Fatty Liver Disease: An Update from AASLD

14th Annual Liver Update

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Objectives

• **Obesity early in life** is a risk factor for NAFLD and cirrhosis.

• Undiagnosed **advanced liver disease** is common in patients with **type 2 diabetes**.

• Effective **treatments** for NAFLD are coming soon!
158. Overweight in late adolescence is associated with decompensated liver disease later in life


• Conscription during this time was mandatory (>97% of the male population).

• Weight and height measured at conscription were used to calculate BMI.

• Data was collected from the national patient registry to identify any diagnosis of liver disease (1971-2009, ICD-coding).
Statistical Analysis

• Multivariate logistic regression model was used to estimate HR of decompensated liver disease.

• Adjusted for
  – Alcohol use
  – Smoking
  – Use of narcotics
  – Social status
  – Blood pressure
Results

• Mean BMI 21 kg/m²
  – 6.6% with BMI > 25 (overweight)
  – 0.8% with BMI > 30 (obese)

• 455 men diagnosed with severe liver disease
  – 214 decompensation (HRS, HCC, ascites, varices, HE)
  – 64 death from liver disease

• Mean time to decompensation was 29.8 years
BMI as a Predictor of Severe Liver Disease

• BMI as a continuous variable:
  – Univariate: HR 1.07 (1.03-1.10, p<0.001)
  – Multivariate: **HR 1.05** (1.01-1.09, p=0.008)

• BMI > 25 (overweight):
  – Univariate: HR 1.83 (1.32-2.52, p<0.001)
  – Multivariate: **HR 1.64** (1.16-2.32, p=0.006)
2231. High prevalence of undiagnosed liver cirrhosis and advanced fibrosis in type 2 diabetic outpatients

- **AIM:** To evaluate prevalence of steatosis, advanced fibrosis and cirrhosis by non-invasive methods in T2DM patients.

- Cross-sectional study in 136 consecutive T2DM patients (>55 years-old).

- 52.6% were women, average age 60 years (57-64), BMI 29.6±4.7 kg/m2 and diabetes duration 7.6±6.9 years.
Diagnosis of Advanced Fibrosis/ Cirrhosis

**NAFLD fibrosis score**

*Online calculator*

- Age (years) 
- BMI (kg/m²) 
- IGF/diabetes 
- AST 
- ALT 
- Platelets (x10⁹/l) 
- Albumin (g/l)

[Calculating fibrosis score]

Images (a) to (f) illustrate different aspects of liver fibrosis pathology.
High Prevalence of NAFLD/NASH/Advanced Fibrosis

- Steatosis: 62.5%
- Presumed NASH: 37.5%
- Advanced Fibrosis: 12.5%
- Cirrhosis: 5.9%
# Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Advanced Fibrosis</th>
<th>No advanced fibrosis</th>
<th>p</th>
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<tbody>
<tr>
<td>% Male</td>
<td>35.3</td>
<td>49.1</td>
<td>0.286</td>
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<tr>
<td>% Hypertension</td>
<td>76.5</td>
<td>57.8</td>
<td>0.141</td>
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<tr>
<td>% Dyslipidemia</td>
<td>47.1</td>
<td>50.9</td>
<td>0.770</td>
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<tr>
<td>Waist circumference</td>
<td>103.6 ± 8.1</td>
<td>98.1 ± 10.6</td>
<td>0.076</td>
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<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% Confidence interval</th>
<th>p</th>
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<tbody>
<tr>
<td>GGT &gt;82 IU/L</td>
<td>6.4</td>
<td>1.8- 22.9</td>
<td>0.004</td>
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<tr>
<td>No alcohol consumption</td>
<td>4.3</td>
<td>1.1- 16.3</td>
<td>0.032</td>
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<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% Confidence interval</th>
<th>p</th>
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<tr>
<td>Neuropathy history, %</td>
<td>18.8</td>
<td>12.1</td>
<td>0.455</td>
</tr>
<tr>
<td>Macrovascular complications, %</td>
<td>12.5</td>
<td>10.3</td>
<td>0.793</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>37 (31- 135)</td>
<td>26 (18- 45.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.53 (0.43- 0.62)</td>
<td>0.51 (0.43- 0.70)</td>
<td>0.584</td>
</tr>
<tr>
<td>Alkaline Phosphatase, IU/L</td>
<td>91 (76.5- 107.5)</td>
<td>83.5 (68.3- 101.8)</td>
<td>0.262</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>96 (79.5- 108.5)</td>
<td>87 (66- 113)</td>
<td>0.622</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47 (42.5- 56.5)</td>
<td>45 (39- 54)</td>
<td>0.471</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>144 (136.5- 207.5)</td>
<td>136 (103- 205)</td>
<td>0.407</td>
</tr>
<tr>
<td>Glycated hemoglobin A1c, %</td>
<td>6.3 (6.1- 7.1)</td>
<td>7 (6.3- 8)</td>
<td>0.072</td>
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107. Efficacy and Safety of Vitamin E in NASH: Pooled analysis from PIVENS and FLINT

