The Future of Fatty Liver Disease

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Outline

- Natural history of disease
- Where are we going?
  - Biomarkers
  - New medications
Natural History of NASH

- Progression of 0.14 NASH stages per year based off non-randomized paired biopsy studies
- Aim: Estimate the number of patients with NASH that will progress to cirrhosis in their lifetime
- Systematic review of placebo treated patients in randomized control trials
- < 1/25 patients will develop cirrhosis
- 7 fold reduction from prior estimates
The Incidence of Extrahepatic Malignancies in Nonalcoholic Fatty Liver Disease (NAFLD)

- Malignancy is the second most common cause of death in NAFLD patients
- Community cohort from Olmsted County, Mn with over 38,000 NAFLD and 15,000 control patients
Prevalence and Long-Term Outcomes of (NAFLD) Among Lean Individuals without Any Components of Metabolic Syndrome

- **Aim:** Determine prevalence and long term outcomes of NAFLD among lean and metabolically normal individuals in the USA
  - BMI ≤ 25 and normal waist circumference (≤ 90cm in male and ≤ 80cm in female)
- **National Health and Examination Survey III and linked mortality data**
- **Overall prevalence of lean NAFLD 7.5%**
  - Without any metabolic abnormalities 5.6%
  - With DMII and HTN prevalence 13.2%
  - With DMII, HTN and HL 42.3%
  - Age adjusted mortality similar to lean controls without NAFLD
Ten-year Analysis of Nonalcoholic Fatty Liver Disease Related Hospitalizations

- **Aim:** To measure trends and socioeconomic impact on outcomes of NAFLD in the USA
- **Methods:** Retrospective study employing Nationwide Inpatient Sample (NIS)
  - Included all pts ≥ 18yo with primary and secondary discharge diagnosis of NAFLD between 2005-2014
Non-Alcoholic Steatohepatitis Predicts Adverse Liver-Related Outcomes and Death in Chronic Hepatitis B patients

- **Aim**: To determine whether biopsy proven NASH impacts outcomes in chronic hep B
- **Retrospective study of HBV patients at 2 tertiary centers from 1985-2018 with clinical and biopsy data**
  - Clinical event: death, liver related event
  - Categorized as no-NASH or probable/definite NASH by histology
- **Results**
  - 1097 patients
    - 83% no NASH, 17% NASH
    - NASH pts 80% men, 68.4% HBeAg (-), 40% F3-4, BMI heavier, ALT higher and lower HBV DNA
Non-Alcoholic Steatohepatitis Predicts Adverse Liver-Related Outcomes and Death in Chronic Hepatitis B patients
Impact of Pre-Screening with Fibrosis-4 Index on a Referral Pathway for Patients with Suspected NAFLD

♦ AIM: Assess the potential impact of implementing a FIB-4 first strategy to triage patients using a clinical referral pathway for NAFLD

♦ Performed at a tertiary care liver center drawing from 8 primary care networks with population of 850,000
  ♦ Age 18-65, elevated ALT and/or steatosis on imaging without other liver diagnosis
  ♦ Pts had blood tests as well as VCTE
Impact of Pre-Screening with Fibrosis-4 Index on a Referral Pathway for Patients withSuspected NAFLD

- Risk of finding VCTE $\geq 8\text{kPa}$ according to FIB-4 values was modelled using Logistic regression

- 433 underwent VCTE
  - 361 (85%) had FIB-4 $<1.3$
    - 10% had VCTE $\geq 8\text{kPa}$, 7% $\geq 9\text{kPa}$
    - 2 had advanced fibrosis
Severity of NAFLD/NASH is Associated with Both More Severe β-Cell Dysfunction and Reduced Insulin Clearance Independently of Body Weight in a Large Cohort of Non-Diabetic Subjects: Further Insights into the Causative Role of NASH in DMII Development

- NAFLD patients have increased risk for DMII
  - β-Cell Dysfunction is a predictor of hyperglycemia and DMII
  - Liver clears 80% of secreted insulin
- Aim: Evaluate if insulin secretion rate and β-Cell function were decreased in NASH vs NAFLD thus predisposing to DMII
- Analyzed glucose, insulin, C-peptide during an oral glucose tolerance test in 503 NAFLD non-DM patients
  - Disposition index=insulin secretion/insulin resistance = determination of β-Cell function
  - Low DI is a pre-disposition to DMII
Severity of NAFLD/NASH is Associated with Both More Severe β-Cell Dysfunction and Reduced Insulin Clearance Independently of Body Weight in a Large Cohort of Non-Diabetic Subjects: Further Insights into the Causative Role of NASH in DMII Development.

