Nonalcoholic Fatty Liver Disease (NAFLD): The Overlooked Complication of T2DM

Endocrine Society Annual Meeting
March 31, 2017– Orlando, Florida

Kenneth Cusi, M.D., F.A.C.P., F.A.C.E.
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Florida, Gainesville, USA

e-mail: Kenneth.Cusi@medicine.ufl.edu
Presenter Disclosures:

- Research support and/or consulting agreements: Janssen, Novo Nordisk, Novartis, Octeta, Zydus.
The trouble with fat

To get an inside look at how fat affects the body's organs, we asked two women—one morbidly obese, the other a healthy weight—to spend five hours under a state-of-the-art open scanner to get a high-resolution magnetic resonance imaging scan (MRI).

Open scanners—as opposed to the more common enclosed MRI tubes—are in demand as patients get larger.

LIVER DISEASE

Many obese people develop deposits of fat inside the liver, a condition that can progress to cirrhosis in about 10 percent of cases, and occasionally to the more serious liver cancer.

COLON CANCER

Obese people are at greater risk of colon cancer. Abdominal fat appears to increase risk more than fat elsewhere, which may explain why men who have more fat in their abdomen have a higher risk.

OSTEOPOROSIS

Being overweight places additional strain on the spine, hips, and bone joints, causing osteoporosis, or bone condition that can lead to fractures.

Threat Grows From Liver Illness Tied to Obesity

By ANAHAD O’CONNOR

Epidemic Is Becoming a Major Cause of Transplants

States spent more than $1 trillion in an eight-year war that Mr. Obama had repeatedly claimed was history when the last troops left in 2011. While Mr. Obama said he would offer some help, it would not include troops, and he asserted that “we’re not going to allow ourselves to be dragged back into a situation in which, while we’re there, we’re keeping a lid on things.”

Seeing Their Gitmo Shiites Floors

Gavin Owenby, a 13-year-old in Hainesville, Ga., learned he had the disease two years ago after developing crippling abdominal pain. “It’s like you’re being stabbed in your stomach with a knife,” he said.

An ultrasound revealed that Gavin’s liver was enlarged and the disease had spread via blood vessels in the liver, which meant he was a candidate for liver transplant.

Doctors say that the disease, which causes the liver to swell with fat, is particularly striking in children.
Obesity/Lipotoxicity and NAFLD: Clinical Implications

Liver
- ↑ Insulin resistance
- ↑ HGP
- ↑ VLDL production
- NAFLD → cirrhosis

Dysfunctional adipose tissue
- ↑ Visceral fat
- ↑ Portal FFA → NAFLD
- ↑ Cytokine production
- ↓ Adiponectin

Muscle
- ↓ Mitochondrial function
- ↓ VO₂ max
- Insulin resistance
- Sarcopenia?

Atherosclerosis
- Endothelial dysfunction
- Plaque formation
- CV events

Heart
- Impaired energy metabolism
- Diastolic dysfunction
- ↑ Risk of CAD?

Pancreas
- ↑ β-cell apoptosis
- ↓ Insulin secretion
- ↑ T2DM
Mr. N is a 55 year old Caucasian male, whom you see for the first time and find elevated AST/ALT on routine labs.

**PMH:** HTN, dyslipidemia and diagnosed T2DM (A1c 7.6%).

**Social:** Non-smoker, no alcohol abuse.

**Meds (among others):** ASA 325 mg/d, losartan 50 mg/d.

**Physical exam:**

BP: 143/80 mmHg; HR: 76 x min, R: 18 x min; BMI: 33.2 kg/m² (total body fat by DXA = 48.2%)

Overall unremarkable.
<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>70-90 mg/dL</td>
<td>142</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>4.5 to 5.8%</td>
<td>7.6%</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>13 to 47</td>
<td>42</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>5 to 40</td>
<td>71</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td></td>
<td>153</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td></td>
<td>51</td>
</tr>
</tbody>
</table>
NAFLD in patients with T2DM

What is the single most important finding in determining her chance of developing cirrhosis?

