2018 Annual Meeting

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Kiawah Island, SC

This continuing medical education activity is jointly provided by the Carolinas Chapter-AACE and Southern Regional Health Education Center.
Acromegaly: What is New?

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Co-director, Emory Pituitary Center

Disclosures

- PI for institution-directed research support from Chiasma, Novartis, Pfizer, and Strongbridge
- Consultant (advisory board): Pfizer
Objectives

1. To review trends in epidemiology and clinical presentation of acromegaly
2. To outline predictors of long-term biochemical remission after surgery
3. To learn about the individualized medical treatment in patients with persistent acromegaly postoperatively

“Acromegaly is a rare disease”

- Population studies used different methods:
  - Cross-sectional, computer database search
  - Cross-sectional, case-finding surveys
  - Hithary registers: medical records or voluntary registering by physicians
  - Health insurance claims
- Population coverage:
  - Nationwide
  - Regional
  - Hospital and community
  - Hospital
  - Geographically diverse: health insurance databases

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Time Interval</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Incidence trends within study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander L, 1980</td>
<td>United Kingdom**</td>
<td>1960-1971</td>
<td>4</td>
<td>0.3</td>
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<td>Björkström K, 1988</td>
<td>Sweden</td>
<td>1955-1984</td>
<td>6.9</td>
<td>0.33</td>
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<td>Vázquez A, 2004</td>
<td>Spain*</td>
<td>2001</td>
<td>3.4</td>
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<td>Bex M, 2007</td>
<td>Belgium**</td>
<td>2003-2004</td>
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<td>Fernández A, 2008</td>
<td>United Kingdom**</td>
<td>2006</td>
<td>8.6</td>
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<td>Van den Bemt, 2010</td>
<td>Finland**</td>
<td>1992-2007</td>
<td>0.3</td>
<td>↑ after 2000 all adenomas</td>
<td></td>
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<td>Basu O, 2013</td>
<td>Korea*</td>
<td>2003-2007</td>
<td>2.8</td>
<td>0.4</td>
<td></td>
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<td>Girgenti R, 2013</td>
<td>Malta*</td>
<td>2000-2011</td>
<td>12.5</td>
<td>0.3</td>
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<td>Sjöberg &amp; 2014</td>
<td>Sweden**</td>
<td>2001-2011</td>
<td>3.3</td>
<td>0.4</td>
<td></td>
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<tr>
<td>Agner H &amp; 2015</td>
<td>Iceland*</td>
<td>1995-2012</td>
<td>13.7</td>
<td>0.8 men, 0.4 women</td>
<td>↑ after 1990</td>
</tr>
<tr>
<td>Binder LE, 2015</td>
<td>UK***</td>
<td>2008-2011</td>
<td>7.8</td>
<td></td>
<td></td>
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<tr>
<td>Dal J, 2016</td>
<td>Denmark*</td>
<td>1999-2010</td>
<td>8.5 (in 2010)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Saito T, 2018</td>
<td>Italy**</td>
<td>2010-2016</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Nationwide, ** Regional, *** Geographically diverse (insurance claims)
Acromegaly affects both genders equally and median age at presentation is 40-47 years. 

Emory experience, patients operated between 1994-2016 by a single neurosurgeon

Acromegaly presents insidiously with typical features:
- Median time to diagnosis is 4.5-5 years
- Typical changes: coarse facial features, acral enlargement
- Several comorbidities:
  - Sleep apnea
  - Type 2 diabetes
  - Debilitating arthritis
  - Carpal tunnel syndrome
  - Hyperhydrosis
  - Hypertension
- Current clinical practice guidelines: screen for typical changes, but also several comorbidities (even in absence of typical changes)
My patient

- 33 yo F took OCP between 17-27 when she sought medical attention for oligomenorrhea and acne after stopping them
- Saw Endo ... dx with insulin resistance and PCOS... resumed OCP
- Sought help again for amenorrhea and infertility at 33
- Reproductive Endo work-up:
  - GH 138 ng/mL (nl: <8), IGF-1 745 ng/mL (nl: 71-252)
  - Retrospectively, she had hyperhidrosis x 4 years, acral enlargement x 2 years, along with headaches, fatigue, joint pain and weight gain
- Exam: classic acromegaly facial features and acral enlargement
- Photos: progressive physical changes over 6 years

My patient (cont)

- Transsphenoidal surgery (TSS) in 2009
- Path: pituitary adenoma, +GH, sparsely granular (SG)
- Postop: IGF-1 (not normalized), +tumor residual
- Tx w/ octreotide LAR 2010-2011
- Pituitary radiation in 2011
- Lanreotide depot 2011-2015
- Off somatostatin receptor ligands (SRL) since 2015 ... IGF-1 normal
- Developed hypopituitarism (takes HC, LT4 and OCP)

Emory experience 1994-2016

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men [%/N]</th>
<th>Women [%/N]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (years)</td>
<td>40.6 (10)</td>
<td>44.3 (15)</td>
<td>0.16</td>
</tr>
<tr>
<td>Transsphenoidal Surgery</td>
<td>84%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Maximal Headache</td>
<td>-</td>
<td>4%</td>
<td>0.61</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>-</td>
<td>1%</td>
<td>0.04</td>
</tr>
<tr>
<td>Retrospective</td>
<td>85%</td>
<td>78%</td>
<td>0.13</td>
</tr>
<tr>
<td>Tumor Enlargement %</td>
<td>11%</td>
<td>13%</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypothalamus Involvement</td>
<td>9%</td>
<td>10%</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumor Extension</td>
<td>18.3%</td>
<td>22.1%</td>
<td>0.15</td>
</tr>
<tr>
<td>Emotional Stress Factors</td>
<td>6%</td>
<td>6%</td>
<td>0.91</td>
</tr>
<tr>
<td>Tissue Weight (g)</td>
<td>8.4 (1.6)</td>
<td>11.7 (3.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean GH Levels</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.2)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Trends over 22 year span:
- Presentation with classical physical changes decreased after 2011 (54% vs 30%)
- Mean GH levels also decreased after 2011
Gender differences - Korean acromegaly study

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>1.1</td>
<td>1.2</td>
<td>0.25</td>
<td>1.1</td>
<td>1.2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Prevalence of acromegaly is increasing
Does this represent a true increase in disease incidence?
Proportion of patients who present with classical changes of acromegaly is decreasing
Endocrine 2014 clinical practice recommendations may have an effect on prevalence and disease presentation
Beware of the PCOS resemblance

Trends in epidemiology and presentation

Transsphenoidal Surgery (TSS): First-line Treatment for Acromegaly

Surgical Remission reported in approximately 50% cases
Current remission criteria:
- Age- and gender appropriate normal IGF-1 level
- GH suppression to OGTT < 0.4 ng/mL (with ultrasensitive GH assay)

Recurrence 4-12% cases
Acromegaly - Prognostic factors of postoperative remission

- Preoperative
  - Age, gender: TBD
  - Biochemical: GH, IGF-1 level
  - Radiological:
    - Diameter
    - Cavernous sinus invasion

- Postoperative
  - Immunohistochemistry:
    - PRL, CAM5.2, MIB-1
  - Biochemical:
    - POD2 GH level

Contrast and compare
Korean study (left) and Emory study (right)

Explanations:
Women returned for check-up more frequently than men (3.2±3.4 years vs. 3.6±3.6 years, p 0.02)
Response to medical treatment is influenced by gender and age

Cavernous sinus invasion and Knosp stages
<table>
<thead>
<tr>
<th>Study No.</th>
<th>Patients</th>
<th>Follow Up (months)</th>
<th>Remission Criteria</th>
<th>Preoperative Predictors of Biochemical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarker S. et al., 2014</td>
<td>113</td>
<td>33.5±26.8</td>
<td>GH &lt;1.0 ng/mL or GH &lt;0.4 ng/mL during OGTT</td>
<td>And Normal IGF-1</td>
</tr>
<tr>
<td>And Normal IGF-1</td>
<td></td>
<td></td>
<td></td>
<td>GH &lt;40ng/ml, Diameter &lt;2 cm, Non-invasiveness, Lack of suprasellar expansion</td>
</tr>
<tr>
<td>Sun H. et al., 2014</td>
<td>86</td>
<td>13.4±15.8</td>
<td>GH &lt;1.0 ng/mL or GH &lt;0.4 ng/mL during OGTT</td>
<td>GH and IGF-1, Microadenoma, Knosp stage</td>
</tr>
<tr>
<td>Shirvani M. et al., 2014</td>
<td>130</td>
<td>35.9±38.9</td>
<td>Postoperative day 1 GH &lt;2.5ng/mL and Normal IGF-1</td>
<td>Lack of cavernous sinus invasion</td>
</tr>
<tr>
<td>Jane J.A. et al., 2011</td>
<td>60</td>
<td>19 (2-68)</td>
<td>GH &lt;1.0 ng/mL or GH &lt;0.4 ng/mL during OGTT and Normal IGF-1</td>
<td>GH and IGF-1, Knosp stage</td>
</tr>
<tr>
<td>Kim M.S. et al., 2009</td>
<td>42</td>
<td>49.4 (3-178)</td>
<td>GH &lt;2.5 ng/ml and GH&lt;1.0ng/mL during OGTT and Normal IGF-1</td>
<td>GH, Diameter</td>
</tr>
<tr>
<td>Shimon I. et al., 2001</td>
<td>98</td>
<td>3.9±2.5</td>
<td>GH &lt;2 ng/ml and Normal IGF-1</td>
<td>GH, Diameter, Biermasz N.R. et al., 2000</td>
</tr>
<tr>
<td>Ahmed S. et al., 1999</td>
<td>139</td>
<td>60 (1-204)</td>
<td>GH nadir &lt;2 mU/L during OGTT or GH &lt;5 mU/L</td>
<td>GH, Diameter</td>
</tr>
<tr>
<td>Freda P.U. et al., 1998</td>
<td>57</td>
<td>65 (0.25-188)</td>
<td>GH nadir &lt;2ng/mL during OGTT Or Normal IGF-1</td>
<td>GH</td>
</tr>
<tr>
<td>Jenkins D. et al., 1995</td>
<td>89</td>
<td>48 (2-348)</td>
<td>GH &lt;5 mU/L</td>
<td>GH</td>
</tr>
<tr>
<td>Sheaves R et al, 1996</td>
<td>100</td>
<td>Mean 45.6 Mean GH &lt; 5 mIU/L (4-point day curve on postoperative day 7)</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>Tindall G.T. et al., 1993</td>
<td>103</td>
<td>102 ± 64</td>
<td>GH &lt;5 ng/mL and Normal IGF-1</td>
<td>Tumor stage</td>
</tr>
</tbody>
</table>

