Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

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FACULTY

Curtis L. Triplitt, Pharm.D.
University of Texas Health Science Center at San Antonio
San Antonio, Texas
VIEW BIO

Eric L. Johnson, M.D.
University of North Dakota School of Medicine and Health Sciences
Grand Forks, North Dakota
VIEW BIO

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Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

Curtis L. Triplitt, Pharm.D., CDE
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Eric L. Johnson, M.D.
University of North Dakota School of Medicine and Health Sciences, Grand Forks, North Dakota

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Learning Objectives

• Review the safety and efficacy of SGLT-2 inhibitors, including recent cardiovascular outcomes trials.
• Compare the various formulations of GLP-1 agonists and their place in type 2 diabetes (T2DM) therapy.
• Discuss the relationship between Non-alcoholic Fatty Liver Disease (NAFLD) and T2DM, including current guidelines.
• Using patient scenarios, apply these concepts to provide interprofessional care to patients with T2DM.

Abbreviations

• AACE=American Association of Clinical Endocrinologists
• ACCORD=Action to Control Cardiovascular Risk in Diabetes trial
• ACP=American College of Physicians
• ADA=American Diabetes Association
• ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial
• ASCVD=atherosclerotic cardiovascular disease
• BMI=body mass index
• BP=blood pressure
• CHF=chronic heart failure
• CKD=chronic kidney disease
• CV=cardiovascular
• CVD=cardiovascular disease
• DCCT=Diabetes Control and Complications Trial
• DKA=diabetic ketoacidosis
• eGFR=estimated glomerular filtration rate
• FPG=fasting plasma glucose
• GFR=glomerular filtration rate
• HTN=hypertension
• MI=myocardial infarction
• NASH=non-alcoholic steatohepatitis
• PPG=postprandial blood glucose
• SU=sulfonylurea
• TZD=thiazolidinedione
• UKPDS=United Kingdom Prospective Diabetes Study
• UTI=urinary tract infection
• VADT=Veterans Affairs Diabetes Trial
On average how many unique patients (not patient encounters) with T2DM do you personally provide care to each week?

a. Less than 10 patients
b. 11-20 patients
c. 21-50 patients
d. More than 50 patients
e. None – I am not directly involved in patient care

Indications and Uses of SGLT-2 Inhibitors and GLP-1 Agonists

Eric L. Johnson, M.D.
University of North Dakota School of Medicine and Health Sciences, Grand Forks, North Dakota
**2018 ADA/EASD Consensus Statement**

**Antihyperglycemic Medication in T2DM: Overall Approach**

*First-line therapy is Metformin and comprehensive lifestyle (including weight management and physical activity)*

**Without Established ASCVD or CKD:** Individualize based on need to minimize hypoglycemia, address weight loss, or ↓ costs

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**ASCVD Predominates**

- **GLP-1 agonist with proven CVD benefit**
- **SGLT-2 inhibitor with proven CVD benefit if eGFR adequate**

- **If A1C above target**
  - Consider adding the other class with proven CVD benefit
    - DPP-4 inhibitor if not on GLP-1 agonist
    - Basal insulin, TZD, SU

**Heart Failure or CKD Predominates**

- **PREFERABLY:** SGLT-2 inhibitor with evidence of reducing HF and/or CKD in cardiovascular outcome trials if eGFR adequate
- **OR**
  - If SGLT-2 inhibitor not tolerated or contraindicated, GLP-1 agonist with proven CVD benefit if eGFR less than adequate
  - Avoid TZD in the setting of heart failure
  - Consider adding the other class with proven CVD benefit
  - DPP-4 inhibitor (not saxagliptin) if not on GLP-1 agonist
  - Basal insulin, SU

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**2018 ADA/EASD Consensus Statement**

**Antihyperglycemic Medication in T2DM: Overall Approach**

**WITHOUT**

- **COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA**
  - DPP-4 inhibitor
  - GLP-1 agonist
  - SGLT-2 inhibitor
  - TZD

