Metabolic Syndrome for hepatologists: Looking beyond NAFLD

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Mayo 2019
Conflicto de interés


• Estudios Clínicos:
  Investigador principal
  - Estudio Resolve-it (Elafibranor in NASH, Genfit), coordinador nacional (Chile)
OUTLINE

✓ NAFLD and Metabolic syndrome

✓ Highlights from the AASLD/EASL/APASL meetings (few!)

✓ CV & Diabetes Risk in NAFLD

✓ The central role of the hepatologist in coordinated care for NAFLD

✓ Conclusions
NASH is a global problem that likely will increase as a health burden in the years to come.

NASH can progress to cirrhosis and hepatocellular cancer in 5–15% of patients.

NASH is rapidly becoming the leading cause for end-stage liver disease.

There are no FDA-approved therapies for NASH although there are many ongoing trials with different agents.
NAFLD and Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that identifies people at risk of diabetes and cardiovascular disease.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Ethnicity-specific definitions</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>$\geq 100 \text{ mg/dL and/or drug treatment of elevated glucose}$</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>$\geq 150 \text{ mg/dL and/or drug treatment for elevated triglycerides}$</td>
</tr>
<tr>
<td>Reduced HDL cholesterol</td>
<td>$&lt;40 \text{ mg/dL in men; } &lt;50 \text{ mg/dL in women}$</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Systolic $\geq 130$ and/or diastolic $\geq 85 \text{ mm Hg}$</td>
</tr>
</tbody>
</table>

Definition of MS: meeting at least 3 of the 5 criteria. Ethnicity specific definitions of elevated waist circumference; (1) Caucasian: 102 cm or greater in men and 88 cm or greater in women (2) Asian: 90 cm or greater in men and 80 cm or greater in women (3) Middle East, Mediterranean, African: 94 cm or greater in men and 80 cm or greater in women (4) Ethnic Central and South American: 90 cm or greater in men and 80 cm or greater in women.

NAFLD and Metabolic syndrome

✓ App 70% of NAFLD patients have MetS

✓ The prevalence of NAFLD in patients with MetS varies depending of the syndrome components (35-70%)

✓ MetS confers an increase risk of histology-confirmed NASH

Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD)

Figure 2. Kaplan-Meier survival curves for 23-years follow-up (average = 19 years) of 3613 NAFLD participants, by MS conditions, NHANES III, 2011 public-use linked mortality files. MS = metabolic syndrome, NAFLD = nonalcoholic fatty liver disease, NHANES = National Health and Nutrition Examination Survey.
Metabolic syndrome & NAFLD Patient Care

Cardiologists

Hepatologist/GI

Metabolic syndrome & NAFLD Patients

Internal Medicine

Primary Care

Endocrinologists

medicina.uc.cl
Lack of awareness of NAFLD: a serious problem

• Non-alcoholic fatty liver disease is not a benign disease (is a marker of metabolic dysfunction)

• A significant proportion of patients and physicians had little awareness of NAFLD and underestimate the prevalence and associated-risks of the disease\(^1,2\)

• Low rates of referral (70% of physicians made no referrals in two studies)\(^3,4\)

• Awareness of NAFLD must be promoted for prevention, for targeting ‘at-risk’ populations and stimulate early detection, appropriate referral and treatment

References:
Two independent national studies have reported high rates of liver disease progression and mortality among patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH).

German study: 11% of the NAFLD/NASH patients progressed to advanced liver diseases

French study: 5.6% of NAFLD/NASH patients progressing to more severe liver disease during 7 years of follow-up
NAFLD and Metabolic syndrome: Which come first?

The relationship between NAFLD and MS is complex and may be bidirectionally associated.