FBM: Hormone levels were adjusted for assay normal range. a: area under receiver operating characteristic ROC curve.

Fig. 1. The relationship between mean daily plasma GH and IGF-I levels in patients with clinically silent GH acromegaly. Dotted line shows the NHANES reference range. GH, IGF-I, and mean 24-hour GH levels correlate linearly until GH level reaches 20 ng/mL. Receiver Operator Statistics Curve for preoperative GH and IGF-1 levels as predictors of long-term remission.
Prediction models - preoperative parameters

- Model 1: diameter and cavernous sinus invasion - AUC 0.800
- Model 2: GH level, tumor diameter and cavernous sinus invasion - AUC 0.933

- GH threshold in our series 40 ng/mL
  - Sensitivity 97%
  - Specificity 42%

- Other studies:
  - Freda et al, 1998: GH ≤ 10 ng/mL – 80-90% remission; GH 20-50 ng/mL – 50% remission; GH ≥ 200 ng/mL – no remission
  - Jurin et al, 2015: GH < 10 ng/mL – 100% remission; GH 10-30 ng/mL – 18.2% remission
  - Sarkar et al, 2014: GH threshold not specified

Prediction models - postoperative parameters

- Early risk stratification pre- and immediately postoperatively is possible and may favorably impact outcomes
- Both biochemical (GH level) and radiological parameters (size, invasion) are important
- Approximately half of the patients will need medical treatment postoperatively
- Mortality in acromegaly and most complications correlate with biochemical activity

Surgical treatment for acromegaly
Somatostatin Receptor Ligands (SRL)

- Cornerstone of medical tx for acromegaly
- First-generation SRL (affinity SSTR2>SSTR3, 5)
  - Octreotide LAR
  - Lanreotide Depot
  - Normalize IGF-1 as monotherapy in up to 50% patients
- Next generation SRL (affinity SSTR5>SSTR1, 2, 3)
  - Pasireotide LAR

Long-acting Octreotide and Lanreotide normalize GH/IGF-1 in 20-40% patients

Response to Octreotide/Lanreotide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect on Response</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
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<tr>
<td>- Age</td>
<td>Old &gt; Young patients</td>
<td>More aggressive tumors</td>
</tr>
<tr>
<td>- Gender</td>
<td>Women &gt; men</td>
<td>SSTR2 up-regulation by estrogen</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
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<tr>
<td>- T2 hyperintensity</td>
<td>Decreased response</td>
<td>Sparse granulation pattern</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Granulation pattern</td>
<td>Densely &gt; Sparsely</td>
<td>SSTR2, adenyly cyclase, E-collents, post-translational modifications of GH receptor</td>
</tr>
</tbody>
</table>

Mutations

- AIP gene
- SSTR5 gene

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Effect on Response</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- AIP gene</td>
<td></td>
<td>Sparse granulation, ZAC1 expression</td>
</tr>
</tbody>
</table>

- H/LAT (H/L-1) index

- SSTR2 expression

- SSTR5 expression
Correlation of tumor markers with clinical outcomes in patients with acromegaly: single center experience (Ioachimescu A et al, Endocrine Society poster presentation)

Response to first generation SRL:
- best predicted by SSTR2 in >80% cells and densely granular pattern (AUC 0.960)
- not associated with hall 5, p53, SSTR5, MITF, or PRL immunoreactivity

Pasireotide LAR versus Octreotide LAR
Biochemical Remission at 12 months

Figure 1. Proportion of patients in the overall population, postulating dopamine release and dopamine release with CGI > 2.5 ml/L and normal GHR after 12 months of treatment with pasireotide LAR or octreotide LAR. Y-axis = 1 - 107 pasireotide LAR is referable LAR in the overall population. The study was not powered to detect treatment differences in subgroups. A. The CGI of the CGI in favor of pasireotide LAR treatment was 5.34% vs 1.14% (P = 0.0001) for continued pasireotide LAR treatment patients. B. 7.54% patients D1 >4700 but not diabetic patients D1 4.1-14 not demonstrate the CGI of 5.34% vs 1.14% (P = 0.0001) for continued pasireotide LAR treatment patients.
Pasireotide LAR versus Octreotide LAR
Tumor control

Pasireotide versus Octreotide
Mean Glucose Levels
Dopamine Agonists for Acromegaly

- Bromocriptine not very effective (<10% patients)
- 2011 cabergoline meta-analysis:
  - 15 trials, 237 pts
  - doses 0.5-7.0 mg/week
- Patients treated with CAB alone:
  - Only 35% pts had hyperPRL at baseline
  - Only 30.5% had a mixed GH-PRL adenoma
- Predictors of success:
  - Lower IGF-1 @ baseline (<150% above nl)
  - Prior XRT

Cabergoline alone - 34% normalized IGF-1

![Graph showing dose response and normalization of IGF-1 levels](image1.png)

Doses used by responders:
- 2.5 ± 1.4 mg/wk

Cabergoline and fg-SRL combination - 52% normal IGF-1

![Graph showing normalization of IGF-1 levels with combination therapy](image2.png)
Pegvisomant

- GH receptor antagonist
- Daily subcutaneous injection
- IGF-1 levels for dose titration (not GH)
- Normalizes IGF-1 in most patients after dose titration
  - Higher doses needed for biochemically severe acromegaly, women, higher BMI and DM
- Improves glucose metabolism
- Side effects:
  - Abnormal liver tests
  - Injection site reactions

Older pegvisomant studies

Acrostudy (1288 patients)

Phase III study:
- 89% patients treated with 20 mg daily reached nIgF-1 at 3 months
Open-label extension study study (N=160):
- 97% patients treated with 40 mg daily reached nIgF-1 (up to 18 months)

Freda PU, Endocr Pract, 2015

Pegvisomant does not target the pituitary tumor

- Some patients experience tumor growth, especially if SRL stopped
- Repeat MRI 6 months after starting pegvisomant
Choice of Medical Treatment in Acromegaly

- Fg-SRLs (octreotide and lanreotide) effective as monotherapy in up to 50% patients and may decrease tumor size.
- Next-generation SRL (pasireotide) may be more effective than fg-SRL, but frequently associates hyperglycemia.
- Dopamine agonist (cabergoline) may be effective in patients with mild biochemical acromegaly or in combination with other acromegaly medications.
- Pegvisomant normalizes IGF-1 in most patients, but further tumor growth may occur.
- Individualized treatment requires evaluation of all aspects of disease.

Thank you!
diagnosis and management of diabetes insipidus

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consultant: Cumberland, Ferring, Otsuka
advisory board: Corcept, Otsuka
data safety board: Ferring
grant support: NIA, NCATS

prevalence & incidence of diabetes

diabetes mellitus
1.6% ages 20-39 to 19.3% ages 75+
15-20,000,000+ cases

diabetes insipidus
1 per 10-15,000 population (0.005-0.01%) 
15-20,000 cases

the number of cases of DI is <0.1% of DM, and has not increased substantially for >50 years
diabetes insipidus: etiologies

disorders of inappropriately decreased AVP or AVP effect

central diabetes insipidus
nephrogenic diabetes insipidus
primary polydipsia
gestational diabetes insipidus
osmoreceptor dysfunction

neurogenic (central) DI

• rare, prevalence <1:25,000
• hypothalamic lesion in ~40-50% (tumor, sarcoidosis, histiocytosis)
• pituitary lesions are generally not sufficient to cause DI until postoperatively
• idiopathic in 20-30% (probable autoimmune process in most of these)
• genetic <5% (often delayed onset)
DI with an intrasellar lesion

- metastatic tumor (lung, breast, lymphoma)
- pituitary apoplexy
- rapidly enlarging pituitary tumor (usually hemorrhage without full apoplexy picture)
- pituitary abcess
etiology of DI in 79 pediatric patients

Maghnie et al, NEJM 343:998-1007, 2000

lymphocytic Infundibuloneurohypophysitis

biopsy of the pituitary stalk in a patient with idiopathic DI and pituitary stalk thickening

immunostaining using a monoclonal antibody directed against a T lymphocyte antigen (CD45-RO)