- **If A1C above target**
  - CONTINUE with ADDITION OF OTHER AGENTS
    - Consider the addition of SU or basal insulin
    - Choose SU with lower risk of hypoglycemia
    - Consider basal insulin with lower risk of hypoglycemia

**COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS**

- **Either/or**
  - GLP-1 agonist with good efficacy for weight loss
  - SGLT-2 inhibitor

- **If A1C above target**
  - SGLT-2 inhibitor
  - GLP-1 agonist with good efficacy for weight loss

- **If triple therapy required or SGLT-2 inhibitor and/or GLP-1 agonist not tolerated or contraindicated, use regimen with LOWEST risk of weight gain**
  - DPP-4 inhibitor (if not on GLP-1 agonist)
  - CAUTION FOR: SU - TZD - insulin
  - Avoid TZD in the setting of heart failure

**COST IS A MAJOR ISSUE**

- **SU**
- **TZD**

- **If A1C above target**
  - Insulin therapy: basal insulin with lowest acquisition cost
  - Consider DPP-4 inhibitor or SGLT-2 inhibitor with lowest acquisition cost

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Focus on Cardiovascular and Renal Benefits of Antihyperglycemic Medications

SGLT-2 Inhibitors
Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Weight Change</strong></td>
<td>Loss</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>High</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral</td>
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</tbody>
</table>

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SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>CV Effects</th>
<th>ASCVD</th>
<th>Benefit: canagliflozin, empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td></td>
<td>Benefit: canagliflozin, empagliflozin, dapagliflozin</td>
</tr>
</tbody>
</table>

Renal Effects

<table>
<thead>
<tr>
<th>Diabetic Kidney Disease (DKD)</th>
<th>Benefit: canagliflozin, empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing/Use Considerations</td>
<td>Canagliflozin: Not recommended with eGFR &lt;45*</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin: Not recommended with eGFR &lt;60*</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin: Not recommended with eGFR &lt;45*</td>
</tr>
<tr>
<td></td>
<td>Ertugliflozin: Not recommended with eGFR &lt;60*</td>
</tr>
<tr>
<td></td>
<td>All: contraindicated with eGFR&lt;30*</td>
</tr>
</tbody>
</table>

*= mL/minute/1.73m²

SGLT-2 Inhibitors

**Additional Considerations**

- FDA Black Box: risk of amputation (canagliflozin)
- Risk of bone fractures? (canagliflozin)
- DKA risk (all agents, rare in T2DM)
- Genitourinary infections, Fournier’s gangrene
- Risk of volume depletion, hypotension
- Increase LDL cholesterol

GPL-1 Agonists

**Dulaglutide, Exenatide, Exenatide extended-release, Lixisenatide, Liraglutide, Semaglutide**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Weight Change</td>
<td>Loss</td>
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<tr>
<td>Cost</td>
<td>High</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>
# Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

## GPL-1 Agonists

**Additional Considerations**
- FDA Black Box: risk of thyroid c-cell tumors (liraglutide, dulaglutide, semaglutide, exenatide extended release)
- Gastrointestinal side effects common (nausea, vomiting, diarrhea)
- Injection site reactions
- Acute pancreatitis risk

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## GPL-1 Agonist + Basal Insulin Combination

**Insulin degludec + liraglutide (iDegLira), Insulin glargine + lixisenatide (iGlarLixi)**

**Considerations**
- Generally recommended for those on basal insulin not achieving goal A1C
- Labels suggest down titration to start
- iDegLira (insulin degludec and liraglutide) 16 units/day initially
- iGlarLixi (insulin glargine and lixisenatide) 15 units/day initially for 15 to <30 units/day glargine, 30–60 units/day glargine start treatment at 30 units/day initially
- Titrate the basal insulin, GLP-1 agonist “along for the ride”

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### GPL-1 Agonist + Basal Insulin Combination