- PIVENS Trial (n= 247, 2005-2009)
  - Pioglitazone (n= 80) vs. Vitamin E (n=84) vs. PBO (n=83) for 96 weeks.
  - Patients with DM2 excluded.

- FLINT Trial (n= 283, 2011-2014):
  - OCA (n= 141) vs. PBO (n= 142) for 72 weeks.
  - FLINT PBO group who did vs. did not report using vitamin E at baseline.

**Fibrosis**

- OCA: 35%
- Placebo: 19%

\[ P = .004 \]

**NASH resolution**

- OCA: 22%
- Placebo: 13%

\[ P = .08 \text{ (NS)} \]
Efficacy of Vitamin E on Histologic Outcomes in Adults w/o DM2

• In non-diabetic patients:
  – 90 patients on vitamin E vs. 107 patients on PBO

![Bar graph showing percent of subjects improved for fibrosis and NASH resolution](attachment:bar_graph.png)

- **Fibrosis**
  - Vit. E: 39%
  - Placebo: 22%
  - *P* = .01

- **NASH resolution**
  - Vit. E: 32%
  - Placebo: 22%
  - *P* = .09 (NS)

Kowdley KV et al. NASH CRN
PPAR α-δ Agonist: A Novel Treatment for NAFLD
An international, phase 2 RCT of the dual PPAR α-δ agonist GFT505 in NASH: GOLDEN 505

Adults with biopsy-proven NASH, NAS ≥ 3, Any Fibrosis Stage (N = 274)

- Biopsy ≤ 9 mos before treatment
  - Elafibranor 80 mg/day (n = 93)
  - Elafibranor 120 mg/day (n = 89)
- Biopsy at Week 52
  - Placebo (n = 92)
Primary Endpoint: Reversal of NASH

<table>
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<tr>
<th>Baseline severity</th>
<th>N =237</th>
<th>Placebo</th>
<th>GFT505 120mg</th>
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<tr>
<td>Severe (6-8)</td>
<td>72</td>
<td>0%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Moderate (4-5)</td>
<td>130</td>
<td>19.5%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Mild (3)</td>
<td>35</td>
<td>57.1%</td>
<td>36.4%</td>
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High PBO response rate in mild NAS3 patients
Results in the NAS ≥ 4 population

\[ P = 0.01 \]

NASH resolution

GFT Placebo 5%

Beneficial on NASH components and fibrosis improvement in Responders to GFT505

- NAS
- Steatosis
- Ballooning
- Inflammation
- Fibrosis

Change in Score

- GFT505 120 mg Responders
- GFT505 120 mg Non responders

\[ p = 0.06 \]

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The Race to Cure NASH!

