>
<td>0.46 (0.35-0.61)</td>
<td>&lt;.001</td>
<td>19</td>
</tr>
</tbody>
</table>

**CONCLUSIONS AND RELEVANCE**  Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack and with prediabetes, particularly in those with good adherence.
ACT NOW study: Pioglitazone prevents Type 2 Diabetes

Hazard ratio, 0.28 (95% CI, 0.16–0.49)
P<0.001

72% reduction in new onset diabetes

DeFronzo et al, NEJM 364, 1104-11, 2011
Pioglitazone profile: pros and cons in diabetes

The “good”

– Liver:
  • Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  • 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

Watch for

– Edema: 5-8% (more if combined with insulin or amlodipine)
– Risk of bone loss: should be monitored
– Bladder cancer? Unclear, likely very small if so (18 out of 23 studies negative)
– Weight gain: 2 to 4 kg (dose-dependent; although less insulin resistance and metabolically healthy fat…)

Khan, Bril, Cusi and Newsome, Hepatology 2019
# Effect of Low-dose (15 mg/day) Pioglitazone in Patients with T2DM

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose (mg/day)</th>
<th>Population</th>
<th>n</th>
<th>Duration (weeks)</th>
<th>diff FPG (mg/dL)</th>
<th>diff A1c %</th>
<th>diff TG %</th>
<th>diff HDL %</th>
<th>Weight change %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose-response studies</strong></td>
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<td>Aronoff et al, 2000* [24]</td>
<td>15</td>
<td>USA</td>
<td>80</td>
<td>26</td>
<td>-39</td>
<td>-1.0</td>
<td>-14</td>
<td>6</td>
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<td></td>
<td>30</td>
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<td>79</td>
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<td>-41</td>
<td>-1.0</td>
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<td>Miyazaki et al, 2002* [25]</td>
<td>15</td>
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<td>Rosenstock, 2002* [26]</td>
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<td>Rajagopalan, 2015* [27]</td>
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<td>India</td>
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<td>-41</td>
<td>-0.7</td>
<td>-24</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Cusi, 2019 (unpublished)
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

Direct and Indirect effects of GLP-1 RA in Humans

GLP-1R Agonist

Heart
- ↑ Cardiac Function
- ↑ LV Ejection fraction
- ↑ Coronary Flow
- ↓ Infarct 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

Brain
- Early Satiety
- Food intake
- Neuroprotection

Hypothalamic Nuclei

Inflammation

Immune cells
- ↓ Inflammation

Dhir G and Cusi K. Journal Invest Med September 2017
**Effect of Liraglutide in Patients with T2DM and 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>
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<tr>
<td><strong>Open-label studies</strong></td>
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<tr>
<td>Ohki et al. (2012)</td>
<td>82</td>
<td>74</td>
<td>Sitagliptin, pioglitazone</td>
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<td><strong>RCTs</strong></td>
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<td>Smits et al. (2016)</td>
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Statistically significant changes vs. comparison(s) indicated by arrows.

* Liraglutide plus insulin vs. insulin alone.
† Ten of 19 had a repeat liver biopsy; NAFLD activity score improved in 6.
‡ Ten of 19 had a repeat liver biopsy; NAFLD activity score improved in 6.
§ Improvement on histology (NAFLD activity score) greater with liraglutide on paired liver biopsies.

Abbreviations: ALT, alanine aminotransferase; n/a, not applicable.
LEAN Study (Liraglutide Efficacy and Action in NASH): Changes in Liver Histologic Features at Week 48


Patients With Improvement

- **NASH Resolution (Primary Outcome)**
  - Liraglutide (n=23): 39%, Placebo (n=22): 9%
  - Improvement: 9% (P=0.02)
  - Placebo: 9%

- **NAFLD Activity Score**
  - Liraglutide: 74%, Placebo: 64%
  - Improvement: 10% (P=0.5)

- **Fibrosis**
  - Liraglutide: 26%, Placebo: 14%
  - Improvement: 12% (P=0.5)

- **Hepatocellular Ballooning**
  - Liraglutide: 61%, Placebo: 32%
  - Improvement: 29% (P=0.05)

- **Steatosis**
  - Liraglutide: 83%, Placebo: 45%
  - Improvement: 38% (P=0.009)

- **Lobular Inflammation**
  - Liraglutide: 48%, Placebo: 55%
  - Improvement: 7% (P=0.7)

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

All Patients

Patients with NAFLD

*C*<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.
Effect of Sitagliptin in Patients with T2DM and NAFLD

<table>
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<tr>
<th>Author</th>
<th>N</th>
<th>Duration (Weeks)</th>
<th>Comparator</th>
<th>Weight</th>
<th>ALT</th>
<th>Liver Fat (IHTG*)</th>
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<td>Iwasaki et al. (2011)</td>
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<td>Fukuhara et al. (2014)</td>
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<td>Sayari et al. (2018)</td>
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<td>Sitagliptin + synbiotic</td>
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<td>RCTs</td>
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<td>Smits et al. (2016)</td>
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<td>Joy et al. (2017)</td>
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<td>24</td>
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<td>No change vs. placebo†</td>
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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.
Effect of SGLT2 Inhibitors on Intrahepatic Triglycerides in Patients with T2DM and NAFLD