**Insulin degludec + liraglutide (iDegLira), Insulin glargine + lixisenatide (iGlarLixi)**

<table>
<thead>
<tr>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can help to simplify treatment regimens into one daily injection, potentially aiding in patient adherence</td>
</tr>
<tr>
<td>• Enhanced glycemic control compared with their constituent components</td>
</tr>
<tr>
<td>• Risk of hypoglycemia comparable to basal insulin</td>
</tr>
<tr>
<td>• Better tolerability compared with the GLP-1 agonist component alone due to the slower titration</td>
</tr>
</tbody>
</table>


### Cardiovascular Benefit of Diabetes Medications
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**SUSTAIN-6**

Semaglutide (GLP-1 agonist)
- 26% risk reduction in the primary outcome, a composite of nonfatal heart attacks, nonfatal strokes, and cardiovascular death


**LEADER**

Liraglutide (GLP-1 agonist)

T2DM at higher CVD risk
- 22% risk reduction of cardiovascular death
- 13% reduction of primary CVD endpoints
- 12% risk reduction of nonfatal heart attacks, 11% risk reduction of nonfatal strokes but neither statistically significant
- 22% risk reduction of nephropathy

**EMPA-REG**

Empagliflozin (SGLT-2 inhibitor)

T2DM patients with high CVD risk (prior events)

- Reduced the primary major adverse cardiac event (MACE) end point (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%
- 38% reduction in CV mortality
- No significant decrease in nonfatal myocardial infarction or stroke
- 35% reduction in hospitalization for heart failure without affecting hospitalization for unstable angina


**EMPA-REG OUTCOME**

Empagliflozin (SGLT-2 inhibitor)

T2DM patients with high CVD risk, eGFR of 30 mL/min/1.73 m²

- 39% relative risk reduction in worsening nephropathy
- Doubling of serum creatinine relative risk reduction 44%
- Renal replacement therapy relative risk reduction 55%
- No difference in albuminuria

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CANVAS

Canagliflozin (SGLT-2 inhibitor)
T2DM patients with high CV risk (no prior events)
• 14% reduction in CV endpoints
  (CV death, nonfatal myocardial infarction and nonfatal stroke composite)
• 40% reduction in renal composite endpoints
• Higher risk of distal amputations
  (7.5/1,000 patients per year for canagliflozin compared to 4.2/1,000 patients per year for placebo)


CVD-REAL Nordic

• Dapagliflozin vs. DPP-4 inhibitor
• Hazard ratio (HR) 0.79 for MACE
• HR 0.62 for hospitalization for heart failure
• HR 0.59 for all-cause mortality
• Numerically lower for MI (HR .91) and CV mortality (HR 0.76)

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Completed and Upcoming CVOT Trials*

<table>
<thead>
<tr>
<th>DPP-4 Inhibitor</th>
<th>SAVOR TIMI-53</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Saxagliptin</td>
<td>Alogliptin</td>
<td>Sitagliptin</td>
<td>Linagliptin</td>
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<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>sulfonylurea</td>
<td>placebo</td>
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<tr>
<td>N</td>
<td>16492</td>
<td>5380</td>
<td>14671</td>
<td>6000</td>
<td>8300</td>
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<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2018</td>
<td>2018</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
<th>HARMONY</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Liraglutide</td>
<td>Lixisenatide</td>
<td>Semaglutide</td>
<td>Exenatide</td>
<td>Albigrutide</td>
<td>Dulaglutide</td>
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<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
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<td>6068</td>
<td>3297</td>
<td>5400</td>
<td>9463</td>
<td>8300</td>
</tr>
<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>EMPA-REG</th>
<th>CANVAS PROGRAM</th>
<th>DECLARE TIMI-58</th>
<th>VERTIS CV</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>N</td>
<td>7020</td>
<td>10142</td>
<td>22200</td>
<td>3900</td>
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<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>

