Is type 2 diabetes and NASH the same disease affecting different organs?

Pr Bertrand CARIOU, MD-PhD
L’unité de recherche de l’institut du thorax
Inserm UMR 1087 / CNRS UMR 6291
Nantes, France
DISCLOSURES

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NAFLD = T2D? What does it mean?
AGENDA

1. EPIDEMIOLOGICAL DATA
2. PATHOPHYSIOLOGICAL DATA
3. GENETIC DATA
4. THERAPEUTIC DATA
5. CONCLUDING REMARKS
AGENDA

1. EPIDEMIOLOGICAL DATA

2. PATHOPHYSIOLOGICAL DATA

3. GENETIC DATA

4. THERAPEUTIC DATA

5. CONCLUDING REMARKS
EPIDEMIOLOGY:
the same world-wide metabolic pandemia for T2D and NAFLD

Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)
EPIDEMIOLOGY:
the same world-wide metabolic pandemia for T2D and NAFLD

EPIDEMIOLOGY: a link between obesity and T2D and NAFLD

Figure 2 | Association between BMI and T2DM.

DeFronzo RA. et al. Nat Rev Dis Primers 2015; 1: 15019

Figure 3: Prevalence of NAFLD according to BMI, age, and sex

WHAT IT IS THE PREVALENCE OF NAFLD in T2D?

Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients

GIOVANNI TAIROLO, MD1,2
LORENZO BERTOLINI, MD1
ROBERTO PADOVANI, MD3
STEFANO RODELLA, MD3

Diabetes Care 30:1212–1218, 2007

N=939 patients

Prevalence of and Risk Factors for Hepatic Steatosis and Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: the Edinburgh Type 2 Diabetes Study

N=939 patients with T2

RESULTS—Hepatic steatosis was present in 56.9% of participants. After excluding those with a secondary cause for steatosis, the prevalence of NAFLD in the study population was 42.6%. Independent predictors of NAFLD were BMI, lesser duration of diabetes, HbA1c, triglycerides, and metformin use. These remained unchanged after exclusion of participants with evidence of hepatic fibrosis from the group with no hepatic steatosis.
Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE


Figure 1 | Prevalence of NAFLD and advanced fibrosis among patients with type 2 diabetes in primary care. Patients with type 2 diabetes in the primary care setting were screened for NAFLD with magnetic resonance imaging-estimated proton density fat fraction (MRI-PDF). NAFLD was defined by the presence of hepatic steatosis ≥5% on MRI-PDF. Screening for advanced fibrosis was performed using magnetic resonance elastography (MRE) with a threshold of 3.6 kPa to identify those with advanced fibrosis.
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1. EPIDEMIOLOGICAL DATA
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NAFLD / NASH  INSULIN RESISTANCE / T2D
Insulin Resistance and Metabolic Syndrome

Visceral Obesity

↑Free Fatty Acids

Insulin Resistance

Inflammation

Altered vascular reactivity

Impaired fibrinolysis

Type 2 Diabetes

Dyslipidemia

Hypertension

NASH

Accelerated Atherosclerosis

NASH = Nonalcoholic steatohepatitis

TG = Triglycerides; HDL = high-density lipoprotein; sdLDL = small dense LDL
RELATION BETWEEN LIVER FAT AND COMPONENTS OF METABOLIC SYNDROME

271 non-diabetic subjects (162 women, 109 men)
Liver fat assessed by proton MRI (spectroscopy)
RELATION BETWEEN LIVER FAT AND HEPATIC INSULIN RESISTANCE

45 non-diabetic men; hyperinsulinemic-euglycemic clamps

Fig. 4 Graph showing the relationship between percentage suppression of endogenous glucose production during the last hour of hyperinsulinaemia (300–360 min, log scale) and liver fat content (log scale) in individual participants (circles). r = -0.30, p<0.05
Patients with NAFLD display insulin resistance as in T2D.