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
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<th>Body weight*</th>
<th>ALT</th>
<th>Liver fat*</th>
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<td>Ito et al, 2017</td>
<td>Ipragliflozin</td>
<td>66</td>
<td>24</td>
<td>Pioglitazone</td>
<td>↓ 3.7%</td>
<td>↓ 1%</td>
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<td>Ohta et al, 2017</td>
<td>Ipragliflozin</td>
<td>20</td>
<td>24</td>
<td>Standard care</td>
<td>↓ 2.5%</td>
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<td>↓ 39%</td>
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<td>Shibuya et al, 2017</td>
<td>Luseogliflozin</td>
<td>32</td>
<td>24</td>
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<td>↓ 3.2%</td>
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<td>Kuchay et al, 2018</td>
<td>Empagliflozin</td>
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<td>Standard care</td>
<td>↓ 1.1%</td>
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<td>Shimizu et al, 2019</td>
<td>Dapagliflozin</td>
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<td>Standard care</td>
<td>↓ 3.1%</td>
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<td>↓ 31%</td>
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<td>Inohue et al, 2019</td>
<td>Canagliflozin</td>
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<td>52</td>
<td>Standard care</td>
<td>↓ 3.4%</td>
<td>↓</td>
<td>↓ 31%</td>
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<td><strong>Randomized controlled trials</strong></td>
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<tr>
<td>Bolinder et al, 2012</td>
<td>Dapagliflozin</td>
<td>67</td>
<td>24</td>
<td>placebo</td>
<td>↓ 2.2%</td>
<td>-</td>
<td>unchanged</td>
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<tr>
<td>Eriksson et al, 2018</td>
<td>Dapagliflozin</td>
<td>84</td>
<td>12</td>
<td>placebo</td>
<td>↓ 2.2%</td>
<td>↓</td>
<td>↓ 10% §</td>
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<td>Cusi et al, 2019</td>
<td>Canagliflozin</td>
<td>56</td>
<td>24</td>
<td>placebo</td>
<td>↓ 3.4%</td>
<td>unchanged</td>
<td>↓ 18% §</td>
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<td>Latva-Rasku et al, 2019</td>
<td>Dapagliflozin</td>
<td>32</td>
<td>8</td>
<td>placebo</td>
<td>↓ 2.1%</td>
<td>unchanged</td>
<td>↓ 13%</td>
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<tr>
<td>Kahl et al, 2019</td>
<td>Empagliflozin</td>
<td>84</td>
<td>24</td>
<td>placebo</td>
<td>↓ 2.4%</td>
<td>unchanged</td>
<td>↓ 22%</td>
</tr>
</tbody>
</table>

Arrows indicate statistically significant changes vs. comparator
* Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques.
† Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. Decrease similar to pioglitazone (comparator) in this trial (also ALT).
§ Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan®).
§ Not significant compared to placebo.

Cusi KL, Diabetes Care 2020 (in press)
Effect of Canagliflozin on Intrahepatic Triglycerides in Patients with Type 2 Diabetes

$r = 0.69, p < 0.001$

Cusi K, Bril F, Polidori D et al, Diabetes, Obesity and Metabolism 2019
NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH
   - Prevalence and risk factors
   - Mechanisms

2. Complications
   - Liver: risk of cirrhosis, hepatocellular carcinoma
   - Extra-hepatic: development of T2DM and of CVD

3. Management
   - Diagnosis
   - Treatment: a) Liver disease
     b) Extra-hepatic: T2DM prevention and CVD
Treatment of NASH

Patient with prediabetes or T2DM and definite NASH

Treatment of NASH

- pharmacological treatment (Pioglitazone as first-line therapy)
- lifestyle intervention (Weight reduction of 8-10%)

- no response
- 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)

- elevated A1c
- elevated BP
- elevated TG and low HDL

- add pioglitazone
- add GLP-1RA or SGLT-2 inhibitors
- second-line therapies
- add fibrates to statins

Bril & Cusi, Diabetes Care 2017 40:419-430
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

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**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
Diagnostic Algorithm for NASH in the Primary Care Setting

Patient with prediabetes or T2DM

ALT or US abnormal

Rule out other causes of liver disease

Higher risk

ALT & US normal

• Long-standing T2DM (>10 yrs)
• Evidence of steatosis*
• A1c ≥ 8.5%
• Triglycerides ≥250 mg/dl
• Genetic testing?

Assessment of fibrosis
• MR elastography, or
• Transient elastography, or
• Fibrosis biomarker panels

NAFLD fibrosis score (NFS)
Fibrosis-4 index (FIB-4)

Liver biopsy

High risk of fibrosis
Referral to hepatology and consider liver biopsy

Lifestyle plus pioglitazone treatment

Definite NASH

Intermediate fibrosis risk
Referral to hepatology

Low risk of fibrosis

Absence of NASH

Periodic evaluation; standard care

Bril & Cusi
Diabetes Care, March 2017 40:419-430
NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH
   - SCREEN high risk populations in obese, T2DM, ↑ AST/ALT
   - Mechanisms: insulin resistance is key

2. Complications
   - Liver: risk of cirrhosis, hepatocellular carcinoma
   - High risk of T2DM and of CVD (use of statins overall safe in NASH)

3. Management (ADA: screen and treat fibrosis)
   - Elevated ALT or steatosis? Use FIB-4, elastography, biopsy (?)
   - Treatment: a) Lifestyle; pioglitazone
     b) Extra-hepatic: aim to prevent CVD