*As of 2-27-19

ADA Standards of Care-2019

- Among patients with T2DM who have established ASCVD, SGLT-2 inhibitors, or GLP-1 agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen
- GLP-1 agonists: liraglutide>semaglutide>extended release exenatide
- SGLT-2 inhibitors: canagliflozin, empagliflozin

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ADA Standards of Care-2019

• Among patients with ASCVD at high risk of heart failure or in whom heart failure coexists, SGLT-2 inhibitors are preferred
• SGLT-2 inhibitor: canagliflozin, empagliflozin


ADA Standards of Care-2019

• For patients with T2DM and CKD, consider use of a SGLT-2 inhibitor or GLP-1 agonist shown to reduce risk of CKD progression, CV events, or both
• SGLT-2 inhibitor: canagliflozin, empagliflozin
  – Determine if eGFR is adequate for SGLT-2 inhibitor (>45mL/min/1.73 m²)
• GLP-1 agonist: liraglutide
  – Watch out for vomiting and dehydration in those with renal impairment

Glycemic Goals by Major Organization

<table>
<thead>
<tr>
<th></th>
<th>AACE</th>
<th>ADA</th>
<th>ACP</th>
<th>Evidence “Weight”</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>≤6.5%</td>
<td>&lt;7%</td>
<td>7-8%</td>
<td><strong>AACE</strong>: weighed observational microvascular reduction data more</td>
</tr>
<tr>
<td>FPG</td>
<td>&lt;110 mg/dL</td>
<td>80-130 mg/dL</td>
<td></td>
<td><strong>ADA</strong>: Less on observational, more on UKPDS and DCCT and follow up of both studies</td>
</tr>
<tr>
<td>PPG</td>
<td>&lt;140 mg/dL</td>
<td>&lt;180 mg/dL</td>
<td></td>
<td><strong>ACP</strong>: weighed ACCORD, ADVANCE, and VADT to greater extent, less UKPDS</td>
</tr>
</tbody>
</table>

All guidelines have language regarding individualizing care


Case 1: MT

- MT is a 58-year-old Hispanic female
- T2DM x 11 years with dyslipidemia, HTN, albuminuria, non-painful peripheral neuropathy, obesity, non-alcoholic fatty liver disease (NAFLD), history of MI 3 years ago
- Current medications:
  - Metformin 1000 mg orally twice a day
  - Glipizide 10 mg orally once daily
  - Pioglitazone 30 mg orally once daily
  - Lisinopril 20 mg orally once daily
  - Metoprolol XL 25 mg orally once daily
  - Atorvastatin 80 mg orally once daily
  - Aspirin 81 mg orally once daily
Case 1: MT

- **Physical exam**
  - Nonproliferative retinopathy, normal heart and lung sounds, obese, decreased vibratory and filament sensation in otherwise healthy appearing feet
- **Concerns**
  - Many blood sugars in 200-300s mg/dL, but occasionally less than 70 mg/dL
  - Fatigue
  - Difficulty losing weight
  - Urinary frequency
- **Labs**
  - A1C 10.2%
  - Lipids in target range (on high-intensity statin), serum creatinine 0.9 mg/dL, GFR 54 mL/minute/1.73 m², hepatic function revealing minor transaminase elevation, urine albumin 110 mg/24 hr (normal <30 mg/24 hr)

What next?

Case 1: MT

- Recall current standards of care recommend a **SGLT-2 inhibitor** (empagliflozin, canagliflozin) or a **GLP-1 agonist** (dulaglutide, liraglutide, semaglutide) in the patient with established CVD
- One of the patient’s main complaints is difficulty losing weight, both of these drug classes are weight-neutral or may promote weight loss
- Basal insulin could also be considered here- A1C >10% with symptoms
Case 1: MT

