(free) CME/CPE/CEU-certified Breakfast Symposium

Managing NAFLD/NASH in People with T2 Diabetes:

Disease Burden • Diagnosis • Current & Emerging Armamentarium

at the American Diabetes Association's 83rd Scientific Sessions

Saturday, June 24, 2023
Breakfast 5:30am PT
Program 5:45 - 7:45am PT
Hilton San Diego Bayfront
Indigo Ballroom DH

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INTENDED AUDIENCE

Diabetologists, Endocrinologists, Hepatologists, Cardiologists, Primary Care Physicians, Physician Assistants, Nurse Practitioners, Pharmacists, Certified Diabetes Care and Education Specialists and other Health Care Professionals interested in the management of diabetes and liver disease.

EDUCATIONAL OBJECTIVES

At the conclusion of this program, participants will be better able to:

1. Recognize the burden of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) in patients with diabetes
2. Discuss comorbidities of persons with NAFLD and NASH
3. Identify current interventions and treatments in development for persons with NAFLD and NASH

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CHAIRPERSON

Understanding the ADA and other Clinical Care Guidelines for Management of NAFLD

Kenneth Cusi, MD, FACP, FACE

Professor of Medicine
Division of Endocrinology
Diabetes and Metabolism
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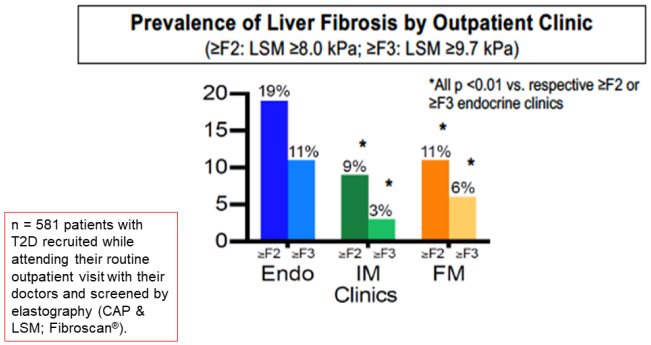
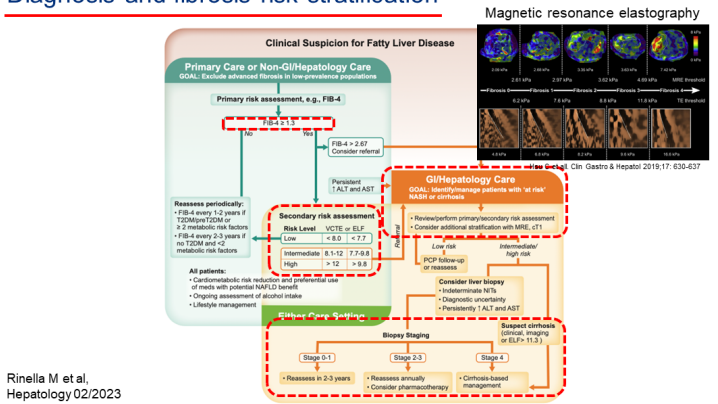
University of Florida
Gainesville, Florida

Role of the Endocrinologist and Diabetes Care Team:
Awareness about the high prevalence of fibrosis in endocrinology clinics



Dr Kenneth Cusi is a Professor of Medicine at the Division of Endocrinology, Diabetes and Metabolism in the Department of Medicine at the University of Florida. He received his medical degree in Argentina from the University of Buenos Aires School of Medicine and is board certified in both Internal Medicine and Endocrinology, Diabetes and Metabolism. He completed his residency at the Center of Medical Education and Clinical Research (CEMIC) in Buenos Aires, Argentina, and a clinical fellowship at Baylor College of Medicine in Houston. Prior to joining the University of Florida, Dr Cusi was a faculty for over 15 years at the Diabetes Division, University of Texas Health Science Center at San Antonio (UTHSCSA) and the Veterans Health Administration System in Texas; one of the leading diabetes programs in the country.

AASLD NAFLD 2023 Update:
Diagnosis and fibrosis risk stratification



He is a fellow of the American College of Physicians (ACP) and the American Association of Clinical Endocrinologists (AACE). He has actively participated in many clinical diabetes programs and in the training of many young researchers and clinicians. He is the principal investigator in ongoing NIH grants, investigator-initiated as well as multicenter industry-sponsored studies, with a focus on obesity, type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD).