• Obeticholic acid (OCA):
  – FXR agonist
  – Anti-fibrotic
  – Increase LDL, decrease HDL, pruritus

• Elafibranor:
  – PPAR α-δ agonist
  – Decrease LDL, increase HDL, favorable metabolic profile
Overweight in late adolescence is associated with decompensated liver disease later in life after 39 years of follow-up

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Background: The prevalence of both obesity and liver diseases is increasing globally. Obesity is associated with a worse prognosis in different liver diseases. If overweight and obesity in late adolescence is an independent predictor of liver disease later in life is not studied. We investigated if overweight per se predicts development of liver disease and decompensated liver disease later in life with a up to 39 year follow-up. Materials and methods: Data from 49,321 men (18-21 years) conscribed to military service in Sweden between 1969 and 1970 was used. Conscription during this time was mandatory and >97% of the male population was available for this study. Weight and height measured at conscription were used to calculate body mass index (BMI). Data was collected from the national patient register to identify any diagnosis of liver disease at a Swedish hospital from time of conscription until the end of 2009. A multivariate logistic regression model was used to estimate odds ratios (OR) of decompensated liver disease (hepatorenal syndrome [HRS], hepatocellular carcinoma [HCC], ascites, varices or hepatic encephalopathy [HE]) for persons with BMI over as compared to under 25. The model was adjusted for alcohol use, smoking, use of narcotics, social status and blood pressure at the time of conscription. Results: Mean BMI at conscription was 20.97 kg/m2, where 6.6% had a BMI > 25 and 0.8% had a BMI > 30. During a follow-up period of in mean 37.9 (+/-4.8 years, range 0-39) years of follow-up, 525 persons were diagnosed with liver disease. Of these, 206 persons developed decompensated liver disease (18 cases of HRS, 31 HCC, 79 ascites, 124 varices and 7 HE as first manifestation of decompensation, where 43 persons had multiple diagnoses at presentation). Mean time to decompensation was 29.8 years (95% Confidence Interval [CI] 28.8-30.8 years). BMI > 25 was significantly associated with development of decompensated liver disease both in the univariate (OR 2.09, 95%CI 1.38-3.16, p<0.001) and the multivariate (OR 1.99, 95%CI 1.25-3.15, p=0.004) models.

Discussion: In this large cohort, overweight in late adolescence was significantly associated with development of decompensated liver disease later in life, even after adjustment for potential confounders. This finding implies that overweight in adolescence is a strong risk factor for development of severe liver disease later in life.

Disclosures: The following authors have nothing to disclose: Hannes Hagström, Per Stål, Rolf W. Hultcrantz, Tomas Hemmingsson, Anna Andreasson
ABSTRACT FINAL ID: 2231

TITLE: High prevalence of undiagnosed liver cirrhosis and advanced fibrosis in type 2 diabetic outpatients

SPONSORSHIP - THIS STUDY WAS SPONSORED BY:(IF THIS ABSTRACT WAS NOT SPONSORED PLEASE INDICATE):
Not sponsored abstract

ABSTRACT BODY:

BACKGROUND: Patients with Type 2 Diabetes Mellitus (T2DM) are at risk for developing end-stage liver disease due to nonalcoholic steatohepatitis (NASH). Non-invasive methods have been validated for assessing the severity of nonalcoholic fatty liver disease (NAFLD). Data on prevalence of advanced fibrosis among T2DM patients evaluated by these methods is scarce. AIM: To evaluate prevalence of steatosis, advanced fibrosis and cirrhosis by non-invasive methods in T2DM patients. METHODS: We conducted a cross-sectional study in 145 consecutive T2DM patients (>55 years-old). The presence of cirrhosis and advanced fibrosis was evaluated by liver morphology assessed by magnetic resonance imaging (MRI) and NAFLD fibrosis score (NFS) respectively. Exclusion criteria included significant alcohol consumption, viral hepatitis or other liver diseases and exposure to hepatotoxic agents. RESULTS: 52.6% were women, average age was 60 years (57-64), BMI was 29.6±4.7 kg/m² and diabetes duration was 7.6±6.9 years. A high prevalence of liver steatosis (62.4%) and steatosis and abnormal ALT (37.6%) was found. The prevalence of advanced fibrosis using the NFS was 12.8 and evidence of liver cirrhosis on MRI was 5.3%. In a multivariate analysis GGT >82 IU/L (P=0.004) and no alcohol intake (P=0.032) were independently associated to advanced fibrosis. CONCLUSION: A high frequency of undiagnosed advanced fibrosis and cirrhosis was observed in otherwise unselected T2DM patients older than 55 y/o. These patients are at high risk of developing liver-related complications such as portal hypertension and hepatocellular carcinoma. Routine screening for liver disease should be considered in this population (Grant Support: FONDECYT 1150327 to M.A.and 1150311 to F.B).
Efficacy and Safety of Vitamin E in Nonalcoholic Steatohepatitis Patients With and Without diabetes: Pooled analysis from the PIVENS and FLINT NIDDK NASH CRN Trials