*J Hepatol. 2015 Apr;62(1 Suppl):S47-64*
NAFLD and Metabolic syndrome

Yki-Järvinen Y. Lancet Diabetes Endocrinol 2014; 2: 901–10
Effects of Alcohol Consumption and Metabolic Syndrome on Mortality in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease

A

No excessive alcohol, no MS

Reference

MS, no excessive alcohol

$\alpha$HR = 1.32 (1.04-1.68), $P = .022$

Excessive alcohol, no MS

$P = .72$

Excessive alcohol and MS

$\alpha$HR = 3.35 (2.02-5.55), $P < .0001$

$\alpha$HR (95% CI)
NAFLD is associated with a range of chronic diseases, most notably cardiovascular disease (CVD), diabetes mellitus type 2 (T2DM) and chronic kidney disease (CKD).

NAFLD can be detected early in life and predict the development of MetS.

Mechanisms are intertwined and difficult to dissect.

J Hepatol. 2015 Apr;62(1 Suppl):S47-64
FIGURE 2  NAFLD: A Multisystem Disease

NAFLD/NASH

- Kidney disease
- Heart disease
- Malignancy
- Overweight/obesity
- Type 2 diabetes mellitus
- Sleep apnea

Abbreviations: NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Central Illustration: Nonalcoholic Fatty Liver Disease Increasing Risk of Cardiovascular Disease: Pathophysiological Mechanisms

- ↑ ADMA
  - Impaired Redox Status
  - ↑ Homocysteine
  - ↑ Platelet Activation
  - ↑ Systemic Inflammation

- ↑ Plasma Free Fatty Acid Level

- ↑ Liver Fat Content
  - ↑ Hepatic Lobular Inflammation

- ↑ Hepatic Fatty Acid Accumulation

- ↓ Hepatic Insulin Signaling

- ↓ Hepatic Insulin Resistance

- ↑ Hepatic Glucose Production

- ↑ Hepatic Fatty Acid Accumulation

- ↑ Homocysteine
  - Impaired Redox Status

- ↑ Hepatic Insulin Resistance

- ↑ Hepatic Fatty Acid Accumulation

- Altered Vascular Tone
  - ↑ Systemic Inflammation
  - ↑ Prothrombotic Factors
  - ↑ Hepatic Angiogenesis & ↑ VEGF
  - ↑ Intestinal Dysbiosis and ↑ Secretion of Bile Acids, TMA, and Short Chain Fatty Acids into Bloodstream

- CVD
  - CV Events/Mortality
  - Atherosclerosis
  - Cardiomyopathy
  - Arrhythmias

- Systemic Insulin Resistance

- Endothelial Dysfunction

- Altered Lipid Metabolism

- Oxidative Stress

- Plaque Formation/Instability

- Systemic Inflammation
  - ↑ IL-6
  - ↑ M1/M2
  - ↑ hsCRP
  - ↑ CCL3
  - ↑ sICAM-1
  - ↑ TNFα
  - ↑ IL-1β

Increased cardiovascular mortality and morbidity are observed in NAFLD.

NAFLD is not only associated with, but also contributes to the pathogenesis (accelerant factor).

Subclinical cardiovascular alterations can be detected in NAFLD and screening is potentially cost-effective in selected patient-groups.

J Hepatol. 2015 Apr;62(1 Suppl):S47-64/JAAC 2019;73:948-63
### NAFLD/NASH & Cardiovascular mortality: selected studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of subjects</th>
<th>Diagnosis of NAFLD</th>
<th>Follow-up duration (yrs)</th>
<th>CVD risk</th>
<th>Primary cause of mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Söderberg(^1)</td>
<td>118</td>
<td>Histology</td>
<td>24 (median)</td>
<td>30%</td>
<td>CVD</td>
</tr>
<tr>
<td>Ekstedt(^2)</td>
<td>129</td>
<td>Histology</td>
<td>13.7±1.3 (mean)</td>
<td>2 fold</td>
<td>CVD</td>
</tr>
<tr>
<td>Dam-Larsen(^4)</td>
<td>170</td>
<td>Histology</td>
<td>20.4 (median)</td>
<td>38%</td>
<td>CVD</td>
</tr>
<tr>
<td>Rafiq(^5)</td>
<td>173</td>
<td>Histology</td>
<td>18.5 (median)</td>
<td>12.7%</td>
<td>CVD</td>
</tr>
<tr>
<td>Ekstedt(^6)</td>
<td>229</td>
<td>Histology</td>
<td>26.4</td>
<td>HR 1.55, 95% CI 1.11-2.15</td>
<td>CVD</td>
</tr>
</tbody>
</table>