FIG. 3. Glucose disposal in the course of the clamp and hepatic glucose production in the subgroup of subjects infused with [6,6-\(^3\)H\(_2\)]glucose. The subgroups—control subjects (CONT; open columns; \(n = 5\)), type 2 diabetic patients (DM2; shaded columns; \(n = 5\)), and NAFLD subjects (hatched columns; \(n = 10\))—are representative of the whole population. Black bars represent hepatic glucose production at the end of the clamp study. Data are presented as means and 95% CI.

Marchesini G. et al. *Diabetes* 2001; 50: 1844-50
Hepatic rather than intramyocellular fat content is associated with features of Met-S

Fig. 3 Bar graphs (log scale) showing liver fat (a) and IMCL (b) in participants without (−) and with (+) the metabolic syndrome (MS). **p<0.01 vs individuals without the metabolic syndrome.
SELECTIVE HEPATIC INSULIN RESISTANCE: A molecular basis for T2D

Brown MS & Goldstein JS. Cell Metab 2008; 7: 95-96
SELECTIVE HEPATIC INSULIN RESISTANCE:
A molecular basis for T2D

Brown MS & Goldstein JS. Cell Metab 2008; 7: 95-96
NAFLD/NASH: PATHOPHYSIOLOGY

Adipose tissue IR

Hepatic IR

CHRONIC OVERNUTRITION

- Insulin resistance
- Compensatory hyperinsulinemia
- Increased lipogenesis
- Etopic lipid deposition
- \(\beta\text{-cell dysfunction and apoptosis}\)
- Chronic hyperglycemia

NAFLD

T2D
NAFLD is a risk factor for new onset type 2 diabetes

Framingham cohort – 20 years follow-up

Table 4. Baseline ALT and AST and the OR of Developing Incident DM Over 20 Years of Follow-Up

<table>
<thead>
<tr>
<th>Overall sample</th>
<th>AST or ALT in the normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>Age/gender adjusted</td>
<td>1.41 (1.25–1.60)</td>
</tr>
<tr>
<td>MV adjusted*</td>
<td>1.33 (1.16–1.52)</td>
</tr>
<tr>
<td>+ glucose adjusted</td>
<td>1.25 (1.08–1.45)</td>
</tr>
<tr>
<td>+ interim weight change</td>
<td>1.33 (1.17–1.53)</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>Age/gender adjusted</td>
<td>1.72 (1.51–1.94)</td>
</tr>
<tr>
<td>MV adjusted*</td>
<td>1.48 (1.30–1.69)</td>
</tr>
<tr>
<td>+ glucose adjusted</td>
<td>1.42 (1.23–1.63)</td>
</tr>
<tr>
<td>+ interim weight change</td>
<td>1.48 (1.30–1.69)</td>
</tr>
</tbody>
</table>

NOTE. The OR of developing incident DM was calculated per 1 genderspecific SD increase in logtransformed aminotransferase levels.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; MV, multivariable.
*Adjusted for age, gender, smoking, menopause, alcohol use (g/day), BMI.