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Background: Vitamin E has been studied for the treatment for nonalcoholic steatohepatitis (NASH) in non-diabetic adult patients in the PIVENS randomized controlled trial (RCT). We present non-randomized safety/efficacy estimates for vitamin E in diabetic adult NASH patients from our recent FLINT RCT, which compared obeticholic acid (OCA) to placebo in diabetic and non-diabetic adult NASH. Results for vitamin E in diabetic NASH were compared to pooled results in non-diabetic NASH derived from the PIVENS vitamin E and placebo groups and from non-diabetics in the FLINT placebo group. Methods: Two efficacy measures from FLINT were applied to our pooled data: histologic improvement, defined as ≥ 2 point improvement in NAS with no worsening of fibrosis or NASH resolution. Safety estimates paralleled those used in FLINT and included incidence of cardiac events and changes in lipid levels. Logistic regression models were used to summarize the odds ratio (OR) effects, confidence limits, and p-values on the pooled vitamin E treatment vs no vitamin E treatment efficacy estimates; Fisher’s exact test was used to assess cardiac events.

Results: A total of 250 patients were randomized to vitamin E (n=80) or placebo (n=72) in PIVENS or to placebo (n=98) in FLINT and had both baseline and end-treatment liver biopsies; 53 had diabetes (21%) and 197 were non-diabetic (79%); 105 (42%) received vitamin E and 145 (58%) did not in the PIVENS or FLINT trials. Vitamin E use was associated with histologic improvement in diabetic (OR 4.4, 95% CI 1.1, 18.0, p=0.04) and non-diabetic patients (OR 3.1, 95% CI 1.7, 5.8, p<0.001) but not significantly greater rate of NASH resolution in diabetic (OR=1.8, 95% CI 0.3, 12.2, p=0.55) or non-diabetic patients (OR=1.7, 95% CI 0.9, 3.3, p=0.09). The incidence of cardiac events was not significantly different among diabetics taking vitamin E vs. not taking vitamin E (0% vs. 12%, p=0.19) nor among non-diabetics taking vitamin E vs. not taking vitamin E (12% vs. 9%, p=0.51). There were no significant differences in net change from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides.

Conclusions: Vitamin E treatment was associated with similar significant improvement in NASH histology in both diabetic and non-diabetic patients. There was no association of vitamin E use with important adverse safety measures using a pooled analysis of patients from two RCTs of adult NASH. These preliminary findings from pooled data support RCTs in diabetic NASH to establish whether the promising safety and efficacy profiles for vitamin E in diabetic NASH are confirmed.