A. Degree of insulin resistance by HOMA-IR
B. Level of A1c and plasma triglycerides
C. Severity of liver steatosis measured by magnetic resonance and spectroscopy (\textsuperscript{1}H-MRS)
D. Severity of inflammation and hepatocyte necrosis (ballooning) on liver biopsy
E. Presence of liver fibrosis
NAFLD in patients with T2DM

What will be the most likely cause of death in this patient?

A. Cardiovascular disease
B. Hepatocellular carcinoma if younger than 45 years of age
C. Cirrhosis if younger than 45 years of age
D. Acute metabolic decompensation from uncontrolled diabetes mellitus
E. None of the above
NAFLD in patients with T2DM

What treatment has proven to improve liver histology in a RCT (cause resolution of NASH in >50% of patients)?

A. Weight loss of 5% (if sustained for 12 months)
B. Exercise 60 minutes 3-4 times per week for 12 months
C. Pioglitazone (Actos®)
D. Liragultide (Victoza®)
E. Vitamin E
F. None of the above
1. A story about obesity, diabetes y “a fat liver”
   - Magnitude of the problem
   - Clinical manifestations: T2D > NASH > cirrhosis > cancer

2. Diagnosis
   - Labs, biomarkers and imaging

3. Treatment
   - Current and future
What is Non-Alcoholic Fatty Liver Disease (NAFLD)?

- 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
Barriers to Optimal Care in Patients with NAFLD

- Unclear natural history of the disease.
- Poor awareness of the significant morbidity associated with NAFLD (i.e., T2DM, CVD, end-stage liver disease, liver cancer).
- Inadequate diagnostic algorithms:
  - Few symptoms and many patients have normal LFTs
  - No reliable diagnostic blood test, poor sensitivity and specificity of liver ultrasound.
- Poor patient compliance with diet/lifestyle interventions.
- Lack of long-term RCTs assessing the efficacy/safety of potentially useful gents (vitamin E, pioglitazone).
From Obesity/Lipotoxicity to NASH and Cirrhosis

Cusi K, Gastroenterology, April 2012, 142:711-725
Elevated ALT may indicate fatty liver (NAFLD) or NASH, BUT ~2/3 of patients with NAFLD/NASH have normal LFTs!

Browning et al, Hepatology 2004, 40, 1387-1395
NAFLD: The Overlooked Complication of T2DM

1. A story about obesity, diabetes y “a fat liver”
   • Magnitude of the problem
   • Clinical manifestations: T2D > NASH > cirrhosis > cancer

2. Diagnosis
   • Labs, biomarkers and imaging
Diagnosis NAFLD & NASH

- **Clinical findings:**
  - Few clinical symptoms (i.e., right upper quadrant discomfort)
  - Requires a high degree of clinical suspicion

- **Laboratory:**
  - May be associated with elevated liver aminotransferases (ALT>AST)
  - May NOT be associated with an elevation in ALT/AST
Causes of Fatty Liver Other than NAFLD

• Hepatitis C genotype 3
• Autoimmune hepatitis
• Primary biliary cirrhosis
• Alpha-1 antitrypsin deficiency
• Wilson’s disease
• HIV infection
• Acute fatty liver of pregnancy
• Drugs: corticosteroids, tamoxifen, diltiazem, amiodarone, methotrexate, valproic acid, anti-retroviral therapy

Ali & Cusi, Annals of Medicine, 2009: 41:265-78
Diagnosis NAFLD & NASH

Clinical findings:
- Few clinical symptoms (i.e., right upper quadrant discomfort)
- Requires a high degree of clinical suspicion

Laboratory:
- May be associated with elevated liver aminotransferases (ALT>AST)
- May NOT be associated with an elevation in ALT/AST

Imaging:
- Ultrasound (echogenicity): 65-80% sensitivity for NAFLD

Liver ultrasound may indicate a fatty liver (NAFLD), BUT:
- misses many cases (> with > BMI)
- cannot quantify the amount of steatosis
- cannot steatosis ≠ fibrosis
Diagnosis of Fibrosis in NASH with Ultrasound Elastography (Fibroscan)

Piscaglia et al, European Journal of Radiology 2013
15-20% of T2DM with steatosis have liver fibrosis.

