The Comprehensive Global Burden and Impact of NASH

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The Comprehensive Burden of NASH

Burden

CLINICAL
- Prevalence and incidence
- Liver outcomes or surrogates of mortality
- CVD and other EHM
- Life-expectancy, expected years of life lost,

PRO
- Symptoms
- HRQOL (Physical, Mental and Social health)

FUNCTIONAL
- Functional status (disability)
- Absenteeism (WP)
- Presenteeism (WP)
- Days of work missed
- Ability to manage ADL

ECONOMIC
- Cost of illness
- Budgetary costs
- Indirect and intangible costs
- Resource utilization
- Cost-effectiveness

Surrogate Endpoints

• Survival
• Patient experience
• Feel
• Function and WP
• Resource utilization
• Value

Outcomes

Lets Get the Terminology Correct: What Is NASH and NAFLD?

- Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria
- Exclusion of secondary causes and AFLD
- Risk factors are components of metabolic syndrome

The Global Prevalence of NAFLD and NASH

Prevalence of NASH in general population is between 1.5–6.5%
Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

The Global Prevalence of NAFLD and NASH

Worldwide prevalence of NAFLD among Children is about 7-10%

- Prevalence is higher in boy and increases with higher BMI
- U.S. studies have revealed a 4-fold higher risk of hepatic steatosis in Hispanic, compared to non-Hispanic
- The prevalence of NAFLD in the US increased 2.7 fold from the late 1980’s to 2010

Prevalence of NAFLD and NASH in Different Regions of the World

Prevalence of NAFLD in Europe: 20-30%

Prevalence of NAFLD in Asia: 29.62%

Prevalence of NAFLD in the Middle East and Africa

Prevalence of NAFLD in Latin America

The Comprehensive Global Burden and Impact of NASH

Although the Prevalence Rates for NASH and NAFLD are Large and Growing, Which Patient Groups and Patient Profiles Indicate Potential Progression?
Clinical Outcomes: Natural History of NAFLD and NASH

The most common cause of death

Non-linear Progression

HCC, hepatocellular carcinoma.
Clinical Outcomes: Natural History of NAFLD and NASH

NASH Denotes Progressive Disease

Components of MS Predicts Mortality-NHANES III

Stage of Fibrosis Predicts Mortality

HCC and NAFLD- SEER 2004–2009

Growing LT Due to NASH in the US

LT Due to NASH-related HCC

Changes in CLD

Changes in CLD Mortality

### Trends in Incidence Rates (2012-2017)

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Liver Cancer</th>
<th>Cirrhosis</th>
</tr>
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<tbody>
<tr>
<td>Global</td>
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<td>1.38</td>
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<tr>
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Models Suggest a Growing Clinical Burden Driven by Advanced NASH

By 2030, there are projected to be nearly 800,000 excess liver deaths

Cases of stage 3 fibrosis due to NASH\(^1\):
- 2015: 2 M
- 2030: 4.5 M

Cases of stage 4 fibrosis due to NASH\(^1\):
- 2015: 1.3 M
- 2030: 3.1 M

Incident decompensated cirrhosis, HCC and liver-related deaths\(^2\):
- +168%
- +178%
- +137%

HCC, hepatocellular carcinoma; M, million; T2DM, type 2 diabetes mellitus.

Models to Predict Future Burden of NASH and Adverse Outcome in Europe and Asia

Models to Predict Future Burden of NASH and Adverse Outcome in Europe and Asia

Incident decompensated cirrhosis, HCC, liver-related deaths among prevalent NAFLD population

Prevalent NASH cases by disease stage in the UAE and Saudi Arabia

Although Most NAFLD Patients Are Obese, There Are Some Patients with Lean NAFLD

Prevalence (%)

