NASH: Emerging concepts in clinical impact, evaluation and care

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DISCLOSURES: Ad hoc Consultant to, Astellas,
Takeda, Exhalenz, Intercept
Nonalcoholic fatty liver disease

H&E stain 20X

Steatosis, ballooning and inflammation

- Alcohol consumption low (< 30 gm/day)
- **Causes:**
  - metabolic syndrome
  - lipid metabolic disorders
  - TPN
  - Malnutrition
  - Drugs: Diltiazem, Amiodarone, Tamoxifen
  - Celiac disease
Why you should worry about NASH?
Subjects with NAFLD have a greater than expected mortality compared to matched controls

- Risk factors for mortality:
  - Age ($p < 0.001$)
  - Diabetes ($p < 0.005$)
  - Cirrhosis ($p < 0.02$)

- Increased mortality:
  - cardiovascular disease
  - liver disease

Adams et al, Gastroenterology, 2005, 129:113-121
Liver enzymes predict development of full blown metabolic syndrome

N= 633
N that developed metabolic syndrome over 5 years: 127

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>2.5 (1.38-4.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>2.28 (1.24-4.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP</td>
<td>1.3 (1.09-1.6)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Hanley et al, Diabetes, 2005, 54:3140-7
NAFLD & incident CVD in T2DM

Nested case-control study in 2,103 T2DM, free of CVD at baseline. 248 cases had a CV event at f-up (5 yrs), and were compared with 496 who remained free of diagnosed CVD.

Logistic Regression: OR

- **Unadjusted**: OR = 1.91, P < 0.001
- **Age- & Sex-adjusted**: OR = 1.9, P < 0.001
- **Multiple Factor-adjusted**: OR = 1.84, P < 0.001
- **Multiple + ATPIII MS-adjusted**: OR = 1.53, P = 0.02

*Age, Sex, Smoking, Duration of diabetes, HbA1c, LDL-cholesterol, drug use (OHA, BP-lowering, Statins/Fibrates, Aspirin)

*Targher, Diabetes 2005*
NAFLD increases the risks of death

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td>Ekstedt</td>
<td>No controls had liver death</td>
</tr>
<tr>
<td>Dunn</td>
<td>4.4 (overall)</td>
</tr>
<tr>
<td>Rafiq</td>
<td>9.2</td>
</tr>
<tr>
<td>Ong</td>
<td>9.3</td>
</tr>
<tr>
<td>Feldstein</td>
<td>13.6 (overall)</td>
</tr>
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</table>
Progression of NASH
Progression of NASH
Natural history of NAFLD: paired biopsy data

<table>
<thead>
<tr>
<th>Final →</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
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<tbody>
<tr>
<td>Initial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>13</td>
<td></td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>F1</td>
<td>7</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>F2</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>F3</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>4</td>
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<tr>
<td>F4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Risk factors for disease progression

• Non-modifiable:
  – age
  – race
  – genetic background
  – baseline histology

• Modifiable:
  – weight gain
  – insulin resistance
  – diabetes
Outcomes of NASH-related cirrhosis: Child Pugh class A

Sanyal et al, Hepatology 2006, 43:682-689
Development of hepatocellular cancer in cirrhosis due to NASH vs HCV

Sanyal et al, Hepatology 2006, 43:682-689
HCC burden of Population-based study of impact of NASH on burden of disease due to HCC

HCC was the first liver disease to be diagnosed in 23.9%

<table>
<thead>
<tr>
<th>Risk Factor (ICD-9-CM code)</th>
<th>HCC Patients (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV (070.41, 070.44, 070.51, 070.54, V02.62)</td>
<td>22</td>
<td>0.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NAFLD/NASH (571.8, 571.9, 573.4, 573.8, 573.9)</td>
<td>54.6</td>
<td>2.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes (250)</td>
<td>33.9</td>
<td>18.6</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Alcohol (571.0, 571.1, 571.2, 571.3)</td>
<td>11.6</td>
<td>0.2</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Cirrhosis*: 69%
Diabetes: 32%
NASH: 68%