Koehler et al, Hepatology 2016;63:138-147
Magnetic Resonance Imaging

Abdominal fat: Visceral and subcutaneous

Liver and Muscle fat

Our patient: 18% liver triglyceride content (normal ≤5.4%)
Diagnosis of Fibrosis in NASH with Magnetic Resonance Elastography

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)
Increased Risk of Hepatocellular Carcinoma in Patients with Diabetes

<table>
<thead>
<tr>
<th>Citation</th>
<th>0.1</th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawson et al. 1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.88</td>
</tr>
<tr>
<td>Yu et al. 1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.40</td>
</tr>
<tr>
<td>Hadziyannis et al. 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.30</td>
</tr>
<tr>
<td>Shibata et al. 1997 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.54</td>
</tr>
<tr>
<td>La Vecchia et al. 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.86</td>
</tr>
<tr>
<td>Braga et al. 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.92</td>
</tr>
<tr>
<td>El-Serag et al. 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.17</td>
</tr>
<tr>
<td>Lagiou et al. 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.81</td>
</tr>
<tr>
<td>Hassan et al. 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.27</td>
</tr>
<tr>
<td>Matsuo et al. 2003 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.51</td>
</tr>
<tr>
<td>Yuan et al. 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.78</td>
</tr>
<tr>
<td>Davila et al. 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.18</td>
</tr>
<tr>
<td><strong>Pooled risk estimate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>2.54</strong></td>
</tr>
</tbody>
</table>

El-Serag et al, Clinical Gastroenterology and Hepatology 2006;4:369–380
Prevalence of NAFLD using different diagnostic tools

- General Population
- T2DM

Prevalence (%)

<table>
<thead>
<tr>
<th>Method</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ALT</td>
<td>10</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>20</td>
</tr>
<tr>
<td>Liver US</td>
<td>30</td>
</tr>
<tr>
<td>Controlled attenuation parameter</td>
<td>40</td>
</tr>
<tr>
<td>$^1$H-MRS</td>
<td>60</td>
</tr>
</tbody>
</table>

Bril & Cusi, Diabetes Care 2017 40:419-430
Diagnostic Algorithm for NASH for PCPs and Endocrinologists

Patient with prediabetes or T2DM

ALT or US abnormal

ALT & US normal

Higher risk

Rule out other causes of liver disease

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

High risk of fibrosis
- Referral to hepatology and consider liver biopsy
- Lifestyle plus pioglitazone treatment
- Definite NASH

Intermediate fibrosis risk
- Referral to hepatology
- Absence of NASH

Low risk of fibrosis
- Periodic evaluation; standard care

- Long-standing T2DM (>10 yrs)
- Evidence of steatosis*
- A1c ≥ 8.5%
- Triglycerides ≥250 mg/dl
- Genetic testing"
Metabolic and CV Impact of NAFLD

Dysfunctional Adipose Tissue
- Hyperinsulinemia
- Insulin Resistance
- Insulin Clearance
- Subclinical Inflammation
- Dyslipidemia
  - Triglycerides
  - HDL-C
  - apo B/small dense LDL-C
  - Give statins to your patients with NASH!

Type 2 Diabetes Mellitus
- Lomonaco et al, D. Care 2016

Hyperinsulinemia
- Insulin Resistance
- Insulin Clearance

Dyslipidemia
- Triglycerides
- HDL-C
- apo B/small dense LDL-C

NAFLD/NASH

Cardiovascular Disease

Lomonaco, R. Chen, J & Cusi, K, Therapeutic Advances in Endocrinology and Metabolism. October 2011
NAFLD: The Overlooked Complication of T2DM

1. A story about obesity, diabetes y “a fat liver”
   - Magnitude of the problem
   - Clinical manifestations: T2D > NASH > cirrhosis > cancer

2. Diagnosis
   - Labs, biomarkers and imaging

3. Treatment
   - Current and future
Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus
A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola 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. (ClinicalTrials.gov: NCT00994682)

Setting: University hospital.

