MASLD

Metabolic Dysfunction-Associated Steatotic Liver Disease

(The new NAFLD)

Montana Diabetes Professional Conference, October 19, 2023
Donita Mariegard, NP Meredith Ross, MD

Disclosures

No financial interest or affiliations

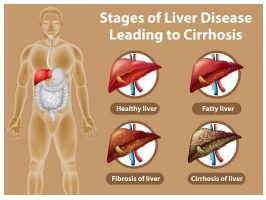
Objectives

1. Raise awareness of Metabolic dysfunction-associated steatotic liver disease (MASLD) and the risk associated with this condition
2. Provide a reasonable framework for identifying patients with MASLD and next steps in treatment

Objective 1

Raise awareness of Metabolic dysfunction-associated steatotic liver disease (MASLD) and the risk associated with this condition.

MASLD



- Most common chronic liver disease in Western countries
- Affects 37% of US adults
- Requires evidence of hepatic steatosis by staging or histology
- Diagnosis of exclusion
- Exclusion of secondary causes such as medications and diseases
  - Corticosteroids, Amiodarone, Methotrexate
  - Hereditary disorders
  - Viral infections

NAFLD and cardiovascular diseases: a clinic review, Kasper et al.

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al.

MASLD: Metabolic dysfunction-associated steatotic liver disease

- Hepatic manifestation of the metabolic syndrome
- Frequently associated with:
  - Sedentary lifestyle/Western diet
  - Obesity
  - Type 2 diabetes mellitus
  - Dyslipidemia
  - Subclinical and clinical cardiovascular disease
  - Risk for development of hypertension, coronary artery disease, cardiomyopathy, cardiac arrhythmias

NAFLD and cardiovascular diseases: a clinic review, Kasper et al.

Dietary Patterns and Components in Nonalcoholic Fatty Liver Disease (NAFLD): What Key Messages Can Health Care Providers Offer, Reman M et al.

Slide 6

RMF18 could we animate a heart coming in over the rib cage when we say the subclinical and clinical CVD
Ross, Meredith F., 10/4/2023

MD1 That's a good idea. Looking for one

Mariegard, Donita, 10/5/2023

MD2 Do you like this one?

Mariegard, Donita, 10/5/2023

RMF20 Yes! I think we should have the first pic you had first then I can add animation and add this one on when we say cardiovascular disease!

Ross, Meredith F., 10/5/2023

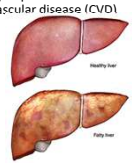
RMF21 could you please send me the one you used to have with the liver? Thank you! :)
Ross, Meredith F., 10/9/2023

MASLD

- The presence of >5% hepatocytes laden with lipid vacuoles in the absence of excessive alcohol consumption or other causes of chronic liver disease.
- Fat deposition in the liver with or without inflammation and fibrosis
- Often asymptomatic, may complain of right abdominal pain or OSA symptoms

MASH

- Metabolic dysfunction-associated steatohepatitis (MASH)
- Hepatocyte ballooning (sign of hepatocellular damage) and liver inflammation with or without fibrosis.
- Majority of patients with MASH die of cardiovascular disease (CVD)



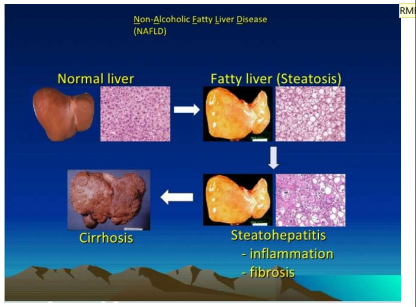
Treating NASH by targeting peroxisome proliferator-activated receptors, Staels et al

Prevalence of MASLD and MASH

- Often undiagnosed
- Expected to increase further, MASH-related cirrhosis is currently the leading indication for liver transplantation in women and those >65 years old.
- Prevalence of MASLD and MASH set to double by 2030
- Incidence of of hepatic decompensation, hepatocellular carcinoma (HCC) and death related to MASH cirrhosis are expected to increase 2-3-fold by 2030

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Rinella et al.

The presence of obesity and T2D increases the risk of developing MASH, more severe hepatocyte necrosis and predominately lobular inflammation and risk of cirrhosis.



RM 22

Diabetes Care 2021, Kanwal et al.