Cirrhosis*: 42%
Diabetes: 36%
HCV: 28%

HCV: 21%
NASH: 58%

*ICD-9-CM code 571.5 or 571.6

Prevalence of HCC in HCV: 7.9/1000
Prevalence of HCC in NAFLD/NASH: 4.7/1000

Sanyal et al, CMRO, 2010
Development of fatty liver disease after liver transplant for cryptogenic cirrhosis

Contos et al, Liver Transplantation, 2001, 7: 363-373
Summary

- Those with fatty liver have a low risk of progression to cirrhosis (< 5%) over 15 yrs.
- Those with NASH have a 15% progression to cirrhosis over 15-20 yrs.
- Increasing obesity, age, diabetes are risk factors for disease progression.
- NAFLD is associated with increased risk of diabetes, cardiovascular disease and cancer.
Who and when to biopsy?
Who to evaluate?

- Persistently abnormal AST, ALT or Alk Phos
- Persistent unexplained hepatomegaly
- Abnormal hepatic imaging suggestive of NAFLD
What information are we looking for?

• Is it fatty liver disease?
  – Biopsy or imaging can answer this question

• Is it fatty liver or NASH?
  – Biopsy is the “gold standard”
  – Biopsy is limited by phenotypic variability and difficulties in assessment

• How far has the person progressed towards cirrhosis i.e. fibrosis stage
  – Biopsy is a mediocre “gold standard”
  – Non-invasive markers rapidly gaining ground
Caspase-3 generated fragments are seen in NASH

Weicocka et al, Hepatology, 2006, 44:27-33
CK-18 fragment: Diagnostic value for NASH

<table>
<thead>
<tr>
<th>Cutoff (u/L)</th>
<th>sensitivity</th>
<th>specificity</th>
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<tbody>
<tr>
<td>216</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td>230</td>
<td>76</td>
<td>69</td>
</tr>
<tr>
<td>246</td>
<td>75</td>
<td>81</td>
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<tr>
<td>279</td>
<td>71</td>
<td>85</td>
</tr>
<tr>
<td>281</td>
<td>61</td>
<td>89</td>
</tr>
<tr>
<td>287</td>
<td>65</td>
<td>92</td>
</tr>
</tbody>
</table>

Feldstein et al, Hepatology 2009;50:1072-1078
Circulating CK 18 fragments are not liver-specific

CK18 and CK8 fragments are expressed in esophageal, colon and pancreatic CA

Increased in coronary syndromes

Increased in smokers

Makino et al, Br J Cancer, 2009, 101, 1298-1306
Ausch et al, J Gastrointest Surg, 2009, 13:2020-2026
How to decide when to do a liver Bx to establish cause of abnormal ALT

↑ ALT

Rule out other causes of liver disease

Causes found → No causes found

Metabolic syndrome present

YES

Will Bx change Rx

Will Bx change Rx

Yes

NO

BX

Consider Bx risks: FIB4, ELF, fibroscan etc

Yes

Discuss risks/benefits
Make patient aware of risks of not doing Bx

Ramesh and Sanyal, J Hepatol, Feb 2005
What is the treatment?
Who to treat and why

• Focus on diabetes and cardiovascular disease:
  – All cases of NAFLD especially NASH
• Focus on prevention of Liver Disease:
  – NASH + high activity score
  – NASH + risk factors for progression
  – NASH + increasing degrees of fibrosis
• Focus on prevention of Cancer deaths:
  – Yet to be defined
Diet
NHLBI guidelines (1998)

• Ideally, should be individualized to achieve energy deficit of 500-1000 Kcal/day
• Decrease saturated fats and keep total fats < 30% of total energy intake
• Decrease refined sugars
• (Avoid high fructose corn syrup enriched foods)
• Increase soluble fiber intake
Rationale for therapeutics for NASH