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

Intervention: All patients were prescribed a hypocaloric diet (500-kcal/d deficit from weight-maintaining caloric intake) and then randomly assigned to placebo or pioglitazone treatment. Follow-up visits at 3, 6, 9, and 18 months, followed by pioglitazone treatment.

Measurements: The primary outcome was histologic improvement of NASH (a decrease in the NASH Activity Score [NAS] of 3 points or more). Secondary outcomes included changes in body weight, waist circumference, insulin sensitivity, liver fat content, and resolution of steatosis.

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, −7 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: Burroughs Wellcome Fund and American Diabetes Association.

Studies:
1) Liver biopsy
2) Liver fat by MRS
3) % body fat (DXA)
4) Insulin clamp, OGTT

n = 101
PIO 45 mg/day
Pioglitazone in NASH:  
The new standard of care

Cusi et al, Annals of Intern Med 2016 (under review)
Effect of Pioglitazone on Primary and Secondary Liver Histologic Outcomes at 18 months*

* In patients with paired biopsies

Effect of Pioglitazone or Placebo for 18 Months on Liver Triglycerides ($^1$H-MRS) and Insulin Sensitivity*

A) Liver fat content by $^1$H-MRS

B) Hepatic Insulin Sensitivity

C) Muscle Insulin Sensitivity

D) Adipose Tissue Insulin Sensitivity
Pharmacological Therapies (RCTs): Resolution of NASH*

* Not head-to-head RCTs (not for comparison among pharmacological agents)

Bril & Cusi, unpublished
TZDs: Benefits and Risks

Yau, Rivera, Lomonaco, Cusi.


Portillo et al - ADA abstract #1127
## New Drugs for NASH under Development

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXR agonist</td>
<td>Obeticholic acid</td>
<td>Intercept</td>
<td>III (Breakthrough)</td>
</tr>
<tr>
<td>Dual PPAR α/delta agonist</td>
<td>Elafibranor</td>
<td>Genfit</td>
<td>III (Fast Track)</td>
</tr>
<tr>
<td>Fatty acid/bile acid modifier</td>
<td>Aramchol</td>
<td>Galmed Pharmaceuticals</td>
<td>IIb (Fast Track)</td>
</tr>
<tr>
<td>CCR2/CCR5 inhibitor</td>
<td>Cenicriviroc</td>
<td>Tobira</td>
<td>IIb (Fast Track)</td>
</tr>
<tr>
<td>LOXL2 mAb</td>
<td>Simtuzumab</td>
<td>Gilead</td>
<td>II</td>
</tr>
<tr>
<td>ASK1 inhibitor</td>
<td>GS-4997</td>
<td>Gilead</td>
<td>II</td>
</tr>
<tr>
<td>Bovine colostrum/anti-LPS Ab</td>
<td>IMM-124E</td>
<td>Immuron</td>
<td>II</td>
</tr>
<tr>
<td>FGF19</td>
<td>NGM282</td>
<td>NGM</td>
<td>II</td>
</tr>
<tr>
<td>FGF21 (peg)</td>
<td>BMS-986036</td>
<td>BMS</td>
<td>II</td>
</tr>
<tr>
<td>Galectin-3 inhibitor</td>
<td>GR-MD-02</td>
<td>Galectin Therapeutics</td>
<td>II; Fast Track</td>
</tr>
<tr>
<td>Caspase inhibitor</td>
<td>Emricasan</td>
<td>Conatus</td>
<td>II; Fast Track</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>LIRAGLUTIDE, SEMAGLUTIDE</td>
<td>Novo Nordisk</td>
<td>II</td>
</tr>
<tr>
<td>ACC inhibitor</td>
<td>NDI-010976</td>
<td>Gilead/Nimbus</td>
<td>I; Fast Track</td>
</tr>
</tbody>
</table>
Clinical Studies in NAFLD/NASH at the Endocrinology & Diabetes Division at UF
Recruitment of patients at the University of Florida: Many options, one target (NASH)