Imura et al, NEJM 329:683-9, 1993
Langerhans’-cell histiocytosis

presentation with DI

10 months later

2 years later

Maghnii et al. NEJM 343:998-1007, 2000

Di Iorgi et al. J Clin Endocrinol Metab 99:1264-72, 2014

progression of pituitary stalk thickening by MRI

n=43 idiopathic CDI

Di Iorgi et al. J Clin Endocrinol Metab 99:1264-72, 2014

high frequency of anterior pituitary deficits (81.4% in the first 2 years) is highly correlated with the degree of pituitary stalk thickening

Table 1. Frequency of Anterior Pituitary Hormone Defects During Follow-Up Based on Pituitary Stalk Size at Diagnosis of Idiopathic CDI

<table>
<thead>
<tr>
<th>Hormone Deficit</th>
<th>Normal (n=49)</th>
<th>Marked (n=24)</th>
<th>Markedly (n=7)</th>
<th>Total (n=70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>0.01 (0.00)</td>
<td>0.05 (0.01)</td>
<td>&lt;0.05 (0.01)</td>
<td>&lt;0.001 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (mIU/L)</td>
<td>0.01 (0.00)</td>
<td>0.05 (0.01)</td>
<td>&lt;0.05 (0.01)</td>
<td>&lt;0.001 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>0.01 (0.00)</td>
<td>0.05 (0.01)</td>
<td>&lt;0.05 (0.01)</td>
<td>&lt;0.001 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>0.01 (0.00)</td>
<td>0.05 (0.01)</td>
<td>&lt;0.05 (0.01)</td>
<td>&lt;0.001 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total number</td>
<td>4 (11%)</td>
<td>6 (11%)</td>
<td>6 (11%)</td>
<td>6 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>3 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>3 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>3 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
<td>3 (11%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Normal, between 1.5 and 3.0 mm; marked, between 3.1 and 5.0 mm, and marked, between 5.1 and 6.0 mm.
1. The probability of development of anterior pituitary hormone deficits is associated with pituitary stalk size at the time of diagnosis.
2. All subjects (< 30) with at least 1 hormone deficit during follow-up have a 20% deficit.
evaluation and follow-up of a thickened pituitary stalk with CDI

1. blood and CSF ACE, AFP and β-HCG levels
2. CSF cytology ± flow cytometry, AFB culture
3. CXR/chest CT
4. bone survey

if above are all negative, repeat MRI every 6 months for 2 years, and then yearly for 1-3 years; assess anterior pituitary function yearly; if stalk thickening persists, repeat CXR and bone survey yearly; consider biopsy of pituitary stalk if stalk thickening exceeds 6.5 mm at any time

nephrogenic (renal) DI

• even less common than neurogenic DI
• familial:
  • X-linked recessive: AVP V2-receptor mutation
  • autosomal dominant: aquaporin-2 mutation
• acquired:
  • hypercalcemia (Ca** > 13)
  • hypokalemia (K+ < 2.5)
  • drugs (lithium, demeclocycline)

mutations in the AVP V2 receptor gene associated with hereditary nephrogenic DI

primary polydipsia

• most common cause of polyuria in Western countries
• dipsogenic DI:
  • reset thirst threshold (mass lesions, granulomatous disease, idiopathic, aging)
• psychogenic DI:
  • increased fluid intake for reasons other than true thirst
  • schizophrenia: psychosis-intermittent hyponatremia-polydipsia (PIP) syndrome

diabetes insipidus: diagnosis

diabetes insipidus is a syndrome characterized by hypotonic polyuria:

• 24-h urine volume ≥50 ml/kg under conditions of ad lib intake
• urine S.G. <1.010, Uosm <300 mOs/m/kg H₂O
• absence of solute diuresis (dipstick negative for glucose)

Failure to meet any of these criteria (24 h urine) renders further evaluation unnecessary
plasma osmolality is usually normal in patients with all causes of polyuria

Robertson, Endo Metab Clin NA 24:549, 1995

if the posterior pituitary “bright spot” is seen, <5% likelihood of central DI

water deprivation tests

1. overnight (outpatient):
   - withhold all fluids after dinner until the next morning
   - measure AM serum [Na⁺] and urine osmolality
   - Uosm >800 eliminates DI, >600 effectively does in most cases as well

2. formal (inpatient):
   - withhold all fluids until BW decreases by 3-5%, urine osmolality plateaus X 2-3 successive measurements, or serum [Na⁺] >145 mmol/L
   - administer AVP (6 U) or dDAVP (1 μg) sc and follow urine osmolality and volume for 2 more hours
   - Uosm increase >50% following AVP/dDAVP indicates central DI, <10% indicates nephrogenic DI, intermediate responses (10-50%) are equivocal
water deprivation test: interpretation

Verbalis, Posterior Pituitary.
In: Cecil Textbook of Medicine, 4th edition, 2011

AVP regulation of water reabsorption from renal tubular cells

failure of patients with CDI, or primary polydipsia, to concentrate urine maximally in response to DDAVP until several days of therapy is due to AQP2 down-regulation

Kishore et al, AJP 271:F62-F70, 1996
plasma AVP levels can differentiate CDI from other types of polyuria, but only when plasma osmolality is >295 mOsm/kg

Robertson, Endo Metab Clin Nth 1995

combined water deprivation test

- withhold all fluids until BW decreases by 3-5%, urine osmolality plateaus X 2-3 successive measurements, or serum [Na+] >145 mmol/L.
- if serum [Na+] is not >145 mmol/L by the end of the test, infuse 3% NaCl (0.1 ml/kg/min) X1-2h until it is
- draw a plasma AVP level, Posm and Uosm both at the start and finish of the test, then administer AVP (5 U) or dDAVP (1 μg) sc and follow urine osmolality and volume for 2 more hours
- analyze basal and post-deprivation AVP levels in relation to both plasma and urine osmolalities for proper diagnosis
vasopressin gene encodes a 145 aa prohormone that is enzymatically cleaved into the 9 aa active hormone, plus neurophysin and a glycoprotein (copeptin)

baseline AVP and copeptin levels both differentiate NDI from CDI and PP

stimulated AVP and copeptin levels following fluid deprivation
144 patients with hypotonic polyuria were tested both with indirect water deprivation (cutoff of 3% increase post desmopressin) and hypertonic saline infusion (250 ml bolus of 3% NaCl followed by 0.15 ml/kg/min to a target of 150 mmol/L, copeptin cutoff of 4.9 pmol/L).

Hypertonic saline-stimulated copeptin levels diagnostic accuracy 96.5% vs 76.6% for indirect water deprivation test.

In difficult cases a short trial of dDAVP while following serum [Na+] levels can identify patients with primary polydipsia; but because [Na+] can fall quickly, electrolytes must be checked 1-2 days after starting dDAVP.
diabetes insipidus: postoperative and post-traumatic

patterns of postoperative and post-traumatic DI

pituitary stalk section:

1. interruption of axons prevents stimulation of AVP release from the nerve endings: DI
2. degeneration of the posterior pituitary releases stored AVP nonspecifically: SIADH
3. once all the stored AVP is released, AVP synthesis is impaired or absent in the damaged neurons: DI

experimental DI in dogs: polyuria does not develop until >85% of all hypothalamic vasopressin neurons are destroyed

Heinbecker & White, Am J Physiol 133:582-593, 1941

triphasic response isolated second phase
Hyponatremia occurs in ~20% of patients 5-9 days following transphenoidal surgery.

Olson et al., J Clin Endocrinol Metab 80:85-91, 1995

Diabetes insipidus: adipsic

Cerebral osmoreceptors

**selective osmoreceptor dysfunction:**
AVP secretion absent to osmotic stimulation, but normal to hypovolemic stimulation

Baylis, Principals and Practice of Endocrinology, 1995

Stricker & Verbalis, Fundamental Neuroscience, 2003
**diabetes insipidus: therapy**

Water

**antidiuretic agents**
- AVP
- desmopressin (DDAVP)

**antidiuresis enhancing agents**
- chlorpropamide
- carbamazepine
- indomethacin
**desmopressin dosing**

**parenteral (sc or iv)**
- 1-2 mcg q 12 h

**intranasal**
- 10-20 mcg q 8-12h

**oral**
- 100-200 mcg (0.1-0.2 mg) q 6-8 h
- 1 h before or 2 h after meals

**post-op DI: initial diagnosis**
- urine volume >250 ml/h for two consecutive hours
- urine S.G. <1.005, Uosm <200 mOsm/kg H₂O
- absence of solute diuresis (dipstick negative for glucose)
- serum [Na⁺] > 145 mmol/L

Do not administer desmopressin (DDAVP) for the first time until all of these criteria are met

**post-op DI: redosing DDAVP**
- urine volume >250 ml/h for two consecutive hours
- urine S.G. <1.005, Uosm <200 mOsm/kg H₂O
- absence of solute diuresis (dipstick negative for glucose)
- serum [Na⁺] > 145 mmol/L

DO NOT PLACE PATIENTS ON A STANDING DOSE OF DDAVP UNTIL STABLE
female rats express twice as much V₂R mRNA and protein as males


females are more sensitive to low doses of desmopressin

Advances in NASH
Disease Burden, Diagnostic/Management Considerations, and Emerging Therapies

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- Patent holder: None
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- Plan to discuss investigational/off-label uses of drugs or devices? N

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Meredith Hawkins, MD, MS
Professor of Medicine
Harold and Muriel Block Chair in Medicine
Director, Global Diabetes Institute
Co-Director, Einstein Diabetes Research Center
Albert Einstein College of Medicine
Bronx, NY

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- You must indicate a unique identification number to attend this lecture:
  - MD/GUPA = NPI Number
  - Other = NPI or State License Number (if available)
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  - Disclosure policy
  - Disclosures of content faculty, reviewers, and planners

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- Reminder email communications will be sent up to 5 days post lecture until the evaluation is completed
- Incomplete evaluations may preclude attendees from receiving their CME certificate & future communications about lectures in your area
- In addition, you will receive a long-term evaluation via email 8 to 12 weeks after completing this course to measure competence, performance, and/or patient outcomes achieved as a result of your participation in this CME sponsored educational activity

(Please note: If you attended multiple Simply Speaking® lectures throughout the year, a separate initial and long-term evaluation will be sent to you for each lecture.)