Figure 1: Disposition index shows that β-cell is more dysfunctional in obese subjects and aggravated by severity of NAFLD (non-ob: non-obese; ob: obese; morb-ob: morbid obese).
Treatment
Factors complicating NASH treatment

- NASH is a dynamic disease process
- Disease heterogeneity
- No ideal biomarkers
  - Able to diagnose steatosis and fibrosis
Physical Activity and Risk of Mortality in Non-Alcoholic Fatty Liver Disease: A Population Based Study of United States Adults

- Aim: to investigate the associations between PA and the risks of mortality related to all-causes, cardiovascular disease and diabetes among U.S. adults with NAFLD.
- Analyzed mortality linked data from NHANESIII data of 2701 adults from age 20-74 with NAFLD as diagnosed as steatosis on ultrasound
- Recommended activity decreases all cause, cardiovascular and diabetes related mortality

<table>
<thead>
<tr>
<th>Physical Activity Status *</th>
<th>Prevalence (n=2701)</th>
<th>All Cause</th>
<th>Cardiovascular Disease</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>N (100,000)</td>
<td>aHR b (95% CI)</td>
<td>aHR b (95% CI)</td>
</tr>
<tr>
<td>Inactive</td>
<td>15.51 (13.09 – 17.93)</td>
<td>45.10</td>
<td>Reference Group</td>
<td>Reference Group</td>
</tr>
<tr>
<td>Insufficiently Active</td>
<td>36.57 (32.98 – 40.15)</td>
<td>106.34</td>
<td>0.75 (0.56 – 1.01)</td>
<td>0.53 (0.30 – 0.95)</td>
</tr>
<tr>
<td>Recommended Active</td>
<td>47.92 (43.84 – 52.01)</td>
<td>139.37</td>
<td>0.64 (0.48 – 0.86)</td>
<td>0.46 (0.25 – 0.84)</td>
</tr>
</tbody>
</table>

a) HR, adjusted hazard ratio; N, projected number of U.S. adults per physical activity status.

* Recommended Active: Adults with recommended levels of physical activity; Inactive: No reported leisure-time physical activity; Insufficiently Active: Adults who were not inactive nor met the recommended physical activity levels.

b) Adjusted for age, gender, education, poverty index, marital status, access to health insurance, smoking, BMI, healthy eating index, race, alcohol intake, high-density lipoprotein, systolic blood pressure, waist circumference, triglycerides, and fasting blood glucose.
Treatment

Tight Glucose Control Improves Liver Tests in Diabetics: A Prospective Analysis

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Background: Glucose control is crucial to prevent adverse outcomes in diabetes. While the strong link between diabetes and nonalcoholic fatty liver disease (NAFLD) is clear, the effect of tight glucose control on the course of NAFLD is poorly described. The aim of this study is to identify the effect of glucose control on ALT using data from the prospective, multi-center Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial.

Methods: The ACCORD trial was a prospective, multi-center, randomized trial comparing cardiovascular outcomes in diabetics with intensive (goal hemoglobin A1C [HbA1c] < 6.0%) or standard glucose control (goal HbA1c 7.0-7.9%). Adults aged 40-79 with type 2 diabetes, a cardiovascular disease risk factor, and a HbA1c ≥ 7.5% were included in the ACCORD study. Our analysis included patients with baseline elevated ALT (> 30 IU/L in women, > 40 IU/L in men), but excluded patients with missing ALT values or excessive alcohol use (defined as > 2 drinks/day for women, > 3 drinks/day for men). The primary outcome of this study was the association HbA1c change with ALT values in patients with baseline elevated ALT. ALT change was measured as the difference from baseline to study exit. Secondary outcomes were decrease in ALT by 10% and normalization of ALT. Multivariate regression controlled for age, gender, randomization into intensive glucose control arm of the study, and change in body mass index (BMI) over the study period.

Results: Of the 9,863 subjects with ALT measurement at study entrance and exit, 1,909 (19.7%) had an elevated ALT at baseline and were followed for a median 4 years. Of patients with baseline elevated ALT, 70% experienced a decrease by at least 10% and 53.6% normalized by the conclusion of the study. The median ALT decreased from 45 IU/L to 33 IU/L. The median BMI increased by a median 0.5 kg/m² over the course of the study. On multivariate regression, decrease in HbA1c significantly predicted decrease in ALT (regression coefficient 2.22, 95% CI 1.44-2.99, p<0.001), decrease in ALT by at least 10% (OR 1.25, 95% CI 1.16-1.35, p<0.001), and normalization in ALT (OR 1.26, 95% CI 1.18-1.37, p<0.001) (see table). Randomization into the intensive glucose arm was not significant in any of the models. Conclusion: Using a randomized, multi-center prospective cohort of type 2 diabetics with cardiovascular disease, our analysis demonstrated that improved glucose control significantly reduces ALT in patients with a baseline elevation. Although the underlying etiology of hepatic inflammation is unclear given the lack of available histology and laboratory information, most patients with diabetes, cardiovascular disease, and elevated ALT have NAFLD. Our findings suggest that tight glucose control may lead to improvement in NAFLD, irrespective of BMI change or underlying liver disease.
Regression of Fibrosis after Disappearance of NASH in Morbidly Obese Patients: A Prospective Bariatric Surgery Cohort with Sequential Liver Biopsies