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**Background and aims:** Cardiovascular disease (CVD) is the most common cause of death of non-alcoholic fatty liver disease (NAFLD) patients. CVD surveillance should be important in the management of NAFLD whereas it has not been well established. Moreover, association between the pathogenesis of CVD and NAFLD remains unclear. We evaluated carotid atherosclerosis and coronary artery stenosis (CAS) and tested utility of carotid ultrasonography for the surveillance of CAS in NAFLD.

**Method:** A total of 100 patients (56 females and 44 males; median age, 60 years old; median body mass index, 28.2 kg/m²) with liver biopsy-proven NAFLD were enrolled in this study. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were examined with FibroScan® in all patients. Maximum intima-media thickness including plaque (max IMT) was measured using ultrasonography. Coronary CT angiography was performed to detect CAS if max IMT > 1.0 mm. Association between pathogenesis of NAFLD and atherosclerosis/CAS was evaluated.

**Results:** Median of max IMT was 1.3 mm, and 60 patients showed max IMT > 1.0 mm and 39 patients showed max IMT > 1.5 mm. Max IMT significantly correlated with age (r = 0.39, p < 0.001). Max IMT of patients with advanced liver fibrosis (Kleiner fibrosis stage ≥ 2) was thicker than those with liver fibrosis ≤ 1 (1.62 mm vs. 1.13 mm, p < 0.05). Multivariate analysis indicated that age, sex and LSM were significant factors associated with max IMT. In the patients with max IMT ≥ 1.0 mm, 38.9% patients showed significant (75% stenosis or severe) CAS in coronary CT angiography. All patients with significant CAS showed max IMT ≥ 1.5 mm, and median max IMT of the patients with significant CAS was thicker than those without significant CAS (2.16 mm vs. 1.79 mm, p < 0.05) and liver fibrosis tended to be advanced in the patients with CAS (LSM, 16.3 kPa vs. 10.5 kPa; Fibrosis stage ≥ 2, 22.7% vs. 8.3%) whereas there were no differences in CAP (265 dB/m vs. 261 dB/m). In the multivariate analysis, max IMT was a risk of significant CAS independent to diabetes.

**Conclusion:** Prevalence of advanced carotid atherosclerosis is surprisingly high and carotid atherosclerosis and CAS relate to liver fibrosis in NAFLD. Surveillance of NAFLD with advanced liver fibrosis is important and carotid ultrasound could be useful to identify the patients with high risk of CAS and CVD.

*Based on multiple observational studies, patients with increased plaque burdens (increased CAC) are approximately ten times more likely to suffer a cardiac event over the next 3–5 years.
Nonalcoholic Fatty Liver Disease Contributes to Subclinical Atherosclerosis: A Systematic Review and Meta-Analysis

FIG. 3. Effect estimate for the association between NAFLD and increased CIMT or plaques using a random-effects model. Forest plot comparison of individuals without NAFLD versus patients with NAFLD. Red squares represent the OR, horizontal lines the CIs, black diamond represent the pooled OR.
Assessing CV risk in NAFLD

✓ Appropriate evaluation of CV risk factors is mandatory in all patients with NAFLD

✓ This assessment can be repeated every 1-2 years

✓ Aggressive modification of CVD risk factors when present

✓ Patients with NASH cirrhosis have high prevalence of CVD. Identification of sub-clinical CVD, should be attempted in any patient particularly during the pre-Tx evaluation

AASLD NAFLD guidance 2018
Assessing CV risk in NAFLD

How?