NAFLD is a risk factor for type 2 diabetes

13 218 non-diabetic Korean subjects followed during 5 years

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incident DM, n (%)</th>
<th>Model 1 Odds Ratio 95% Cls P Value</th>
<th>Model 2 Odds Ratio 95% Cls P Value</th>
<th>Model 3 Odds Ratio 95% Cls P Value</th>
<th>Model 4 Odds Ratio 95% Cls P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fatty liver at both baseline and at follow-up, no fatty liver (n = 7918)</td>
<td>39 (0.5%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatty liver at baseline but not follow-up (n = 828)</td>
<td>12 (1.5%)</td>
<td>2.63 (1.36, 5.07) .004</td>
<td>0.89 (0.44, 1.82) .75</td>
<td>0.98 (0.48, 2.02) .97</td>
<td>0.95 (0.46, 1.6) .89</td>
</tr>
<tr>
<td>No fatty liver at baseline, but fatty liver at follow-up (n = 1640)</td>
<td>35 (2.1%)</td>
<td>4.06 (2.55, 6.47) &lt;.001</td>
<td>2.86 (1.73, 4.71) &lt;.001</td>
<td>2.59 (1.56, 4.30) &lt;.001</td>
<td>2.49 (1.49, 4.14) &lt;.001</td>
</tr>
<tr>
<td>Fatty liver at baseline and at follow-up (n = 2832)</td>
<td>148 (5.2%)</td>
<td>9.93 (6.88, 14.35) &lt;.001</td>
<td>3.27 (2.14, 5.02) &lt;.001</td>
<td>3.13 (2.04, 4.81) &lt;.001</td>
<td>2.95 (1.91, 4.54) &lt;.001</td>
</tr>
<tr>
<td>Fatty liver at baseline and remaining static at follow-up (n = 2275)</td>
<td>98 (4.3%)</td>
<td>8.22 (5.55, 12.17) &lt;.001</td>
<td>2.97 (1.83, 4.81) &lt;.001</td>
<td>2.92 (1.80, 4.75) &lt;.001</td>
<td>2.78 (1.70, 4.53) &lt;.001</td>
</tr>
<tr>
<td>Fatty liver at baseline and worsening in severity at follow up (n = 324)</td>
<td>27 (8.3%)</td>
<td>15.6 (9.23, 26.18) &lt;.001</td>
<td>9.28 (4.42, 19.46) &lt;.001</td>
<td>7.82 (3.63, 16.86) &lt;.001</td>
<td>7.38 (3.36, 16.22) &lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus. Model 1 was adjusted for baseline age and sex. Model 2 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, and physical activity. Model 3 was adjusted for baseline age, sex, BMI, glucose, insulin, baseline triglycerides, HDL-C, systolic BP, alcohol, smoking, physical activity, and change in BMI between baseline and follow-up. Model 4 was adjusted for baseline age; sex; BMI; glucose; insulin; baseline triglycerides; HDL-C; systolic BP; alcohol use; smoking; physical activity; change in BMI between baseline and follow-up; and ALT, AST, and GGT.

Sung KC et al J Clin Endocrinol Metab 2013; 98: 3637-43
AGENDA

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NAFLD and T2D: a same disease? The dilemma of genetics
GENETICS OF T2D: THE GWAS ERA

Figure 1. Identification of T2D susceptibility genes.

GENETICS OF NAFLD: THE PREDOMINANT ROLE OF PNPLA3

Exome-wide association study with hepatic TG content in the Dallas Heart study (n=2736)

NAFLD does not always correlates with insulin resistance...

1. The SNPs rs738409 of PNPLA3 correlates with liver fat content BUT NOT with insulin sensitivity¹

2. PNPLA3 (Ile148 Met) impairs hepatic TG hydrolysis but does not associate with insulin resistance

3. A similar dissociation between liver fat content and insulin sensitivity is also observed with the E167K variant in TM6SF2² and in familial hypobetalipoproteinemia³

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...and cardiovascular diseases

PNPLA3 genotypes
100 patients with MetS and CC genotype (Gpe M)
100 patients with NAFLD and GG genotype (Gpe G)
100 controls with CC genotype

CIMT as primary endpoint

NAFLD is associated with an increased burden of subclinical atherosclerosis only when it is linked to MetS traits rather than when it occurs owing to the PNPLA3 rs738409 gene polymorphism

Life style changes improve both T2D and NAFLD

**Intervention**

- 750 kcal/day less than daily energy need
- 64% carbohydrates, 22% fat (< 10% SFA), 14% Prot
- Physical activity: 200 min walk /week

BARIATRIC SURGERY

362 patients who underwent bariatric surgery (gastric banding of RYGB)

➔ significant decrease of steatosis and ballooning
➔ maximal effect at 1 year
➔ early improvement of insulin resistance (QUICKI) is the best predictor of the long-term outcome
- Metformin is the first choice therapy in T2D regarding its hypoglycaemic efficacy and potential cardiovascular benefit (UKPDS 34)