Summary of Clinical Practice Guidelines (CPGs) in NAFLD
Take home message: A call to action

1. **Why NAFLD clinical practice guidelines now?**
   - People with obesity and T2D are at the highest risk of NASH, cirrhosis and hepatocellular carcinoma (HCC)
   - Screen today and treating early-on obesity and T2D can prevent cirrhosis and even HCC
2. **Clinical Practice Guidelines**
   - The new ADA recommendations and other recent guidelines highlight the need for routinely using FIB-4 +/- elastography in all patients with T2D and cardiometabolic risk factors
3. **Multidisciplinary teams**
   - The PCP, diabetologist/diabetes care team, and hepatologist must work together to initiate treatment as soon as possible of comorbidities
   - Treat obesity and T2D with GLP-1RA and/or pioglitazone and engage the patient in long-term follow-up

UF FLORIDA

Current Therapies and Novel Therapeutic Phase III Data

Juan Pablo Frías, MD

Medical Director
Principal Investigator
Velocity Clinical Research
Los Angeles, California

American Association for the Study of Liver Diseases (AASLD)

Practice Guidance on the Clinical Assessment and Management of NAFLD

Off-label use of approved medications for comorbid conditions

- There are **currently no FDA-approved medications for the treatment of NAFLD**, but drugs approved to treat associated comorbidities with potential benefit in NAFLD may be considered in the appropriate clinical setting
- **Semaglutide** can be considered for its approved indications (T2DM/obesity) in patients with NASH as it confers a cardiovascular benefit and improves NASH
- **Pioglitazone** improves NASH and can be considered for patients with NASH in the context of patients with T2D
- **Vitamin E** can be considered in select individuals as it improves NASH in some patients without diabetes
- Available data **on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit**, and these compounds have **not been carefully studied in patients with cirrhosis**

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Adapted from Rinella ME, et al.. Hepatology. 2023;77:1797-1835; Adapted from Table 7, p.1819. Summary of key concepts to guide clinical practice

Four agents currently in phase 3 of clinical development

Drug Name	Obeticholic Acid	Lanifibranor	Resmetirom	Semaglutide
Therapeutic class	FXR agonist	Pan-PPAR agonist	THRβ agonist	GLP-1 RA
Phase 3 trial name(s)	• REGENERATE • REVERSE	NATiV3	• MAESTRO-NAFLD 1 • MAESTRO-NAFLD-OLE • MAESTRO-NASH-Outcomes • MAESTRO-NASH	ESSENCE
Phase 3 histological endpoints (non-cirrhotic population)	At 72 weeks • At least 1 point improvement of fibrosis with no worsening of NASH *OR* • NASH resolution with not worsening of fibrosis	At 72 weeks • Resolution of NASH *AND* • Improvement in fibrosis	At 52 weeks • At least 1 point improvement of fibrosis with no worsening of NASH *OR* • NASH resolution with not worsening of fibrosis	At 72 weeks • At least 1 point improvement of fibrosis with no worsening of NASH *OR* • NASH resolution with not worsening of fibrosis
Phase 3 histological results (non-cirrhotic population)	Fibrosis improvement: PBO: 12% OCA 10mg: 18% (P=.045) OCA 25mg: 23% (P=.0002) NASH resolution: PBO: 8% OCA 10mg: 11% (P=.18) OCA 25mg: 12% (P=.13)	Expected Q1 2024	Fibrosis improvement: PBO: 14% Res 80mg: 24% (P=.0002) Res 100mg: 26% (P<.0001) NASH resolution: PBO: 10% Res 80mg: 26% (P<.0001) Res 100mg: 30% (P<.0001)	Expected Q2 2024
Date of long-term outcomes (non-cirrhotic population)	Expected 2025	Expected 2028	Expected 2026	Expected 2028

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Adapted from Harrison SA, Loomba R, Dubourg J, et al. Clin Gastroenterol Hepatol. 2023;12:S1542-3565(23)00265-3. Epub ahead of print.

Juan Pablo Frías, MD, is Medical Director and Principal Investigator of Velocity Clinical Research in Los Angeles, California. He earned his medical degree from the Vanderbilt University School of Medicine and completed his fellowship in Endocrinology, Diabetes and Metabolism at the University of California, San Diego. Dr Frías has held academic positions at the University of Colorado Health Sciences Center, Barbara Davis Center for Diabetes, and the University of California San Diego School of Medicine, where he is currently on the clinical faculty. He has been involved in diabetes and metabolism-related research for over 25 years and has authored numerous peer-reviewed publications in journals including the New England Journal of Medicine, The Lancet, Lancet Diabetes and Endocrinology, Cell Metabolism, Diabetes, and Diabetes Care.