- **Could do any of the following in the patient with established CVD**
  - Add liraglutide, semaglutide, or dulaglutide (drug class: GLP-1 agonist)
  - Add empagliflozin, canagliflozin, or dapagliflozin (drug class: SGLT-2 inhibitor)
  - Using both GLP-1 agonist or SGLT-2 inhibitor for maximal weight loss
- **Would definitely**
  - Continue metformin (renal function is OK)
  - Refer to diabetes educator and dietician for interprofessional team care
  - Review physical activity level/exercise prescription
  - Stop glipizide
  - Stop pioglitazone

Case 1: MT Summary

- What if A1C was not at target in 3 months?
  - If not on insulin yet, would definitely consider
- Advance therapy, avoid clinical inertia
- Remember appropriate interprofessional team-based diabetes self-management education and support
Case 2: GM

- GM is a 64-year-old white male
- Diagnosed with T2DM after 2 fasting blood sugars of 154 mg/dL and 142 mg/dL, respectively, and A1C of 6.8%
- Saw diabetes educator and dietician at diagnosis
- Preexisting conditions
  - HTN (on lisinopril 10 mg orally once daily)
  - Dyslipidemia (on atorvastatin 40 mg orally once daily)
  - No history of ASCVD
- Aspirin 81 mg orally daily (over 50 years-old + diabetes)

Case 2: GM

- Physical Exam
  - BP 132/78 mm Hg, pulse 80 bpm
  - Fundi normal
  - Obese, BMI 34 kg/m²
  - Feet healthy appearing other than benign calluses

- Lipids in target range (measure of compliance), hepatic and renal chemistries all normal
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Case 2: GM

- Current diabetes medications:
  - Metformin 1000 mg orally twice a day
  - Glimepiride 4 mg orally once daily
  - Basal insulin 40 units subcutaneously daily
- Current glycemic measures
  - A1C 8.2%
  - FPG values 110-120s
  - 2-hour PPG 220-250s

- Notable: eGFR is 58 mL/min/1.73 m²
- What next?

Case 2: GM

- Adding GLP-1 agonist or SGLT-2 inhibitor shown to slow progression of renal disease
- Or switch to combination GLP-1 agonist + basal insulin
  - Insulin degludec + liraglutide, or insulin glargine + lixisenatide
Case 2: GM

• Other Options
  – Add rapid-acting insulin before the largest meal of the day- however, no data on patients with renal disease
  – No matter the choice, would also consider stopping sulfonylurea (glimepiride)

Case 2: GM Summary

• Patient should see the diabetes educator (again) and dietician for regimen change/instruction and lifestyle evaluation
• If not reaching glycemic targets, consider multiple daily injections of insulin per algorithm
• Could consider stopping glimepiride, the sulfonylurea may not be adding a lot of benefit, or could contribute to hypoglycemia
• Avoid clinical inertia by moving forward every 3 to 6 months
Non-alcoholic Fatty Liver Disease (NAFLD) and T2DM

Curtis L. Triplitt, Pharm.D., CDE
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Why should we worry about NAFLD/NASH?

- Predicts risk of T2DM
- Higher risk of total mortality
- Higher risk of CVD
- Increased risk of liver-related death with NASH
- Third most common cause of hepatocellular carcinoma (HCC)

Non-Alcoholic Fatty Liver Disease: Epidemiology

- United States: ~80-100 million with NAFLD
- 8% in United States have unexplained transaminase elevations, with 2/3 having unexplained liver disease
- Other regions with high prevalence:
  - Middle East
  - Brazil
  - “Westernized” populations

Definitions of NAFLD, NAFL, and NASH

- Non-alcoholic Fatty Liver Disease (NAFLD)
  - Excessive hepatic fat accumulation with insulin resistance
  - Steatosis in >5% of hepatocytes
  - Exclusion of secondary causes and Alcoholic Fatty Liver Disease

- Non-alcoholic Steatohepatitis (NASH)
  - Pure steatosis
  - Steatosis and mild lobular inflammation

- Cirrhotic F4 fibrosis
- Hepatocellular carcinoma (HCC)
  - F0/F1 fibrosis
  - 2F2 to 2F3 fibrosis