Disclosures:
Kris V. Kowdley - Advisory Committees or Review Panels: Achillion, BMS, Evidera, Gilead, Merck, Novartis, Trio Health, Abbvie; Grant/Research Support: Evidera, Gilead, Immuron, Intercept, Tobira; Speaking and Teaching: Abbvie, Gilead Arun J. Sanyal - Advisory Committees or Review Panels: Bristol Myers, Gilead, Genfit, Abbott, Ikaria, Exhalenz; Consulting: Salix, Immuron, Exhalenz, Nimbus, Genentech, Echosens, Takeda, Merck, Enanta, Zafgen, JD Pharma, Islet Sciences; Grant/Research Support: Salix, Genentech, Intercept, Ikaria, Takeda, GalMed, Novartis, Gilead, Tobira; Independent Contractor: UpToDate, Elsevier The following authors have nothing to disclose: Laura A. Wilson, Mark L. Van Natta, Rish K. Pai
An international, phase 2 randomized controlled trial of the dual PPAR agonist GFT505 in adult patients with NASH

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Peroxisome proliferator-activated receptor - dual agonists, such as GFT505, are a promising therapy for NASH as they improve hepatic insulin sensitivity, glucose homeostasis, lipid metabolism, and inflammation. Methods. In this randomized controlled trial (56 European and US centers) 274 patients (pts) (full analysis set, FAS) with histologically-defined non-cirrhotic NASH received GFT505 80 mg or 120 mg QD vs placebo (PLB) for one year. The primary outcome was resolution of NASH without worsening of fibrosis. Data were analyzed according to baseline severity (histological NAS score) and center effect. Biopsies were read by a single pathologist.

Results. 237 pts had entry and end-of-treatment biopsies (ITT population). While the a priori primary endpoint did not meet significance, after controlling for baseline severity and center effect, pts in the 120 mg arm had a 1.94 (CI 1.08-3.48, p=0.027) higher relative risk (RR) of achieving the primary end-point compared to PLB, while the RR was 1.68 (0.92-3.05, p=0.091) for the 80 mg arm. Results were similar in the FAS where pts missing the second biopsy were counted as failures. In pts with moderate activity (NAS 4 or 5) the response rate was 27.5% in the 120 mg arm vs. 19.5% for the PLB arm. In those with severe activity (NAS>5) it was 14.8% vs. 0%, respectively. In the 120 pts with NAS>4 from centers that recruited >1 patient/arm, the response rate was 29% and 5% in the 120 mg and PLB arms, respectively, p=0.01. A >2 point NAS reduction was obtained in 48% and 21% of patients respectively, p=0.01. Compared to PLB, the 120 mg arm improved ballooning (45% vs. 23%, p=0.02), inflammation (55% vs. 33%, p=0.05) and steatosis (35.5% vs. 18%, NS). In the 120 mg arm, resolution of NASH, resulted in a significant improvement in fibrosis (mean change -0.67 vs. +0.09 in non-responders, p<0.001). In the ITT population, pts in the 120 mg arm had improved ALT, GGT and ALP, non-invasive fibrosis panels (NFS Angulo score and Fibro-Test) and systemic inflammatory markers, hsCRP, haptoglobin, fibrinogen, 2macroglobulin. Importantly, cardiometabolic risk markers such as triglycerides, LDL-C, HDL-C, improved significantly in the 120 mg group (ITT population) vs. PLB, as well HEPATOLOGY, VOLUME 62, NUMBER 1 (SUPPL) AASLD ABSTRACTS 263A as HbA1c and FFA in diabetic pts, all on top of standard of care therapies. Tolerability was excellent without weight gain, cardiac events or safety signal. Conclusion. In NASH patients 120 mg daily of GFT505 induced histological improvement and resolution of NASH, significantly more often than PLB. The excellent safety and tolerability and the improvement in cardiometabolic risk profile makes GFT505 an ideal drug candidate to be tested in phase 3 trials

Disclosures: Vlad Ratziu - Advisory Committees or Review Panels: GalMed, Abbott, Genfit, Enterome, Gilead; Consulting: Tobira, Intercept, Exalenz, Sanofi-Syntelabio, Boehringer-Ingelheim; Stephen A. Harrison - Advisory Committees or Review Panels: Merck, Nimbus Discovery, Fibrogen, RuiYi, CLDF; Consulting: NGM Biopharmaceuticals; Speaking and Teaching: Gilead, Abbvie, Janssen,