Summary and Conclusions

- Management of patients with T2D should include therapeutics with efficacy beyond glycemic control, including improvement in liver health
- There are currently no FDA-approved medications specifically for the management of NAFLD
- Pioglitazone and semaglutide have demonstrated important benefits in patients with fatty liver disease, and should be considered in patients with T2D with NASH
- Four drugs are currently in Phase 3 of clinical development (obeticholic acid, lanifibranor, resmetirom, and semaglutide)
- Other incretin-based therapies are in clinical development for obesity and/or NASH
- Combination therapy, addressing the broad pathophysiology of NAFLD, will likely be necessary in many patients to achieve desired outcomes

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Case Studies in Screening, Diagnosis & Management of NAFLD/NASH

Davida F. Kruger, MSN, APN-BC BC-ADM

Certified Nurse Practitioner
Henry Ford Health System
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Bone and Mineral Disease
New Center One
Detroit, Michigan

64-year-old man with 14-year history of T2D

- 64-year-old Latino man
- Seen in clinic for T2D management; No complaints
- PMH: T2D x 14 yrs, obesity, dyslipidemia, no known ASCVD, abdominal ultrasound ~9 months ago with incidental finding of NAFLD
- Social History: Musician, very active, non-smoker and no alcohol

- Meds: metformin 1,000 mg BID, insulin glargine 40U QHS, atorvastatin 40 mg QD
- BP 132/74 mmHg; Weight 108 kg (BMI 34 kg/m^2); Otherwise normal exam
- FPG 182 mg/dL; HbA_{1c} 8.8%

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Davida F. Kruger, MSN, APN-BC, BC-ADM, has been a certified nurse practitioner in diabetes for more than 40 years at Henry Ford Health System in Detroit, Michigan. Her role includes both clinical practice and research. She is board certified by the American Nurses Association Credentialing Center in Primary Care and by the American Association of Diabetes Educators in Advanced Diabetes Management. She is past Chair of the American Diabetes Association's Research Foundation and has served on the American Diabetes Association's Research Policy Committee. She is also a Past President, Health Care and Education of the American Diabetes Association.

Moderate with Progression

- 48-year-old female presented in 2008 with 10-year history of prediabetes and recent conversion to diabetes, presented for routine follow up. CT scan ordered for follow up of left adrenal nodule showed hepatic steatosis.
- She was asymptomatic.

- Currently only taking metformin 1000 mg BID
- Exam: BMI 63. BP-128/76
- Labs: ALT – 78, AST – 65, plt – 195, A1c – 5.8%, T/cholesterol – 204, TG – 281, HDL – 33, LDL 115.
- Fib-4 index: 2.51

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She served as Editor of both Diabetes Spectrum and Clinical Diabetes. Ms Kruger has been a principal investigator on numerous research projects and has written widely on diabetes care, authoring the book The Diabetes Travel Guide 2nd edition (2006). Her awards include the Florence Nightingale award for excellence in research, ADA's Rachmeil Levine Award for Distinguished Service, ADA's Award for Outstanding Service in Diabetes Research Funding, The ADA Wendell May's Award, Wayne State University School of Nursing 2014 Alumna of the year and Henry Ford Health System Nursing Excellence Clara Ford Pillar award in Research and Education 2014.

Long history of "mild" fatty liver, with progression to early cirrhosis

- I saw him in 2018 as transfer of care. Obesity for "all of his life", complicated by type 2 diabetes for 23 years, HTN, dyslipidemia, gout, OSA. Presented about 6 months after a STEMI, with resultant HFrEF. Review of chart revealed an US in 2006 which was done for "elevated liver function tests" showing mild heterogeneous echogenic appearance of liver, consistent with hepatic steatosis.