Learning Objectives (CME)

- Upon completion of this educational activity, participants should be able to:
  - Identify patients with liver disease, specifically non-alcoholic steatohepatitis/NASH/non-alcoholic fatty liver disease (NAFLD)
  - Discuss appropriate diagnostic and staging tests for patients with suspected NASH/NAFLD according to the practice guidance provided by the American Association for the Study of Liver Diseases (AASLD)
  - Discuss important counseling, treatment, and referral priorities in patients with NASH/NAFLD
  - Discuss first-line therapies for patients with NASH/NAFLD
Overview

- Burden of disease
  - Diagnostic considerations
  - Management approaches
  - Emerging therapies

Fatty Liver Disease

- Alcoholic (ALD)
- Nonalcoholic Fatty Liver (NAFL)
- Nonalcoholic Steatohepatitis (NASH)

NAFL and NASH

- NAFL
  - Hepatic steatosis (excess fat accumulation in liver) which can progress to steatohepatitis
  - No causes of secondary hepatic fat accumulation (e.g., significant alcohol accumulation, use of steatogenic medication, or hereditary disorder)
- NASH
  - Steatohepatitis defined by histology (hepatocyte injury, inflammation, and fibrosis)
  - Can be due to multiple etiologies which can be present alone or in combination
  - Most common cause of fibrosis/cirrhosis with unexplained increased ALT levels
  - Insulin resistance and metabolic syndrome
  - Commonly associated with obesity, diabetes, hypertension, and/or insulin resistance
  - Less common causes of NASH
  - Medical/surgical conditions or drugs

In the US:

- 3rd leading cause of cirrhosis
- 2nd most common indication for liver transplantation


NAFL and NASH

- NAFL
  - Hepatic steatosis (excess fat accumulation in liver) which can progress to steatohepatitis
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  - Insulin resistance and metabolic syndrome
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  - Less common causes of NASH
  - Medical/surgical conditions or drugs
Estimated Global Prevalence of NAFLD: 25%

- General population prevalence estimated by indirect means:
  - Liver biopsy not feasible for this purpose
  - Meta-analysis (n=15 studies of NAFLD patients)
  - NASH diagnosed by histology
  - NASH prevalence among NAFLD patients: 50%
  - Estimated NASH prevalence in general population: 1.45% to 8.45%

Estimated Global Prevalence of NASH

- NASH Prevalence Among NAFLD Patients

Risk Factors Associated With NAFLD

- Obesity
- Type 2 diabetes
- Dyslipidemia
- Metabolic syndrome* 
- Polycystic ovary syndrome

- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreaticobiliary resection
- Pericarditis

*ATP III definition (requires the presence of ≥3 of the following features):
1. Waist circumference >102 cm in men or >88 cm in women;
2. Triglyceride level ≥150 mg/dL;
3. HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women;
4. SBP ≥130 mm Hg or DBP ≥85 mm Hg;
5. Fasting plasma glucose level ≥110 mg/dL.

*Biopsy indicated (elevated liver enzymes, clinical signs of liver disease, or retrospective biopsy assessment from tertiary care centers). Biopsy not indicated (based on study design: biopsy offered to all identified NAFLD patients or offered by random selection).
Risk Factors for NASH Among NAFL Patients

**Main Factors**
- Obesity
- Older age
- Female sex
- Non-African American race/ethnicity
- Diabetes mellitus
- Hypertension

**Other Factors**
- High AST/ALT
- Low platelet count
- Elevated C-peptide level
- Ultrasound steatosis score

Comorbidities Associated With NASH: Global Prevalence Among NAFLD Patients

NASH is Associated With a High Burden of Metabolic Comorbidities

- Obesity: 87%
- Type 2 Diabetes: 44%
- Hypertension: 79%
- Dyslipidemia: 60%
- Metabolic Syndrome: 75%

PRELHIN Study: Cardiovascular Disease Is the Most Common Cause of Death/Liver Transplantation in NAFLD/NASH

- Cardiovascular Disease: 38%
- Non-Liver Cancer: 19%
- Other: 14%
- Complications: 8%
- Infections: 8%
Predictors of All-Cause and Liver-Related Mortality in Biopsy-Proven NAFL/NASH

NASH Patients Have a Higher Risk of Liver-Related Mortality Than NAFL Patients

Overall Mortality | Liver-Related Mortality | Cardiac Mortality

<table>
<thead>
<tr>
<th>NAFL (n=118)</th>
<th>NASH (n=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23%</td>
<td>38%</td>
</tr>
<tr>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

NASH patients have a higher risk of liver-related mortality than NAFL patients.

Overall Mortality: NASH HR 6.3 (P=0.0003) NAFL HR 0.65 (P=0.09)

Liver-Related Mortality: NASH HR 1.13 (P=0.8)

NAFLD/NASH: Why It’s Important for Patients With Type 2 Diabetes

- NAFLD/NASH prevalence: 2-3 fold higher versus non-diabetics
- Faster progression to NASH and advanced fibrosis
- NASH is associated with increased overall and liver-related mortality (type 2 diabetes increases the risk of both)
- Established link between type 2 diabetes, cirrhosis, and HCC
- Type 2 diabetes: 2-4 fold higher prevalence rates of cirrhosis and HCC
- Presence of NAFLD in type 2 diabetics
  - Significantly increases the risk of cardiovascular disease
  - Promotes dyslipidemia, hyperinsulinemia
  - Subclinical inflammation

Type 1 and 2 Diabetes: NAFLD Prevalence and Metabolic Associations

- Post-hoc analysis of baseline data from 4 phase 3 trials (n=589)
- Type 1 diabetes (IMAGINE 1 and 2); insulin-naive type 2 diabetes (IMAGINE 2); insulin-experienced type 2 diabetes (IMAGINE 5)
- Mean hepatic fat fraction: 2.0% versus 15.0% versus 10.2%, respectively
- NAFLD: hepatic fat fraction ≥6% by MRI
- NAFLD associated with several markers of insulin resistance
  - Higher triglycerides, ALT, and plasma free fatty acid levels
  - Lower adiponectin levels
- No association of HbA1c with hepatic fat content, but insulin doses were higher in patients with NAFLD
High Prevalence of NAFLD in Type 2 Diabetics With Normal AST/ALT Levels

- Cohort of type 2 diabetics with normal AST/ALT levels (n=103)
  - No prior diagnosis of NAFLD
  - Other causes of liver disease excluded
  - Male (80%), obese (70%)
- Liver triglyceride content by 1H-MRS

- Overall prevalence of NAFLD: 50%
  - Prevalence increased with increasing BMI ($P<0.001$)
  - NASH prevalence: 36%

- Confirmation of results from larger studies is needed

Potential implications for need of early screening for liver disease in type 2 diabetics


Prevalence of NAFLD in Type 2 Diabetics With Normal AST/ALT

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese</td>
<td>36%</td>
</tr>
<tr>
<td>30-34.9</td>
<td>36%</td>
</tr>
<tr>
<td>35-39.9</td>
<td>68%</td>
</tr>
<tr>
<td>≥40</td>
<td>90%</td>
</tr>
</tbody>
</table>

Metabolic Impact of NASH in Obese Type 2 Diabetics

- Adipose Tissue Insulin Resistance Index

<table>
<thead>
<tr>
<th>Group</th>
<th>Insulin Resistance Index (mmol/L·µU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese controls</td>
<td>3.8</td>
</tr>
<tr>
<td>Obese</td>
<td>4.2</td>
</tr>
<tr>
<td>No NAFLD</td>
<td>6.3</td>
</tr>
<tr>
<td>NAFL</td>
<td>6.6</td>
</tr>
<tr>
<td>NASH</td>
<td>7.1</td>
</tr>
</tbody>
</table>

- Hepatic Insulin Resistance Index

<table>
<thead>
<tr>
<th>Group</th>
<th>Hepatic Insulin Resistance Index (mg·kg⁻¹·µU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese controls</td>
<td>12</td>
</tr>
<tr>
<td>Obese</td>
<td>14</td>
</tr>
<tr>
<td>No NAFLD</td>
<td>21</td>
</tr>
<tr>
<td>NAFL</td>
<td>25</td>
</tr>
<tr>
<td>NASH</td>
<td>31</td>
</tr>
</tbody>
</table>