Long-Term Outcomes of Lean NAFLD

- The lean study cohort consisted of 5,375 individuals
- 10.8% of lean cohort (N = 581) had NAFLD
- Compared to lean individuals without NAFLD, lean NAFLD subjects were significantly more likely to be
  - Older: 50.92 ± 1.26 vs. 41.8 ± 0.60, p < 0.001
  - Male: 58.67 ± 3.13 vs. 39.19 ± 0.86, p < 0.001
  - Diabetes 20.28 ± 2.27 vs. 0.29 ± 0.11, p < 0.001
  - High cholesterol 35.03 ± 2.52 vs. 13.19 ± 0.74, p < 0.001
  - Hypertension 31.29 ± 2.59 vs. 13.29 ± 0.80, p < 0.001
- In the fully adjusted model, NAFLD was independently associated with increased risk of all-cause (aHR = 1.54, 95% CI: 1.25 – 1.89) and cardiovascular (aHR = 2.38, 95% CI: 1.50 – 3.77) mortality.
Contribution of Superimposed NAFLD on Other Liver Diseases

• Since components of Metabolic syndrome (DM, HL, HTN, Visceral obesity) are risk factors for NAFLD, they can increase the risk for accelerating progression either through superimposed NAFLD or directly through DM and obesity (inflammatory states)

• Evidence available for the following
  – Chronic hepatitis C
  – Chronic hepatitis B
  – Overlap with alcoholic liver disease
  – Contribution to HCC
What Are Economic and Patient Reported Outcomes of NASH?
Patient Reported Outcomes
Fatigue and Health Related Quality of Life in NAFLD and NASH

- Highest rate of Fatigue in real world setting was observed in NASH/NAFLD

- Biopsy proven NASH from STELLAR 3 and 4 (N=1667) completed 4 PRO questionnaires [SF-36, CLDQ-NASH, EQ-5D, WPAI:SHPF] pre treatment

- Fatigue and physical health related PRO scores were lower than population norms (all p<0.01)

- Compared to NASH patients with F3, those with cirrhosis (p<0.02) had lower fatigue scores

- MVA: Independent predictors of lower PRO scores included female gender, lower albumin and presence of DM and other comorbidities (p<0.01)

Impact of Fatigue on Health Related Quality of Life in NASH

- Patients with biopsy-proven NASH (N=1679) enrolled in clinical trials
- Prevalence of clinically reported history of fatigue: 10.3%
- NASH patients with fatigue has significant lower PROs that subjects without fatigue

![Graph showing the impact of fatigue on health-related quality of life in NASH](image-url)

Mean PRO score, 0-100 scale

- Fatigue
- No fatigue

all p<0.02 except for Work productivity

The Economic Burden of NASH

- 6.65 million adults with NASH
- 688,000 advanced NASH
- $222.6 billion in lifetime direct costs of total NASH population
- $95.4 billion in lifetime direct costs of advanced NASH
- Indirect cost of WP loss and other indirect costs are enormous

What Are Some Potential Pathogenic Pathways That Can Promote Progression of NASH?
Pathogenesis of NASH and Related Fibrosis

DAMP, danger-associated molecular patterns; ECM, extracellular matrix; IL-1β, interleukin-1beta; PAMP, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-β, tumor necrosis factor-beta.

The Comprehensive Global Burden and Impact of NASH

Invasive and Non-Invasive Tests to Identify NASH Patients At Risk?
Diagnostic Modalities for NAFLD, NASH and Fibrosis

- **Invasive Modalities:**
  - Histology (liver biopsy is the imperfect gold standard to diagnose NASH and stage fibrosis)
  - Z Goodman
- **Non-invasive Modalities:**
  - Non-invasive modalities for NASH are not very fruitful.
  - Better opportunities to find non-invasive tests for fibrosis
  - International efforts to find NITs: LITMUS (EU-Q Anstee) and NIMBLE (US-A Sanyal)

### Clinical/lab tests
- NAFLD fibrosis score
- FIB-4 index
- AST:ALT ratio
- AST:platelet ratio index
- Hepascore®
- FibroTest®
- FibroMeter®
- Fatty liver index
- Index of NASH

### Imaging
- Ultrasound
- Computer tomography
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Transient elastography
- Acoustic radiation force impulse
- Magnetic resonance elastography