✓ Population-based scoring algorithms based on traditional risk factors

✓ Framingham Risk Score (FRS) has been validated in NAFLD
Modification of CVD risk factors in NAFLD

✓ Promote lifestyle changes
✓ Aim for a weight loss of up to 10%
✓ Aggressive modification of CVD risk factors when present
✓ Use statins when indicated
Statins are effective in reducing CVR and reduce mortality. Statins are rarely hepatotoxic. Emerging data suggest that these drugs may be even beneficial for NASH and cirrhosis.
Diabetes & NAFLD: a complex and bidirectional relationship

Patients with NAFLD should be screened for the metabolic syndrome and T2DM

Diagnosis of NAFLD suggested by:
- Elevated serum liver enzyme levels
- Ultrasonography
- Fibroscan
- Biomarkers*

Screening for...

- Insulin resistance
  - HOMA-IR

- Metabolic syndrome
  - Increased fasting blood glucose level
  - Hypertriglyceridaemia
  - Low HDL cholesterol level
  - Increased waist circumference
  - High blood pressure

- T2DM
  - HbA$_{1c}$
  - 75 g OGGT

Patients with T2DM are at very high risk for NAFLD

- Screening for NAFLD irrespective of serum liver enzyme levels
- Consider use of elastography

Tig, Moschen and Roden 2016
Causality between non-alcoholic fatty liver disease and risk of cardiovascular disease and type 2 diabetes: A meta-analysis with bias analysis

Amy E. Morrison¹ | Francesco Zaccardi¹,² | Kamlesh Khunti¹,² | Melanie J. Davies¹
Cardiometabolic issues in NAFLD: goals and interventions

**Diagnosis of NAFLD**

**Screen for Metabolic Risk Factors**

- **Obesity**  
  Body mass index >30

- **Diabetes Mellitus**  
  Hemoglobin A1c >6.5%, random glucose >200 mg/dL, or fasting glucose >126 mg/dL on 2 separate occasions

- **Dyslipidemia**  
  10-year atherosclerotic cardiovascular disease risk score >7.5%, LDL >190 mg/dL, or LDL >70-189 mg/dL with diabetes

- **Hypertension**  
  Blood pressure >140/90 mm Hg on at least 2 separate measurements

**Management Goals of Metabolic Risk Factors**

- **Obesity**  
  Weight loss of 7%-10% over 48%-52 weeks

- **Diabetes Mellitus**  
  Hemoglobin A1c <7.0% with lifestyle modifications +/- antiglycemic agent(s)

- **Dyslipidemia**  
  Treat using a moderate- to high-intensity statin. Expect 50% reduction in LDL from baseline using high-intensity statin. Expect 30%-50% reduction in LDL from baseline using moderate-intensity statin.

- **Hypertension**  
  Systolic blood pressure <150 or <140 mm Hg depending on age, presence of diabetes, and/or chronic kidney disease; diastolic blood pressure <90 mm Hg
The central role of the hepatologist in coordinated care for NAFLD

✓ Optimal NAFLD care: collaborative efforts (primary care, endocrinology, and cardiology)

✓ Increased awareness, early lifestyle intervention are needed

✓ Are we prepared?
Hepatologists & Coordinated Care For NAFLD

Primary Care
- Awareness
- Recognition
- Action
- Advocacy
- Healthcare design

Key clinical resources
- Ensure available elastographic tools
- Arrange nutritionist counselling
- Offer specific exercise programs

Develop partnerships:
- Bariatric surgery
- Endobariatrics
- Preventative cardiology
- Endocrinology

Healthcare Systems
- Active case-finding
- Electronic health supports
- Linkage to care

Collaborative Networks
- Streamlined referral systems
- Multidisciplinary clinics
- Shared conferences

Tapper & Loomba, 2018
CONCLUSIONS

✓ NAFLD AND MetS are closely associated

✓ The relationship is complex and bi-directional

✓ CV-related mortality is the first cause of death in NAFLD patients

✓ Incident diabetes is higher in NAFLD patients

✓ Appropriate evaluation and treatment of cardio-metabolic risk factors must be conducted in every patient with NAFLD
Coordinadores: Adrian Gadano & Marco Arrese

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