Definitive diagnosis of NASH requires a liver biopsy

If you have T2DM, your risk of NAFLD is very high

If you have NAFLD, your risk of T2DM is very high

Risk Factors for NAFLD: Established Associations

THINK INSULIN RESISTANCE

• Obesity- risk increases as BMI increases
• T2DM: insulin resistance (IR)
• Metabolic syndrome (MetS)
• Dyslipidemia
  – High triglycerides, low HDL (a component of MetS)
• Hispanic>White>African American

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Pathogenesis of NAFLD

- Obesity
- Dietary FFA
- Other dietary factors
- Genetic Epigenetics
- Gut Microbiome
  - Intestinal permeability
  - Inflammatory factors
- Adipose tissue
  - Increased FFA release
  - Adipokines
  - Lower adiponectin
  - Higher IL-6, IL1B, TNF-alpha
- Increased Free Fatty Acids (FFA)
- Insulin resistance
  - Higher de novo lipogenesis
  - Less beta oxidation of fat
  - Decreased VLDL synthesis
- Mitochondrial dysfunction
- Endoplasmic Reticulum stress
- Increased reactive oxygen species (ROS)
- Inflammation
- Apoptosis
- Fibrosis
- NASH

Increased Triglycerides


Natural history of NAFLD

- Steatosis
  - 8% over 8-13 years
  - 7% over 3-7 years
  - 40-60% over 3-7 years

- NASH
  - ~25% over 8 years
  - 8-13% over 8 years
  - 40-60% over 3-7 years

- Advanced Fibrosis/ Cirrhosis
  - ~25-50% over 8 years

- Hepatocellular Carcinoma
  - ~25% over 8 years

- Death/Liver Transplant

As liver “stiffness” increases, worsening of the liver fibrosis is expected. This is also tied with a measure of steatosis called a “CAP” or controlled attenuation parameter.

Summary: NAFL/NASH Treatment

Cardiovascular Risk Reduction:
1. Dyslipidemia
2. HTN - treat as appropriate for comorbidities
3. Obesity
4. Exercise
5. +/- antiplatelet as indicated

Summary: NAFL/NASH Treatment

**Cause of death**
- CVD event/extrahepatic cancer
- Liver-related diseases

**Life style intervention**: co-morbidities treatment

**Bariatric surgery**

**Pharmacotherapy**
- Evidenced Based Medication
  - Vitamin E (non-T2DM)
  - Pioglitazone
- Metabolic Disease
  - GLP-1 agonists
  - SGLT-2 inhibitors

**Surveillance for HCC/varices**

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NASH: Lifestyle Intervention

52 weeks of lifestyle intervention
- Lower by 750 kcal/day low-fat diet
- Walk minimum 200 minutes/week
- Behavior/adherence visits every 2 months

<table>
<thead>
<tr>
<th>% Weight loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH-resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>FIBROSIS-regression</td>
<td>45%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>STEATOSIS improvement</td>
<td>35%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>% Patients achieving WL</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

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Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

AASLD: Bariatric Surgery

- Can be considered in otherwise eligible patients
  - No randomized controlled trials
  - Prospective studies
    - 96% maintained fibrosis scores at 5 years\(^2\)
    - NASH at baseline- 85% had resolution by 1 year\(^3\)
      - Fibrosis improvement in 33%
      - Higher BMI reduction was related to better odds of NASH resolution


AASLD = American Association for the Study of Liver Disease

Pharmacologic Treatment of NAFLD*

Currently no FDA-approved pharmacologic treatment, although many are in clinical trials

- Pioglitazone
  - PPAR-\(\gamma\) drug currently approved for treatment of T2DM
  - Shifts “fat” from hepatic and splanchnic tissue to subcutaneous fat tissue
  - Decreases inflammation (reduction in adipokines)

- Vitamin E (\(\alpha\)-tocopherol)
  - Decreases reactive oxygen species (ROS)