NASH CRN: Factors Associated With Different Stages of Fibrosis in NAFLD/NASH

- Observational study (2004-2008; n=693 with liver biopsy obtained within enrollment)
- Suspected or histologically-proven NAFLD
- Factors associated with definite NASH
  - Women, diabetes, met the NCEP criteria for the metabolic syndrome
  - Higher levels of AST, ALT, GGT, triglycerides, HbA1c, HOMA-IR
  - Lower levels of HDL-C
- Factors associated with advanced fibrosis
  - Older patients, diabetes, hypertension, increased waist circumference
  - Metabolic syndrome (NCEP criteria) was not associated with advanced fibrosis

Estimated Transition Rates in NAFLD: Non-Diabetic and Diabetic Patients

Non-Diabetic
- 25% of US population have NAFLD
  - 40% - 25% NAFLD
  - 70% - 25% NASH
  - 10% - 15% Cirrhosis
  - 2% - 14% HCC
  - 2% - 14% Liver Transplant

Diabetic
- 10% of NAFLD patients have diabetes
  - 40% to 84% of diabetics have NAFLD
  - 60% - 20% NAFLD
  - 60% - 25% NASH
  - 1% - 5% Cirrhosis
  - 10% - 14% HCC
  - 0% - 2% Liver Transplant

Mortality:
- 10% - 20% Non-Diabetic
- 10% - 15% Diabetic

The exact circumstances under which patients with NASH can progress or regress is not well defined.
In general, the progressive course of NASH has been closely linked to the increasing number of metabolic comorbidities, especially type 2 diabetes.

Changing Trends in Chronic Liver Disease Indications for Liver Transplantation in the US

- In 2016, ALD became the leading chronic liver disease indication for liver transplantation
- ALD and NASH combined accounted for 51% of all additions to the waitlist
- Total number of liver transplants/year continues to rise
- Sharp decline in HCV-related liver transplant waitlist additions and surgeries
- NASH continues to grow as an indication for liver transplantation

NASH and HCC

- NASH is an etiology of HCC
- NASH-HCC prevalence is increasing, but relatively uncommon
- Routine HCC screening among NASH patients is not recommended at this time
- Main risk factors for NASH-HCC
  - Older age
  - Type 2 diabetes
  - HCC is the most common cancer among diabetics
  - Advanced fibrosis
  - Obesity
  - Almost doubles HCC risk

References:
NASH and HCC

- NAFLD/NASH-related HCC
  - ~5-months shorter survival time, higher incidence of CVD, and more likely to die from primary liver cancer versus HCC due to other causes
- HCC in NASH is influenced by the presence of cirrhosis
  - Cumulative incidence of HCC
    - Range: 2.4%-12.8% over 3.2-7.2 years
  - Cumulative mortality due to HCC
    - Range: 0%-3% over 5.6-21 years
- Magnitude of HCC risk in non-cirrhotic NASH remains to be defined

Changing Burden of NAFLD/NASH in the US

Overview

- Burden of disease
- Diagnostic considerations
  - Management approaches
- Emerging therapies
AASLD Practice Guidance: Screening for NAFLD in Primary Care, Diabetes, and Obesity Clinics

- Routine screening for NAFLD in high-risk groups
  - Not advised because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening
  - There should be a high index of suspicion for NAFLD/NASH in type 2 diabetes
    - Clinical decision aids can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis)
    - NAFLD fibrosis score (NFS)
    - Fibrosis-4 index (FIB-4)
    - Vibration controlled transient elastography (VCTE)


Considerations in the Diagnosis

NAFLD

- No significant alcohol consumption
- No competing etiologies for steatosis and coexisting chronic liver disease
- Imaging evidence of hepatic steatosis
- Aminotransferases may or may not be elevated
- Carefully consider presence of associated comorbidities
  - Obesity, dyslipidemia, insulin resistance or diabetes, hypothyroidism, polycystic ovary syndrome, and sleep apnea

NASH

- Beyond NAFLD criteria, liver biopsy is needed to establish presence of NASH
- Steatohepatitis defined by histology (hepatocyte injury, inflammation, and fibrosis)
- Can be due to multiple etiologies which can be present alone or in combination
  - Most common cause of fibrosis/cirrhosis with unexplained increased ALT levels
  - Commonly associated with obesity, diabetes, hyperlipidemia, and/or insulin resistance


Histopathology of NASH: Necessary Components for a Diagnosis

- Steatosis (≥5%)
  - Macro>Micro
  - Accentuated in zone 3
  - Periporal areas usually spared in early disease

- Lobular Inflammation
  - Any degree (mild, mild-moderate, severe)
  - Scattered polymorphonuclear leukocytes typically in portal areas
  - Macrophages and multinucleated giant cells

- Hepatocellular Ballooning
  - Markedly enlarged oval hepatocytes
  - Typically zone 3

Symptoms and Signs of NASH

- NASH is usually a silent disease with minimal symptomatology
- Symptoms and signs may emerge as the disease becomes advanced
  - Fatigue, weight loss, general malaise, and abdominal pain
  - Potential complications of NASH
    - Fibrosis
    - Cirrhosis
    - Variceal hemorrhage
    - Sepsis
    - Hepatocellular carcinoma
    - Liver failure

Pathomechanisms During Progression to NASH

Factors Associated With Fibrosis Progression
Grading and Staging of NASH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Steatosis</th>
<th>Ballooning</th>
<th>Intralobular Inflammation</th>
<th>Portal Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Up to 50%</td>
<td>Occasional zone 3</td>
<td>Scattered polymorphs ± lymphocytes</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Any degree</td>
<td>Predominantly zone 3</td>
<td>Polymorphs and chronic inflammation noted</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Predominantly zone 3</td>
<td>Scattered polymorphs ± mild chronic inflammation</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Staging:
- 1: zone 3 perisinusoidal/pericellular fibrosis, focal or extensive.
- 2: zone 3 perisinusoidal/pericellular fibrosis + focal or extensive periportal fibrosis.
- 3: zone 3 perisinusoidal/pericellular fibrosis + portal fibrosis + bridging fibrosis.
- 4: cirrhosis.

NAFLD Activity Score (NAS)

- NAS is not a tool to diagnose NASH
- NAS was designed to use in clinical research to measure histologic changes over time
- Histologic grading and staging system for NAFLD
- Semi-quantitative measure of disease activity and acknowledges that steatosis, inflammation, and ballooning are key drivers of disease activity

<table>
<thead>
<tr>
<th>NAS Components</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis (%)</td>
<td>0</td>
</tr>
<tr>
<td>5 to 33</td>
<td>1</td>
</tr>
<tr>
<td>&gt;33 to 66</td>
<td>2</td>
</tr>
<tr>
<td>&gt;66</td>
<td>3</td>
</tr>
<tr>
<td>Lobular Inflammation (foci/200x field)</td>
<td>0</td>
</tr>
<tr>
<td>2 to 4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;4</td>
<td>2</td>
</tr>
<tr>
<td>Ballooning</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Few balloon cells</td>
<td>2</td>
</tr>
<tr>
<td>Many balloon cells</td>
<td>3</td>
</tr>
</tbody>
</table>

Noninvasive Predictors of Advanced Fibrosis in NAFLD

Serum-Based Tests
- AST to Platelet Ratio Index (APRI)
- BARD score
- Enhanced Liver Fibrosis (ELF) score
- FibroTest (FibroSure)
- FibroMeter
- HepaScore
- NAFLD fibrosis score (NFS)

Serum-Based Tests
- FIB-4
- APRI
- BARD score
- Enhanced Liver Fibrosis (ELF) score
- FibroTest (FibroSure)
- FibroMeter
- HepaScore
- NAFLD fibrosis score (NFS)
Clinical Performance Characteristics of Non-Invasive Predictors of Advanced Fibrosis in NAFLD

<table>
<thead>
<tr>
<th>Test Method</th>
<th>AUROC F2-F4</th>
<th>AUROC F4</th>
<th>Externally Validated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proprietary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APRI</td>
<td>0.74</td>
<td>0.75</td>
<td>+++</td>
</tr>
<tr>
<td>BARD</td>
<td>0.78</td>
<td>0.78</td>
<td>+++</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.90</td>
<td>0.82</td>
<td>+++</td>
</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>0.85</td>
<td>0.85</td>
<td>+++</td>
</tr>
<tr>
<td>Proprietary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELF</td>
<td>0.86</td>
<td>0.86</td>
<td>+</td>
</tr>
<tr>
<td>Fibrometer</td>
<td>0.94</td>
<td>0.94</td>
<td>+</td>
</tr>
<tr>
<td>FibroTest</td>
<td>0.80</td>
<td>0.91</td>
<td>+</td>
</tr>
<tr>
<td>HepaScore</td>
<td>0.81</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Imaging Techniques for Evaluating Hepatic Steatosis

- Ultrasound
- Computed tomography
- Magnetic resonance imaging
  - Percent fat calculations
  - Estimated protein-density fat-fraction
  - Magnetic resonance spectroscopy
- Controlled attenuation parameter
  - FibroScan

Use All Available Resources to Access Fibrosis: No Single Test Accurately Assesses Hepatic Fibrosis