- Metformin failed to demonstrate some clinical efficacy in NAFLD

Table 3. Change From Baseline to End of Treatment in Liver Histology by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E (n = 50)</th>
<th>Metformin (n = 50)</th>
<th>Placebo (n = 47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) improved</td>
<td>18 (57) [23 to 52]</td>
<td>22 (44) [30 to 59]</td>
<td>19 (40) [23 to 56]</td>
<td>.71</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−0.3 (−0.6 to 0.0)</td>
<td>−0.4 (−0.7 to −0.0)</td>
<td>−0.2 (−0.6 to 0.1)</td>
<td>.48</td>
</tr>
<tr>
<td>Steatosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) improved</td>
<td>27 (64) [39 to 88]</td>
<td>26 (62) [37 to 68]</td>
<td>19 (40) [23 to 56]</td>
<td>.18</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−0.8 (−1.1 to −0.5)</td>
<td>−0.6 (−0.9 to −0.2)</td>
<td>−0.4 (−0.6 to −0.1)</td>
<td>.24</td>
</tr>
<tr>
<td>Lobular infiltration score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) improved</td>
<td>22 (44) [30 to 59]</td>
<td>23 (49) [32 to 61]</td>
<td>20 (43) [29 to 58]</td>
<td>.69</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−0.4 (−0.6 to −0.2)</td>
<td>−0.3 (−0.5 to −0.0)</td>
<td>−0.3 (−0.6 to −0.1)</td>
<td>.14</td>
</tr>
<tr>
<td>Ballooning degeneration score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) improved</td>
<td>22 (44) [30 to 59]</td>
<td>22 (44) [30 to 59]</td>
<td>19 (40) [23 to 56]</td>
<td>.02</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−0.5 (−0.8 to −0.3)</td>
<td>−0.3 (−0.6 to −0.0)</td>
<td>0.1 (−0.2 to 0.3)</td>
<td>.006</td>
</tr>
<tr>
<td>Change in NASH Activity score, mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Resolution of NASH, No. (%) (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>.006</td>
</tr>
</tbody>
</table>

*Values derived from either χ² test for binary outcomes or analysis of covariance model assessing change from baseline to 96 weeks on treatment group and baseline value of the outcome for continuous outcomes.

Lavine JE et al. JAMA 2011
DIFFERENCES BETWEEN METFORMIN AND GLITAZONES MECHANISMS OF ACTION

Double-blind, randomized study in 20 drug-naïve T2DM patients, comparing metformin, 2g/j and Rosiglitazone 8g/j for 16 weeks

*Hyperinsulinemic-Euglycemic clamps*

⇒ Glitazones improve both hepatic and peripheral insulin sensitivity

Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis

M. O. Rakoski*, A. G. Singal*, M. A. M. Rogers† & H. Conjeevaram*

Table 2 | Summary of effect sizes (weighted mean difference) for all insulin sensitizers, glitazones and metformin compared with controls

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>All insulin sensitizers</th>
<th>Glitazones</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WMD* 95% CI</td>
<td>P-value</td>
<td>WMD* 95% CI</td>
</tr>
<tr>
<td>Primary outcome: histological response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>0.40 0.14, 0.65</td>
<td>0.003</td>
<td>0.57 0.36, 0.77</td>
</tr>
<tr>
<td>Ballooning</td>
<td>0.16 −0.031, 0.35</td>
<td>0.10</td>
<td>0.36 0.24, 0.49</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0.17 −0.15, 0.48</td>
<td>0.29</td>
<td>0.29 −0.05, 0.63</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.24 0.053, 0.42</td>
<td>0.011</td>
<td>0.21 −0.046, 0.46</td>
</tr>
<tr>
<td>Secondary outcome: biochemical and anthropometric response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>11.9 2.4, 21.5</td>
<td>0.004</td>
<td>16.4 7.70, 25.0</td>
</tr>
<tr>
<td>BMI</td>
<td>−1.23 −1.61, −0.85</td>
<td>&lt;0.001</td>
<td>−0.90 −1.59, −0.22</td>
</tr>
</tbody>
</table>

WMD, weighted mean difference; CI, confidence interval; DM, diabetes mellitus; ALT, alanine aminotransferase; BMI, body mass index.

* WMD: a positive WMD indicates greater improvement in the treatment group compared with controls.