- Bariatric surgery induces disappearance of NASH and improves pathologic features of disease at 1 year
- Aim: Assess outcomes at 5 years post bariatric surgery
- 198 patients from 1994-2017 with biopsy proven NASH underwent bariatric surgery at University Hospital in France
- Results
  - 69% had 1 year and 55% had 5 year follow up biopsy
  - 85% of patients had disappearance of NASH at 1 year and at 5 years
  - Improvement in fibrosis was noted with improved disease control and higher weight loss at 1 year
Bariatric Surgery is Associated with Increased Mortality in Compensated and Decompensated Cirrhosis: A Population-Based study

✧ Aim: To examine the impact of bariatric surgery amongst all cirrhotics in the community

✧ Examined all patients with and without bariatric surgery in North Texas using a collaborative data warehouse

✧ 292 patients with bariatric surgery and cirrhosis compared with 29,987 cirrhotics
  
  ✧ 73% vs 38% female with 16.1% vs 3.2% NASH and similar EtOH cirrhosis and decompensation
  
  ✧ 5 year survival was 57.9 vs 62.8% p<0.04
Thyroid hormone and NAFLD

- Good biologic rationale
  - More overt and subclinical hypothyroidism in NASH

THRβ
(Liver, brain)
lipid metabolism,
inflammation

THRα: (heart)
heart rate,
contractility

Liangpunsakul S, Chalasani N, J Clin Gastroenterol. 2003;
Pagadala MR et al., Dig Dis Sci. 2012
Kim D et al., Clin Gastroenterol Hepatol. 2018
In a Placebo-Controlled 36-Week Phase 2 Trial, Treatment with Mgl-3196 Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in Nash on Serial Liver Biopsy

- MGL3196 is a liver-directed, orally active, highly selective THRβ agonist, which may reduce lipotoxicity in NASH by increasing hepatic fat metabolism.

- MGL3196505 (NCT02912260) is a 36-week multicenter, randomized, double-blind, pbo controlled serial MRI-PDFF, paired liver biopsy study in adults with biopsy-confirmed NASH (NAS ≥4, F1 to F3) and hepatic fat fraction ≥10%, by MRI-PDFF.

- Sustained highly significant reduction in hepatic fat at Weeks 12 and 36 (figure 1). At optimized doses of 80-100 mg, 50% median relative fat reduction, 10% absolute fat reduction, and 87% responders with ≥30% liver fat reduction.

- Sustained statistically significant (p<0.001) reduction in lipids, Weeks 12 and 36, LDL-C (-22.3%), triglycerides (-36%), Lp(a) -37%

- Reduction and normalization of liver enzymes ALT (figure 2), AST, GGT
  - Mean -26.4 U/L absolute change; p=0.002 MGL-3196 relative to placebo
  - At Week 36, 60.3% of MGL-3196 patients had ALT <30 vs 35.8% of placebo patients (p=0.029).

- Reduction in fibrosis markers, ELF, CK-18, and Pro-C3 (figure 3), Pro-C3, by 40 to >80% (placebo adjusted); significant reduction in fibrosis biomarkers in F2/F3 MGL-3196 patients

- Statistically significant dose and exposure dependent improvement in NAS and NASH resolution (figures 3, 4) with low/no effect dose demonstrated

- Excellent safety, balanced AEs between pbo and drug-treated with increase only in incidence of transient mild to moderate loose stools in MGL-3196-treated compared with placebo patients, often a single episode, occurring during the first few days of treatment

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Fig 1. Relative Change in MRI-PDFF (%).

Fig 2. ALT (IU/L).

Fig 3. 2 pt NAS reduction with ≥ 1 pt decrease in ballooning or inflammation.

Fig 4. Nash Resolution (%).

# Exposure (exp) measured, 80 mg dose at Week 2; prespecified 2 groups with higher exposure or > increase in SHBG (sex-hormone binding globulin), a target-specific biomarker.

* Prespecified endpoint: at least 2 pt reduction in NAS; ballooning=0, inflammation=0, =1; <9.5% weight loss.

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VK2809, a Novel Liver-Directed Thyroid Receptor Beta Agonist, Significantly Reduces Liver Fat in Patients with Non-Alcoholic Fatty Liver Disease: A Phase 2 Randomized, Placebo-Controlled Trial

**Conclusions:** VK2809 produced significant reductions in LDL-C and robust improvements in liver fat content in patients with NAFLD.
One-Year Results of the Global Phase 2b Randomized Placebo-Controlled Arrest Trial of Aramchol, a Stearoyl CoA Desaturase Inhibitor, in Patients with NASH

- Aramchol down regulates SCD1 in hepatocytes and hepatic stellate cells resulting in fatty acid normalization, reduction in collagen production, and less liver stress
- 247 patients with centrally-read biopsy-proven NASH were randomized 2:2:1 to Aramchol 600mg:400mg: placebo
- 60% had stage 2 and 3 fibrosis
- 70% had NAS $\geq$ 5 at baseline