- Serum markers of fibrosis
- AST/ALT ratio
  - >0.8 suggests advanced fibrosis if no alcohol (F3/F4)
  - APRI (AST/ULN divided by platelet count x 100)
    - >2 suggests cirrhosis
- Platelet count
  - <150,000 suggests portal hypertension
- CT/MR-ultrasound
  - Splenomegaly or PV diameter >11 mm suggests portal hypertension
- Elastography
  - ≥7.5-<10 kPa suggests moderate fibrosis (F2)
  - ≥10-<14 kPa suggests pre-cirrhosis (F3)
  - ≥14 kPa suggests cirrhosis (F4)
AASLD Practice Guidance: Evaluation of Patients With NAFLD

Noninvasive Assessment of Advanced Fibrosis
- Metabolic syndrome
  - Strong predictor for the presence of steatohepatitis in NAFLD patients
  - Its presence can be used to target NAFLD patients for a liver biopsy
- NAFLD score or FIB-4 index
  - Clinically useful to identify those with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)
- Vibration controlled transient elastography (VCTE) or magnetic resonance elastography (MRE)
  - Clinically useful to identify advanced fibrosis
- Consider liver biopsy
  - NAFLD patients at increased risk of having steatohepatitis and/or advanced fibrosis
  - Suspected NAFLD patients where competing etiologies for hepatosteatosis and the presence and/or severity of coexisting chronic liver diseases cannot be excluded without a liver biopsy
- Non-invasive assessments that may be used to identify those at risk for steatohepatitis and/or advanced fibrosis
  - Presence of metabolic syndrome, NAFLD score or FIB-4, or liver stiffness measured by VCTE or MRE

Liver Biopsy: Technical Considerations
- Liver biopsy remains the "suboptimal" gold standard to characterize liver histology in NAFLD/NASH
  - Confirms the diagnosis and staging of disease
  - Determines prognosis by severity of liver injury and fibrosis
  - Limitations: high cost, potential complications, sampling/reader error
- Ideal specimen
  - ≥2 cm in length
  - 16 or 14 gauge needle (1.4 mm wide)
  - ≥11 portal tracts should be represented to get accurate assessment of fibrosis
- If cirrhosis is suspected, a cutting rather than a suction needle is recommended
- Absence of key finding from liver biopsy does not necessarily rule out a suspected diagnosis

A Clinical Model for NASH and Advanced Fibrosis in Diabetics
- Cross-sectional analysis of NASH CRN in patients with biopsy-proven NAFLD (n=1249; of these, 346 had type 2 diabetes)
  - Prevalence of NASH and advanced fibrosis among type 2 diabetics: 69% and 41%
- Developed predictive models for the presence of NASH and advanced fibrosis in diabetic patients with NAFLD
  - Correctly classified 67% and 77% of patients with NASH and advanced fibrosis, respectively
  - Model performed better than NAFLD fibrosis score in detecting advanced fibrosis

Predictive Model Performance in Diabetic Patients With NAFLD

<table>
<thead>
<tr>
<th></th>
<th>NASH</th>
<th>Advanced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>57</td>
<td>48</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Positive Predictive Value (%)</td>
<td>75</td>
<td>50</td>
</tr>
</tbody>
</table>
AASLD Practice Guidance: Clinical Practice Considerations

- Patients with NASH cirrhosis
  - Screen for gastroesophageal varices according to the AASLD and ACG practice guidelines
- Cirrhosis suspected because of NAFLD
  - Consider HCC screening according to the AASLD practice guidelines
- Current evidence does not support
  - Routine screening and surveillance for HCC in NASH patients without cirrhosis
  - Routinely repeating a liver biopsy in patients with NAFL or NASH, but this may be considered on a case-by-case basis


Overview

- Burden of disease
- Diagnostic considerations
- Management approaches
  - Emerging therapies

AASLD Practice Guidance: Whom to Treat

- Management of NAFLD should consist of treating liver disease and associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance, and type 2 diabetes
- Pharmacologic treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Dietary and lifestyle modification (basis of any management strategy, but challenging for many patients to achieve and maintain)
  - Weight loss (hypocaloric diet ± physical activity)
    - 2% to 5% loss: generally reduces hepatic steatosis
    - 7% to 10%: needed to improve most histopathologic features of NASH, including fibrosis
  - Exercise alone
    - May improve or reduce hepatic steatosis
    - Impact on liver histology is unknown

### Weight Loss Pyramid

- **25% Weight Loss**
  - NASH Resolution (64% to 95%)
  - Achieved by 18% in 1 Year
- **30% Weight Loss**
  - Ballooning/Inflammation (41% to 100%)*
  - Achieved by 30% in 1 Year
- **≥10% Weight Loss**
  - Achieved by <10% in 1 Year
  - 20% Weight Loss
  - Steatosis (35% to 100%)

*Depending on degree of weight loss.

### Carbohydrate-Restricted Diet: Impact on Hepatic Steatosis

- Isocaloric low-carbohydrate diet with increased protein content in obese NAFLD subjects
- Rapid and dramatic reductions in liver fat and other cardiometabolic risk factors paralleled by
  - Decrease in hepatic de novo lipogenesis
  - Increased serum b-hydroxybutyrate concentrations (increased mitochondrial beta-oxidation)
  - Increased folate-producing *Streptococcus* and serum folate concentrations
- Liver transcriptomic analysis (liver biopsy cohort)
  - Downregulation of the fatty acid synthesis pathway
  - Upregulation of folate-mediated one-carbon metabolism and fatty acid oxidation pathways


<30 g of carbohydrates and an average of 3,115 kcal/day for 14 days (n=10).
Multi-omics profiling.

### AASLD Practice Guidance: Ursodeoxycholic Acid and Omega-3 Fatty Acids

- **Ursodeoxycholic Acid**
  - Not recommended for the treatment of NAFLD or NASH
  - Offers no histologic benefit over placebo in NASH
- **Omega-3 fatty acids**
  - Should not be used as a specific treatment of NAFLD or NASH
  - Failed to show convincing therapeutic benefit in NAFLD
  - May be considered for treating hypertriglyceridemia in patients with NAFLD

### Non-Insulin Agents for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Non-Insulin Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-glucosidase inhibitors</strong></td>
<td>Acarbose, miglitol</td>
</tr>
<tr>
<td>Decrease carbohydrate absorption from intestine</td>
<td></td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>Decrease glucagon secretion</td>
<td></td>
</tr>
<tr>
<td>Slow gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Increase satiety</td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
</tr>
<tr>
<td>Decrease HGP</td>
<td></td>
</tr>
<tr>
<td>Increase glucose uptake in muscle</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Colesevelam</td>
</tr>
<tr>
<td>Decrease HGP?</td>
<td></td>
</tr>
<tr>
<td>Increase incretin levels?</td>
<td></td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Alogliptin, linagliptin, saxagliptin, sitagliptin</td>
</tr>
<tr>
<td>Increase glucose-dependent insulin secretion</td>
<td></td>
</tr>
<tr>
<td>Decrease glucagon secretion</td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 agonist</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>Activates dopaminergic receptors</td>
<td></td>
</tr>
<tr>
<td>Glinides</td>
<td>Nateglinide, repaglinide</td>
</tr>
<tr>
<td>Increase insulin secretion</td>
<td></td>
</tr>
<tr>
<td>GLP1 receptor agonists</td>
<td>Albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide</td>
</tr>
<tr>
<td>Increase glucose-dependent insulin secretion</td>
<td></td>
</tr>
<tr>
<td>Decrease glucagon secretion</td>
<td></td>
</tr>
<tr>
<td>Slow gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Increase satiety</td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Canagliflozin, dapagliflozin, empagliflozin</td>
</tr>
<tr>
<td>Increase urinary excretion of glucose</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride, glipizide, glyburide</td>
</tr>
<tr>
<td>Increase insulin secretion</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td>Increase glucose uptake in muscle and fat</td>
<td></td>
</tr>
<tr>
<td>Decrease HGP</td>
<td></td>
</tr>
</tbody>
</table>

ADA. *Diabetes Care*. 2018;41(suppl 1):S73-S85.

DPP4: dipeptidyl peptidase; HGP: hepatic glucose production; GLP1: glucagon-like peptide; SGLT2: sodium-glucose cotransporter.

### Agents Available for Type 2 Diabetes: Effects on NAFLD-Related Factors

<table>
<thead>
<tr>
<th>Potential Beneficial Impact on NAFLD</th>
<th>Lack of Beneficial Impact on NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAFLD Benefit</strong></td>
<td><strong>Hypoglycemia</strong></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Moderate</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Neutral</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Neutral</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Neutral</td>
</tr>
</tbody>
</table>


DPP4: dipeptidyl peptidase 4; GLP1: glucagon-like peptide 1; SGLT2: sodium-glucose cotransporter.