Pioglitazone > Rosiglitazone on ballooning and fibrosis
GLP-1 R agonists and liver steatosis: molecular mechanisms

• It is unclear whether or not GLP-1 R is expressed in hepatocytes


• GLP-1 R agonists can improve steatosis in an indirect manner through body weight loss

• Pilot mechanistic study with liraglutide 1.8 mg/d (n=7) or PCB (n=7) in patients with liver biopsy-proven NASH

Armastrong ME et al. J Hepatol 2016; 64: 399-408

Hyperinsulinemic-euglycemic clamps

Human hepatocytes

Improved hepatic IR

Reduced lipolysis

Reduced hepatic DNL
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study


92 patients assessed for eligibility
40 excluded
1 did not meet histology inclusion criteria
27 did not meet other inclusion criteria
8 declined to participate

52 randomised

26 assigned to receive liraglutide
26 assigned to receive placebo
23 included in the analysis of primary outcome of histological improvement
22 included in the analysis of primary outcome of histological improvement

Disappearance of ballooning without worsening of fibrosis

35% of patients with T2DM
### Table 1 | Medical treatment modalities in NASH and T2DM

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Metformin</th>
<th>GLP-1</th>
<th>Thiazolidinediones</th>
<th>SGLT2 inhibitors</th>
<th>DPP4 inhibitors</th>
<th>Sulphonylurea</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose lowering efficacy</td>
<td>++</td>
<td>++</td>
<td>+ or ++</td>
<td>+ or ++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Hypoglycaemia risk</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Effect on body weight</td>
<td>Loss</td>
<td>Loss</td>
<td>Gain</td>
<td>Loss</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
<td>• Oedema</td>
<td>• Genitourinary infections</td>
<td>Pancreatic</td>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Heart failure</td>
<td>• Dehydration</td>
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<td>Liver-specific effects</td>
<td></td>
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</tr>
<tr>
<td>Steatosis</td>
<td>NE</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>NE</td>
<td>↑</td>
</tr>
<tr>
<td>Inflammation</td>
<td>NE</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Hepatocyte ballooning</td>
<td>NE</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>NE</td>
<td>NE</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>RCTs showing effectiveness in NAFLD</td>
<td>NE</td>
<td>Liraglutide</td>
<td>Pioglitazone</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Rosiglitazone)</td>
<td></td>
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</tr>
</tbody>
</table>

Diet and exercise should be advised for all patients, and continued throughout medical treatments. DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; ND, not done; NE, no effect; RCT, randomized controlled trial; SGLT2, sodium glucose co-transporter 2.
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TAKE HOME MESSAGES

• NAFLD is the « liver » feature of Metabolic syndrome (Met-S)

• **Selective hepatic insulin resistance** is the main underlying molecular common driver for both NAFLD and Met-S

• Interventions should target insulin resistance (« insulin sensitizers »)

• A tight **collaboration between diabetologists & hepatologists** is required
  - Hepatologists for screening Met-S and T2D in patients with NAFLD
  - Diabetologists for screening NAFLD and NASH in patients with T2D

• Genetics tell us that we need « Precision Medicine » to stratify NAFLD (rs738409 PNPLA3 vs other) and optimize therapeutic management
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables


Cluster-analysis with 6 variables: GAD antibodies, age at diagnosis, BMI, HbA1C, HOMA-IR & HOMA-B
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables


Cluster-analysis with 6 variables: GAD antibodies, age at diagnosis, BMI, HbA1C, HOMA-IR & HOMA-B

Prevalence of NAFLD in ANDIS estimated from ALT measurements
THANK YOU FOR YOUR ATTENTION
Organized by

Veronica Miller
UC Berkeley School of Public Health, Washington DC, USA

Arun Sanyal
Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

Lawrence Serfaty
Hôpital Hautepierre Hôpitaux Universitaires de Strasbourg, France

Scientific committee

Quentin Anstee
Pierre Bedossa
Jean-François Dufour
Scott Friedman
Fabio Marra
Manuel Romero-Gómez
Frank Tacke
Michael Trauner

With the partnership of

AFE F
Société francophone du diabète
THE FORUM