*“Treatment of NAFLD/NASH is considered off-label for all medications” Chalasani N et al. *Hepatology*. 2018; 67:328-57.*
Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

# Pioglitazone*

- **Belfort et al.**
  - Biopsy proven NASH in pre-DM/DM (n=55)
  - Pioglitazone 45 mg daily
  - NAFLD activity score (NAS) improved in ¾ vs. ¼ in placebo group
  - Fibrosis improved (p=0.08)

- **Cusi et al.**
  - Biopsy proven NASH in pre-DM/DM subjects (n=101)
  - Pioglitazone 45 mg or placebo daily for 18 months
  - 58% improved NAS (p<0.001)
  - 51% had resolution of NASH (p<0.001)

**PIVENS trial**

- Non-DM patients with biopsy proven NASH
- Pioglitazone 30 mg daily, Vit E 800 IU daily, or placebo
- Followed for 24 months
- NAS/histology composite improvement
  - 19% Placebo
  - 34% Pioglitazone
  - 43% Vitamin E
- Resolution of NASH
  - 21% Placebo
  - 47% Pioglitazone
  - 34% Vitamin E


*Treatment of NAFLD/NASH is considered off-label for all medications

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# Non-Alcoholic Fatty Liver Disease: AASLD Pharmacologic Recommendations*

- **Diabetes**
  - Pioglitazone
    - No dose listed
  - (Limited data on Vitamin E but not recommended in guidelines)

- **Non-DM**
  - Vitamin E at 800 IU/day
  - Pioglitazone daily
    - No dose listed

*Treatment of NAFLD/NASH is considered off-label for all medications


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NAFLD and AASLD: Other Medications Not Recommended*

- **Metformin**
  - No improvement in histology (fibrosis, ballooning of hepatocytes, etc.)
  - HCC prevention-consider when risk is high

- **GLP-1 agonists**
  - Insufficient data to currently recommend
  - LEAN trial- 48 weeks treatment in biopsy proven NASH
    - Liraglutide (n=23) vs. placebo (n=22)
      - Resolution of NASH
      - Liraglutide: 9 (32%) vs. placebo 2 (9%)

- **Ursodeoxycholic Acid**
  - Did not improve liver histology

- **Omega-3s**
  - Did not improve liver histology
  - Consider only for high triglycerides in patients

*Treatment of NAFLD/NASH is considered off-label for all medications


NAFLD and AASLD: Other Medications Not Mentioned*

**SGLT-2 inhibitors**

- Insufficient Data
  - Reduces weight and improves liver transaminases
  - Modest improvement in Fibroscan

- Potential Future Medications
  - PPAR α,δ,γ drugs
  - Farnesoid X receptor drugs/lipid metabolism drugs
  - Anti-inflammatory/anti-apoptosis drugs
  - Antifibrotic agents
  - Microbiome alteration

*Treatment of NAFLD/NASH is considered off-label for all medications

Ask the Experts: Exploring Newer Treatments and Challenges in Type 2 Diabetes

Key Takeaways

- NAFLD is the “new” insulin resistance comorbidity
- Associated with significant mortality and CVD risk
- If advanced- risk of liver-related death
- Treatment in T2DM
  - Treat NAFLD co-morbidities aggressively (lipids, HTN, etc.)
  - Lifestyle for all
    - Weight loss and exercise
  - NASH
    - Pioglitazone can be considered in appropriate patients in conjunction with lifestyle
    - Role of Vit E is controversial
    - GLP-1 agonists and SGLT-2 inhibitors
      - May be considered if clinically appropriate for DM treatment

Consider these practice changes. Which will you make?

- Read the current diabetes guidelines.
- Compare the current guidelines to my institutional and personal protocols.
- Consider the role of stepwise and combination therapy.
- Discuss with colleagues the importance of avoiding clinical inertia.
- Look for opportunities to collaborate with my interprofessional colleagues to overcome clinical inertia.
- Consider patient factors in individualizing treatment plans.