### AASLD Practice Guidance: Use of Insulin Sensitizers to Treat NAFLD/NASH

- Metformin is not recommended for treating NASH in adult patients
  - Improves serum aminotransferases and IR, but does not significantly improve liver histology

- Thiazolidinediones
  - Pioglitazone improves liver histology in patients with and without type 2 diabetes with biopsy-proven NASH
  - It may be used to treat these patients (counsel patients on risks and benefits)
  - Pioglitazone should not be used to treat NAFLD without biopsy-proven NASH
  - More data on safety and efficacy are needed

- Glucagon-like peptide-1 analogues
  - It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH

**Thiazolidinediones**

- Improve insulin resistance through different pathways
- Promote the differentiation of insulin-resistant large pre-adipocytes into small and insulin-sensitive adipocytes
- Reduce inappropriate fat storage in muscle and adipocyte tissue with subsequent improvement in insulin sensitivity despite the expansion in fat mass
- Upregulate production of adiponectin, an insulin-sensitizing and anti-steatogenic adipokine that increases fatty acid beta-oxidation in liver and muscle


**Glucagon-Like Peptide-1 Analogue: Liraglutide**

- GLP-1
  - Controls serum glucose
  - Induces insulin secretion
  - Reduces glucagon secretion
  - Induces weight loss, suppression of appetite and delayed gastric emptying


**LEAN Study: Liraglutide in Overweight NASH Patients Without Cirrhosis**

- Double-blind, placebo-controlled phase 2 study (n=52)
- Histologic evidence of definite NASH
- Patients stratified by diabetes status
- Liver biopsy within 6 months of entry
- No Child-Pugh B/C cirrhosis
- Liraglutide or placebo for 48 weeks
- Primary endpoint (week 72, ITT)
  - Improvement in liver histology without worsening of fibrosis
  - Improvement: disappearance of hepatocellular ballooning
  - Worsening of fibrosis: any increase in Kleiner fibrosis stage

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=26)</th>
<th>Placebo (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>35</td>
<td>58</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean NAFLD score (0-8)</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Hepatocyte ballooning score (0-2)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Steatosis score (0-3)</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Fibrosis stage (0-4)</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>F0-F2</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>F3-F4</td>
<td>46</td>
<td>58</td>
</tr>
</tbody>
</table>

LEAN Study: Changes in Histologic Features at Week 48

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NASH Resolution (Primary Outcome)</th>
<th>NAFLD Activity Score</th>
<th>Inflammatory Infiltration</th>
<th>Steatosis Lobular Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (n=23)</td>
<td>9%</td>
<td>34%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Placebo (n=22)</td>
<td>39%</td>
<td>32%</td>
<td>26%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Patients (%)

AASLD Practice Guidance: Vitamin E

- Vitamin E (rrr α-tocopherol) 800 IU/day
  - May be considered for nondiabetic adults with biopsy-proven NASH (counsel patients on risks and benefits)
  - Improves liver histology, but not fibrosis
  - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy are needed


NASH CRN PIVENS Trial: Pioglitazone Versus Vitamin E in Biopsy-Proven NASH

- Phase 3 study in biopsy-proven NASH (n=247)
  - No diabetes or cirrhosis
  - Pioglitazone, vitamin E, or placebo for 96 weeks
- Key outcomes versus placebo
  - Vitamin E significantly improved histologic features of NASH (primary outcome); no benefit with pioglitazone
  - Vitamin E and pioglitazone
    - No difference in fibrosis improvement
    - Significantly reduced ALT, AST, and hepatic steatosis (P<0.001)

Main Outcomes


PIVENS: Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis.
Impact of Pioglitazone in Biopsy-Roven NASH in Patients With Prediabetes or Diabetes

- Double-blind, placebo-controlled, single-center study in biopsy-proven NASH (n=101)
  - Prediabetes or type 2 diabetes mellitus
  - Pioglitazone 45 mg/day or placebo for 18 months, then open-label pioglitazone for another 18 months
  - Primary outcome at 18 months
    - Reduction of at least 2 points in 2 histologic categories of the NASH without worsening of fibrosis
  - Key outcomes versus placebo
    - Pioglitazone significantly improved histologic features of NASH (primary outcome) and greater percentage of patients achieving NASH resolution versus placebo
    - Improvement was maintained during open-label extension


AASLD Practice Guidance: Bariatric Surgery

- Foregut bariatric surgery
  - Can be considered in otherwise eligible obese individuals with NAFLD or NASH
  - It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH
  - Cirrhosis attributed to NAFLD
    - Type, safety, and efficacy of foregut bariatric surgery in otherwise eligible obese are not established
  - In otherwise eligible patients with compensated NASH or cryptogenic cirrhosis
    - Foregut bariatric surgery may be considered on a case-by-case basis by an experienced bariatric surgery program


Long-Term Effects of Bariatric Surgery on Liver Injury in Patients Without Advanced Disease

- Prospective study (1994-2005; n=381; 99 with probable or definite NASH)
  - Severely obese patients who underwent bariatric surgery
    - BMI >35 kg/m², no excessive alcohol (past or current), no chronic liver disease, no cirrhosis
    - ≥5-year history of arterial hypertension or diabetes mellitus
  - Liver biopsy 1 to 5 years after surgery
  - 5-years after bariatric surgery in NASH patients
    - Significantly improved NASH steatosis, ballooning, and NAS
    - 88% of patients maintained a fibrosis score ≤1
    - Decreased those with NASH from 27% to 14%

AASLD Practice Guidance: Management of CVD and Dyslipidemia in NAFLD/NASH

- Patients with NAFLD are at high risk for cardiovascular morbidity and mortality
- Aggressive modification of CVD risk factors should be considered in all patients with NAFLD
- Statin use in NAFLD and NASH
  - Patients are not at higher risk for serious liver injury from statins
  - Statins can be used to treat dyslipidemia
  - Avoid statin use in patients with decompensated cirrhosis


Overview

- Burden of disease
- Diagnostic considerations
- Management approaches
- Emerging therapies

Current and Potential Therapeutic Targets in NASH

- Liraglutide (GLP-1)
- BMS-986036 (FGF-21)
- NGM-282 (FGF-19)
- Tesamorelin (GHRH)
- Pioglitazone
- Elafibranor
- Saroglitazar
- Obeticholic Acid
- GS-0976
- GS-9674
- Pentoxifylline
- Emricasan
- Selonsertib
- Cenicriviroc
- Simtuzumab
- GR-MD-02
- IMM-124e
- Fecal Microbiota Transplantation
- Orlistat
- Sevelamer
- Volixibat
- Solithromycin
Investigational Agents for NASH

**Metabolic Homeostasis**
- Insulin sensitizer
- Farnesoid X receptor (FXR) agonist
- Peroxisome proliferator-activated receptor (PPAR) agonist
- Fibroblast growth factor (FGF) analogue
- Glucagon-like peptide-1 (GLP-1) analogue
- Acetyl-CoA carboxylase (ACC) inhibitor
- Stearoyl coenzyme A desaturase 1 (SCD) inhibitor
- Growth Hormone-Releasing Hormone
- Thyroid hormone receptor beta (THR-β) activation
- Apical sodium-dependent bile acid transport inhibitor

**Oxidative Stress**
- Antioxidant: Vitamin E
- Apoptosis signal-regulating kinase 1 (ASK1) inhibitor
- Vascular endothelial growth factor (VEGF) inhibitor
- Phosphodiesterase (PDE5) inhibitor

**Inflammation**
- C-C chemokine receptor (CCR) antagonist

**Apoptosis**
- Caspase inhibitor

**Fibrosis**
- Galectin-3 protein inhibitor

Agents in Registrational Trials

- Currently in phase 3 trials
  - Obeticholic acid
  - Elafibranor
  - Selonsertib
  - Cerivastatin
- AASLD Practice Guidance
  - Until further safety and efficacy data become available in patients with NASH, obeticholic acid should not be used off-label to treat NASH

FXR Agonist: Obeticholic Acid

Key FXR Pathways Described in Multiple Animal Models

**FLINT Study: Obeticholic Acid in NASH Patients Without Cirrhosis**

**Phase 2b (n=141)**
- Placebo-controlled
- Histologic evidence of definite or borderline NASH (liver biopsy within 90 days of entry)
- NAFLD activity score ≥4 (individual scores each ≥1)
- No cirrhosis

**Week 0**
- Obeticholic Acid 25 mg qd (n=141)
- Placebo (n=142)

**Patients stratified by diabetes status.**

**Primary endpoint (week 72, ITT):**
- Improvement in liver histology without worsening of fibrosis.
  - Improvement: decrease in NAFLD score ≥2 points.
  - Worsening of fibrosis: any increase in fibrosis stage.

**Changes in Histologic Features at Week 72**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Obeticholic acid (n=110)*</th>
<th>Placebo (n=109)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>21%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Definite NASH Resolution</strong></td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td>31%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Hepatocellular Ballooning</strong></td>
<td>35%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Steatosis Lobular Inflammation</strong></td>
<td>38%</td>
<td>61%</td>
</tr>
</tbody>
</table>

*Number of patients for changes in histologic features: obeticholic acid (n=102), placebo (n=98).

**PPARα/δ Agonist: Elafibranor**
- PPARα/δ regulate lipid metabolism in liver and glucose homeostasis
  - Control of lipid influx
    - Improves fatty acid oxidation
    - Lowers triglyceride level
  - Inhibit HSL, CPT1a
  - Induce inflammatory genes and increase necro-inflammatory activity
  - Activation of both PPARα/δ leads to improvement of different pathways to regulate liver metabolism involved in NASH pathogenesis

**PPARα Activation**
- Improves glucose homeostasis
- Inhibits hepatic lipogenesis
- Anti-inflammatory activity in macrophages and Kupffer cells

**PPARδ Activation**

**References:**
GOLDEN-505 Study: Elafibranor in NASH Patients Without Cirrhosis

Proof-of-Concept, Phase 2 (n=276) (US, EU)
Placebo-controlled
NASH (biopsy diagnosis)
Steatosis >5% hepatocytes
Hepatocyte ballooning
Lobular inflammation
NAS score 3-8
F0-F3
No cirrhosis

Week
Elafibranor 80 mg po qd (n=93)
Elafibranor 120 mg po qd (n=91)
Placebo (n=92)

Patients stratified by diabetes status.
Primary endpoint (week 52, ITT):
Reversal of NASH without worsening of fibrosis.
Reversal: absence (score of 0) of at least 1 of the 3 components of NASH (steatosis, ballooning, and inflammation).
Worsening of fibrosis: progression to bridging fibrosis or cirrhosis in patients without bridging fibrosis at baseline.
Post-hoc analysis of a modified definition of response:
Resolution of NASH: disappearance of ballooning (score 0), together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation.
Worsening of fibrosis: any stage increase in fibrosis.