### Biomarkers
- Hyaluronic acid
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- ELF score
- FIBROSpect®
- PRO C3

**Example of Risk Stratification: Preliminary Data**

### Primary Care and Endocrinology Practices

1. T2DM with one additional component of metabolic syndrome (BMI>29.9 or Dyslipidemia treated with meds or Hypertension treated with meds) or
2. T2DM with a history of elevation of AST or ALT (1.5-times ULN in the past 6 months) or
3. T2DM with a history of fatty liver by any radiologic modality (US, CT, MRI) or liver biopsy (any historical test will be sufficient)
4. Non-diabetics with 3 components of MS (BMI>29.9, Dyslipidemia treated with meds and Hypertension treated with meds)

- **Research Flier:** If interested to contact Central Research Staff

- **Phone consent**
- **Basic clinical and demographic data**
- **Any 2/3 of the following:**
  - NFS>1.45
  - FIB-4>1.45
  - APRI>1.0

- **Agreed to participate by phone N=364**
- **Did not meet criteria N=270**

- **Linked to care N=94**

- **Link to NASH Care**

- **TE<8**
- **Send back to primary MD/Endo for follow up and evaluation of abnormal LE**
- **Consider annual TE for 7-8 kPa**

**Completed Linkage N=51**

- **TE>9 kPa 19.6%**
- **≥ 9 kPa 18.9%**
- **≥ 8 kPa 25%**

- **Linkage to NASH standard of care to GI and Hepatology**

- **Strict life style modifications**
- **Consider biopsy for prognosis or clinical trials candidates**
- **Annual TE and clinical data to monitor**

K Corey and R Basu; Younossi Z. 2019.
Not to Forget NASH as a Part of a Multisystem Disorder

Addressing the Epidemic of NASH: Today and Tomorrow

Public Health Interventions
- Patients (D Cryer), Policy (Z Younossi, D Cryer, A Sanyal, V Ratziu, Q Anstee, K Cusi and others)

Outcomes and Endpoints
- Histology: Z Goodman
- Fibrosis: S Freidman
- NIT: Q Anstee, M Nouredine
- Imaging: M Middleton
- Overall: A Sanyal and S Caldwell

Screening and Linkage from Different Settings
- Overall Screening and Linkage: K Carey and R Basu
- Linkage with Diabetes: K Cusi
- Linkage with CVD: L Sperling
- Linkage with Primary Care: M Abdelmalek

Role of Current Interventions
- Diets and Nutrition: S Zelber-Sagi
- Exercise and Function: L Gerber
- The Role of Surgery and Weight loss Medication: S Klein
- Current Medical Regimens: K Kowdley

Current and Future Clinical Trials
- New Therapeutic: V Ratziu
- Challenges in Trial Design: V Ratziu and N Alkhouri
- Clinical Trial in Pediatrics: J Lavine
- Optimal Design: N Chalasani
- Regulatory Perspective: A Sanyal

Addressing the Epidemic of NASH: Today and Tomorrow
NAFLD and NASH are growing globally with epidemic of obesity
NASH is predominantly progressive
Fibrosis is important predictor of long-term outcomes
Patients with NASH, especially those with fibrosis will need treatment and should be identified
Although liver biopsy is the current imperfect gold standard for NASH diagnosis, a number of non-invasive tests are being developed
Management of NASH requires a multidisciplinary teams
Critical issues for treatment of NASH:
  - Most meaningful surrogate endpoints
  - Finding the right targets and development of regimens (combinations)
  - Finding the patients (screening and Linkage with NITs)
  - Managing as teams
  - Understanding the differences and similarities across the globe

To Address the Global Burden of NASH, Creation of NASH Global Council and Associated Registries
The Council of world renowned hepatologists with interest in NASH to collaborate in NASH from different regions of the world. Global NASH Council include over 30 countries from all the continents across the globe with 65 members. Members of the Council carry out multiple collaborative projects to better understand NASH, its clinical, economic and PRO burden.
The Global NASH Registry™
The Global Liver Registry™

- Number of Subjects Enrolled: 7,385
- Number of Total Sites: 38 sites
- Number of Active Sites: 25 sites (9 sites in North America, 6 sites in Europe, 6 sites in Asia, 2 sites in Australia and 2 sites in Africa)
- A total of 7,385 enrolled among 3 disease types: NAFLD/NASH = 3,992
- Hepatitis C = 2,546, Hepatitis B = 847
Acknowledgements

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Beatty Liver and Obesity Research Program