- Insulin sensitizers
- Insulin resistance
- FFA + insulin+ cytokines

Steatosis + metabolic dysregulation

ER stress  Oxidative stress  Mitochondrial injury

Inflammatory signaling

Aptosis  Cell death

Stellate cell activation

Fibrosis

Multiple sources
PIVENS Study Design
(a study performed by the NASH CRN)

Randomization
Eligibility assessed by local pathologist
(1:1:1) Wk 0

Month -6

Liver biopsy

End of treatment
Liver Biopsy
Wk 96

Week 120
end of study

Vitamin E (rrr α-tocopherol) 800 IU/day

Pioglitazone (30 mg/day)

Placebo

Primary endpoint
Decrease in NAS by 2 or more points, with at least a 1 point drop in ballooning, and no worsening of fibrosis
Pioglitazone or Vitamin E vs placebo for NASH: vitamin E was superior

Sanyal for NASH CRN, NEJM, 2010, April 28 EPub
Both Vitamin E and Pioglitazone improve steatosis

Improvement in severity of steatosis grade
- Vit E vs placebo: p< 0.0001
- Pio vs placebo: p< 0.0001

Sanyal for NASH CRN, NEJM, 2010, April 28 EPub
Changes in insulin resistance in PIVENS

HOMA-IR

- Placebo
- Vitamin E
- Pioglitazone

Sanyal for NASH CRN, NEJM, 2010, April 28 EPub
Both vitamin E and pioglitazone increased the proportion of subjects with resolution of NASH.
Effects of vitamin E or pioglitazone on liver enzymes

![Chart showing the effects of vitamin E or pioglitazone on liver enzymes over 96 weeks. The x-axis represents weeks, from 0 to 96, and the y-axis represents change in ALT levels (U/L), ranging from -40 to 0. The chart compares placebo, vitamin E, and pioglitazone groups.]
Change in body weight

![Graph showing change in body weight over weeks for Placebo, Vitamin E, and Pioglitazone.](graph.png)

*Placebo* - Black triangles
*Vitamin E* - Orange circles
*Pioglitazone* - Green squares

*Source:* Sanyal for NASH CRN, NEJM, 2010, April 28 Epub
Vitamin E for NASH: safety issues

• Mixed data from large clinical trials
• Role of confounders not accounted for:
  – High dose Zn supplementation
  – Use of concomitant vitamin A
  – Smoking
• Competing risk benefits in use as a general supplement vs treatment of a disease that can cause death
## Comparison of Vitamin E and Pioglitazone

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase IIb/III trial data (better than)</td>
<td>Placebo, Pio</td>
<td>Placebo</td>
</tr>
<tr>
<td>Weight gain</td>
<td>None</td>
<td>Yes, continuous</td>
</tr>
<tr>
<td>Improvement in insulin resistance</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Fracture risk</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>?? Slight increase</td>
<td>??</td>
</tr>
</tbody>
</table>
Things to remember when using vitamin E

• Not validated in those with NASH + diabetes
• Not validated in those with cirrhosis
• Need to monitor cardiac risk profile
• It does not work for everyone and so one must monitor for efficacy
What to do with non-responders?
NASH: pre vs post treatment with pioglitazone + vitamin E

Sanyal et al, Clin Gastroenterol and Hepatol, Dec 2004
Effect of weight loss on NAFLD

Pathophysiology-based rationale for treatment strategies

Insulin sensitizers → Insulin resistance

FFA + insulin+ cytokines

Steatosis + metabolic dysregulation

ER stress

Oxidative stress

Mitochondrial injury

Inflammatory signaling

Apoptosis

Stellate cell activation

fibrosis

CB1 antagonists
PUFAs

Anti-miR 34

JNK inhibitors

TNF modulator
FXR agonists
ARBs
Incretins
PDE

Vitamin E
Silymarin
betaine

Multiple sources
Dr. Sanyal: please confirm reference.
Jenny Schulz, 6/17/2007
The future of NASH management

Risk identification at birth
(race, family history, genes, epigentics)

Primary prophylaxis

Screening and Identification of Disease

First line treatment based on response predictors

Non-invasive response assessment

Second-line treatments
Livin' La Vida Sofa