GOLDEN-505 (Elafibranor in NASH Patients Without Cirrhosis): Response in More Severe NASH (NAS ≥4 at Baseline)

All Patients
End of Trial Liver Biopsy Patients

Apoptosis Signal-Regulating Kinase 1 Inhibitor: Selonsertib

- ASK1
  - Mitogen-activated protein kinase
  - Transmission of apoptotic signals under oxidative stress conditions
  - ASK1 pathway activated in NASH and correlates with fibrosis stage
  - Inhibition improves steatosis, inflammation, and fibrosis in rodent models
- Selonsertib
  - ASK1 EC50: 10.8 nM

Oxidative Stress and Unfolded Protein Response

- Hepatocyte injury
  - Inflammation
  - Hepatic stellate cell activation
  - Fibrosis

*Elafibranor 120 mg versus placebo.
Protocol-defined response results.

Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Elafibranor 80 mg</th>
<th>Elafibranor 120 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NAS ≥4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2/F3 Fibrosis</td>
<td>9%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>P = 0.01*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-F3 Fibrosis</td>
<td>13%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>P = 0.009*</td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td>71%</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>P = 0.001*</td>
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Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Elafibranor 80 mg</th>
<th>Elafibranor 120 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Baseline NAS ≥4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2/F3 Fibrosis</td>
<td>7%</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>P = 0.02*</td>
<td></td>
<td></td>
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<tr>
<td>F1-F3 Fibrosis</td>
<td>18%</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>P = 0.03*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>25%</td>
<td>33%</td>
<td>21%</td>
</tr>
<tr>
<td>P = 0.002*</td>
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Study 1497: Selonsertib ± Simtuzumab in NASH Patients Without Cirrhosis

Phase 2 (n=72) (US)
Open-label
Biopsy proven NASH
NAS ≥5 (individual scores each ≥1)
F2-F3 fibrosis
No cirrhosis

Endpoints:
- Fibrosis improvement in ≥1 stage.
- Fibrosis improvement without NASH worsening.
- Progression to cirrhosis.


Preliminary Results
- Selonsertib ± simtuzumab had beneficial effects (by biopsy) on:
  - Fibrosis improvement (≥1 fibrosis stage) and reduced progression
  - Generally well tolerated
    - No deaths
    - Discontinuations due to adverse events (15 versus 6 mg): 6% versus 3%
    - Serious adverse events (15 versus 6 mg): 3% versus 0%
    - Most common adverse events:
      - Headache, nausea, sinusitis, nasopharyngitis, abdominal pain, fatigue
  - Overall progression to cirrhosis: 7%

Data for patients with liver biopsies evaluable for fibrosis at baseline and week 24.

Study 3914: Selonsertib (ASK1 inhibitor) + GS-0976 (ACC inhibitor) or GS-9674 (FXR agonist) in NASH
Proof-of-concept study
Open-label
Clinical diagnosis of NAFLD
MRI-PDFF ≥10% and MRE ≥2.88 kPa
or biopsy consistent with NASH and F2-F3 fibrosis
No cirrhosis (FibroTest <0.75, histologic imaging and liver biopsy)

Demographics (median values):
- Age: 50-59 years
- Male: 33%
- BMI: 35-37 kg/m2
- Diabetes: 59%
- Glucose: 97-133 mg/dL
- HbA1c: 5.8%-7.7%
- Triglycerides: 151-208 mg/dL
- ALT/AST: 43-101/36-72 U/L
- MRI-PDFF: 15%-20%
- MRE-stiffness: 3.2-3.9 kPa

Study 3914: Selonsertib (ASK1 inhibitor) + GS-0976 (ACC inhibitor) or GS-9674 (FXR agonist) in NASH

- Combination regimens demonstrated beneficial effects in:
  - Hepatic DNL and steatosis
  - Liver biochemistry
  - Markers fibrosis
- Selonsertib + ACC inhibitor or FXR agonist was safe and well tolerated
- Ongoing phase 2 study


<table>
<thead>
<tr>
<th></th>
<th>Selonsertib (n=10)</th>
<th>GS-0976 (n=10)</th>
<th>Selonsertib GS-0976 (n=20)</th>
<th>GS-9674 (n=10)</th>
<th>Selonsertib GS-9674 (n=20)</th>
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<tbody>
<tr>
<td>DNL and FSR</td>
<td>Lumican FSR</td>
<td>-22</td>
<td>-16</td>
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<tr>
<td>MRI-PDFF</td>
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<td>-43</td>
<td>-16</td>
<td>-32</td>
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<td>Liver biochemistry</td>
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<td>ALT</td>
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<td>GGT</td>
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<td>-4</td>
<td>2</td>
<td>-19</td>
<td>10</td>
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</tbody>
</table>

DNL: de novo lipogenesis; FSR: fractional synthesis rate

Mean Relative (%) Change at Week 12

Boxed bolded values: P<0.05 versus within group baseline.

CCR Type 2/5 Antagonist: Cenicriviroc

- Activation of CCR type 2/5 receptors
  - Promotes recruitment and migration of monocytes to the liver
  - Matures into pro-inflammatory macrophages


- Leads to activation of:
  - Kupffer cells
  - Hepatic stellate cells
  - Collagen production
  - Fibrogenesis
CENTAUR Study: Cenicriviroc for Treatment of NASH

**Phase 2b (n=289)**
(US, EU, Australia, Hong Kong)

- **Double-blind**
- **Placebo-controlled**
- NASH (biopsy diagnosis)
- Biopsy-verified, NAS ≥4, fibrosis stage 1-3 (NASH-CRN)
- Stratified by NAS (4 or ≥5) and fibrosis stage (2 or ≥2)

**Primary Endpoint**
- Cenicriviroc 150 mg
- Placebo
- Cenicriviroc 150 mg
- Placebo
- Cenicriviroc 150 mg
- Placebo

**Secondary Endpoints**
- Improvement in fibrosis ≥1 stage (NASH-CRN) and no worsening of steatohepatitis
  - Achieved by significantly more cenicriviroc patients versus placebo (20% versus 10%; *P* = 0.02)

**Year-1 Primary Analysis:**
- Primary and Key Secondary Endpoint Results
  - No significant difference between cenicriviroc and placebo (16% versus 19%)
  - Complete resolution of steatohepatitis and no worsening of fibrosis stage
    - No significant difference between cenicriviroc and placebo (8% versus 6%)
  - ≥1 stage improvement in fibrosis (NASH-CRN) and no worsening of steatohepatitis
    - No significant difference between cenicriviroc and placebo (8% versus 6%)

**Year-2 Exploratory Analyses**
- ≥1 stage improvement in fibrosis (NASH-CRN) and no worsening of steatohepatitis
  - No significant difference between cenicriviroc and placebo after 2 years
  - ≥1 stage fibrosis improvement at year 1: patients who maintained this benefit through year 2
    - Cenicriviroc versus placebo (80% versus 30%)
  - Substantial “seesaw” effect in fibrosis improvement observed in serial biopsies in the placebo arm
  - Safety and tolerability of cenicriviroc was comparable to placebo
Summary

- Overall worldwide prevalence of NAFLD and NASH is 25% and 7%.
  - The most important risk factor is type 2 diabetes.
- NASH
  - Common comorbidities: obesity, type 2 diabetes, hyperlipidemia/dyslipidemia, hypertension, and metabolic syndrome.
  - Pathologic assessment remains the gold standard for diagnosis.
  - There should be a high index of suspicion for NAFLD/NASH in patients with type 2 diabetes.
  - Fibrosis stage is the strongest predictor for disease-specific mortality in NASH.
- Management of biopsy-proven NASH should begin with lifestyle modifications.
  - Bariatric surgery, vitamin E and pioglitazone may be useful.
  - Risks and benefits of these treatments should be weighed.
- New molecules targeting different pathways, such as liver metabolic homeostasis, inflammation, oxidative stress and fibrosis, are being tested for the treatment of NASH in ongoing clinical trials.

Evaluation and Outcomes Measurement Process

- You will receive an electronic initial evaluation to the email address provided within 1 business day.
- Reminder email communications will be sent up to 5 days post lecture until the evaluation is completed.
- Incomplete evaluations may preclude attendees from receiving their CME certificate & future communications about lectures in your area.
- In addition, you will receive a long-term evaluation via email 8 to 12 weeks after completing this course to measure competence, performance, and/or patient outcomes achieved as a result of your participation in this CME sponsored educational activity.

(Please note: If you attended multiple Simply Speaking™ lectures throughout the year, a separate initial and long-term evaluation will be sent to you for each lecture.)