• Primary care clinics
  – About 50,000 annual visits, 20% for diabetes
  – Strong network with PCPs from prior trials in NAFLD and diabetes
  – Regular interaction by our study coordinator and Dr. Cusi

• Endocrinology outpatient clinics:
  – About 14,000 outpatient visits; 50% with T2DM
  – Two-thirds of all patients are obese

• Liver health (NASH) clinic with Hepatology staff

• Established UF database (~20,000 patients, i2b2):
  – Patients accept to be contacted for research studies
Treatment of NASH

Patient with prediabetes or T2DM and definite NASH

Control of other CV risk factors

Treatment of NASH

Pharmacological treatment
- Pioglitazone as first-line therapy

Lifestyle intervention
- Weight reduction of 8-10%

No response

Pharmacological treatment or metabolic surgery

Not achieved

Second-line therapies

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

Add pioglitazone
- Add GLP-1RA or SGLT-2 inhibitors

Elevated BP

Second-line therapies

Elevated TG and low HDL

Add fibrates to statins

Bril & Cusi, Diabetes Care 2017 40:419-430
NAFLD in patients with T2DM

What is the single most important finding in determining her chance of developing cirrhosis?

A. Degree of insulin resistance by HOMA-IR
B. Level of A1c and plasma triglycerides
C. Severity of liver steatosis measured by magnetic resonance and spectroscopy (¹H-MRS)
D. Severity of inflammation and hepatocyte necrosis (ballooning) on liver biopsy
E. Presence of liver fibrosis
NAFLD in patients with T2DM

What is the single most important finding in determining her chance of developing cirrhosis?

A. Degree of insulin resistance by HOMA-IR
B. Level of A1c and plasma triglycerides
C. Severity of liver steatosis measured by magnetic resonance and spectroscopy (1H-MRS)
D. Severity of inflammation and hepatocyte necrosis (ballooning) on liver biopsy
E. Presence of liver fibrosis
NAFLD in patients with T2DM

What will be the most likely cause of death in this patient?

A. Cardiovascular disease
B. Hepatocellular carcinoma if younger than 45 years of age
C. Cirrhosis if younger than 45 years of age
D. Acute metabolic decompensation from uncontrolled diabetes mellitus
E. None of the above
NAFLD in patients with T2DM

What will be the most likely cause of death in this patient?

A. Cardiovascular disease
B. Hepatocellular carcinoma if younger than 45 years of age
C. Cirrhosis if younger than 45 years of age
D. Acute metabolic decompensation from uncontrolled diabetes mellitus
E. None of the above
NAFLD in patients with T2DM

What treatment has proven to improve liver histology in a RCT (cause resolution of NASH in >50% of patients)?

A. Weight loss of 5% (if sustained for 12 months)
B. Exercise 60 minutes 3-4 times per week for 12 months
C. Pioglitazone (Actos®)
D. Liragultide (Victoza®)
E. Vitamin E
F. None of the above
NAFLD in patients with T2DM

What treatment has proven to improve liver histology in a RCT (cause resolution of NASH in >50% of patients)?

A. Weight loss of 5% (if sustained for 12 months)
B. Exercise 60 minutes 3-4 times per week for 12 months
C. Pioglitazone (Actos®)
D. Liragultide (Victoza®)
E. Vitamin E
F. None of the above
NASH mechanisms and treatment: Conclusions

• NASH in obesity and type 2 diabetes:
  – Destined to become an increasingly common problem.
• Diagnosis:
  – Better methods will streamline diagnosis by PCPs
• Treatment of NASH:
  – Many agents being tested, some promising.
  – Pioglitazone – the new standard of care in preDM/T2DM
  – Other: liraglutide, PPAR α/δ, novel TZDs, OCA, CCH2.
Thank you!
e-mail: cusil@uthscsa.edu