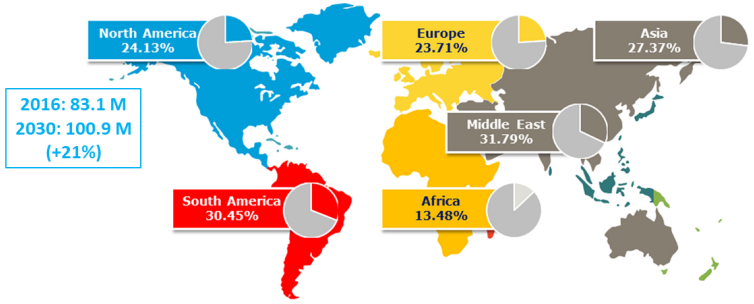
- At the time of his presentation, he was on metformin 500 mg BID, Empagliflozin 10 mg daily, U-500 Human regular insulin at 200 units with each meal and snack. He was also on metoprolol 50 mg QD, losartan 100 mg daily, allopurinol 300 mg daily, Atorvastatin 80 mg daily. He complained that he could not afford his insulin
- Wt. – 355, BMI – 55
- Labs: A1c – 7.2%, AST -16, ALT – 31, plt – 137. FIB-4 Index not calculated at the time (but calculated at 3.67 – advance fibrosis).

Worldwide Burden of NAFLD: Time for Action

Prof Michael Roden, MD

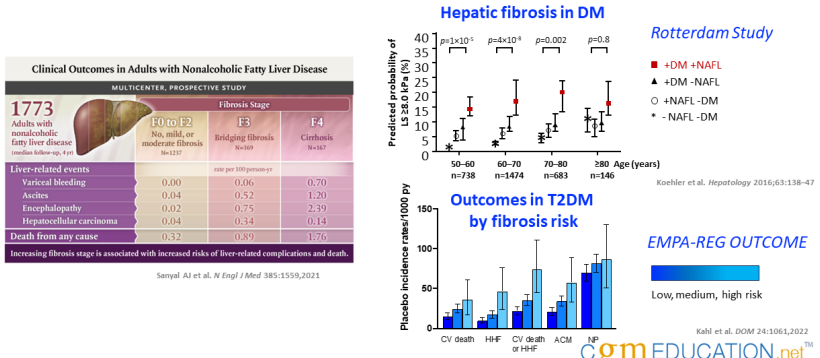
Chair/Professor of Endocrinology and Metabolic Diseases
Director
Department of Endocrinology and Diabetology
Heinrich-Heine University
University Hospital Düsseldorf
CEO of the German Diabetes Center
Dusseldorf, Germany

Epidemiology: Global prevalence of NAFLD



Prof Michael Roden is Chair/Professor of Endocrinology and Metabolic Diseases as well as Director of the Department of Endocrinology and Diabetology, Heinrich-Heine University, University Hospital Düsseldorf, and CEO of the German Diabetes Center (DDZ). He was trained at University Vienna and Yale University. His translational research addresses insulin resistance, energy metabolism, diabetes and its comorbidities, with specific interest in fatty liver disease and diabetes subtyping to foster precision medicine. He has published 700+ peer-reviewed papers, received several awards (e. g. Oskar-Minkowski Prize, G. B. Morgagni Gold Medal, Paul-Langerhans Medal) and holds honorary doctorates of the Universities of Athens and Belgrade.

Liver fibrosis: excess morbidity and diabetes



Prof Roden was president/congress president of the Central European, the Austrian and the German Diabetes Associations and chairman of the European Federation for the Study of Diabetes (EFSD). From 2017-2022, he was head of the Committee Medicine of the German Council of Science and Humanities, appointed by the President of Germany.

https://en.wikipedia.org/wiki/Michael_Roden

Take home

- About 50% of PW T2D have any NAFLD, 25% NASH and up to 2fold risk of liver fibrosis and cancer
- NAFLD increases risk of CVD and CKD
- Lifestyle and MetSy play a key role, but not always co-exist with NAFLD
- Lipotoxicity, abnormal mitochondria and inflammation promote NAFLD progression
- Screening for fibrosis risk is most important (FIB-4)
- Management is based on weight loss and addressing comorbidities of both NAFLD and DM

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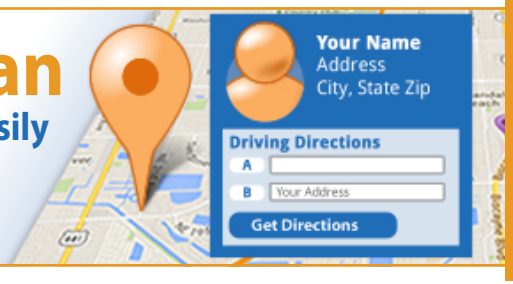

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