Slide 9

RMF22 source -Mere

Ross, Meredith F., 10/9/2023

nature > communications medicine > collection

Collection

Advances in MASLD/NAFLD

Submission status
Open

Submission deadline
30 December 2023

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is a chronic, progressive condition affecting about 38% of the global population and is strongly associated with features of the metabolic syndrome, including obesity and type 2 diabetes mellitus. MASLD is caused by a build-up of fat in the liver and includes a range of disease states, from isolated lipid accumulation or steatosis (metabolic dysfunction-associated steatotic liver, MASL) through to its active inflammatory

Preparing for the NASH Epidemic: A Call to Action

Diabetes Care 2021;44:2162–2172 | https://doi.org/10.2337/dci21-0020

Call to Action-September 2021

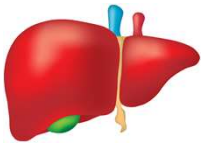
★ Call to Action ★

- Significant management gaps, no single global guiding strategy for management of MASLD and MASH
- NASH (sic) Needs Assessment Survey
- Formulate comprehensive unified strategy for primary care providers and relevant specialists for MASLD/MASH care

Diabetes Care 2021, Kanwal et al.

RMF17

Treatment team



- Previously only hepatologists
- Because of noninvasive diagnostic procedures, other health care professionals can more easily identify and care for these patients
- Gastroenterologists, endocrinologists, obesity medicine specialists, diabetes educators, and primary care providers
- Need more education and engagement among specialists and primary care

Diabetes Care 2021, Kanwal et al.

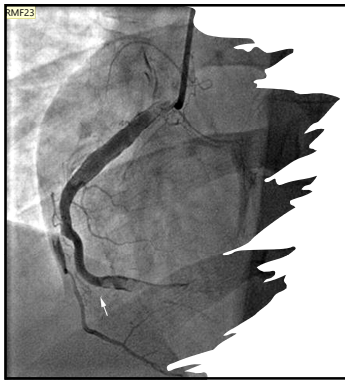
RMF34
RMF35

Screening is critical

- MASLD generally asymptomatic
- Optimal treatment timing depends on accurate staging of **fibrosis risk**, therefore screening at Primary care level is critical

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al.

RMF23



Cardiovascular disease

- Risk of CVD is 2-fold higher in MASLD patients than the general population and is the leading cause of death in MASH
- MASLD/MASH patients are 2 times more likely to die of heart disease than liver disease

Slide 13

RMF17 Ross, Meredith F., 8/21/2022

Slide 14

RMF24 We say the 37% earlier in the talk too. Do we want to say it x 2? :)

Ross, Meredith F., 10/9/2023

RMF35 Should we put a pic???
Ross, Meredith F., 10/17/2023

Slide 15

RMF23 I love this slide! Such important information... just wondering if we have it in the right place!

Ross, Meredith F., 10/9/2023

Objective 2

Provide a reasonable framework for identifying patients with MASLD and next steps in treatment.

RMF28

Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease

Fasiha Kanwal[1,2], Jay H. Shubrook[3], Leon A. Adams[4], Kim Pfotenhauer[5], Vincent Wai-Sun Wong[6], Eugene Wright[7], Manal F. Abdelmalek[7], Stephen A. Harrison[8], Rohit Loomba[9], Christos S. Mantzoros[10], Elisabetta Bugianesi[11], Robert H. Eckel[12], Lee M. Kaplan[10,13], Hashem B. El-Serag[1,2], Kenneth Cusi[14,15]

RMF29

Multidisciplinary Pathway Development Taskforce

- Developed a "NAFLD/NASH (sic) Clinical Care Pathway" to assist clinicians in diagnosing and managing MASLD with clinically significant fibrosis (stage F2-F4)
- Screening ⟶ Diagnosis ⟶ Management
- Intended to be applicable in any setting where care is provided for MASLD patients
- Clinical care pathways have been shown to improve the quality of health care delivery

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al

Slide 17

RMF26 Published in Gastroenterology, November 2021.
Ross, Meredith F., 10/9/2023

RMF28 Ken Cusi is the big name on this paper, he is out of University of Gainsville in Florida.
Ross, Meredith F., 10/9/2023

Slide 18

RMF29 15 experts from American diabetes association , American Osteopathic Association, Endocrine Society, and Obesity Society, convened a multidisciplinary task force of 15 experts to develop an NAFLD/NASH Clinical care pathway.
Ross, Meredith F., 10/9/2023

RMF32

Step 1

- Taskforce included PCP's, Gastroenterologists, Hepatologists, Endocrinologists from US, Europe, Australia, Asia
  - Identify at-risk patients
    1. Patients with T2DM
    2. Patients with 2 or more risk factors
       - Central obesity
       - Raised serum triglycerides
       - Reduced serum HDL
       - Hypertension
       - Prediabetes
    3. Patients with incidental finding of hepatic steatosis or elevated aminotransferases

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al

RMF33

Step 2

- History and Labs
  - Comprehensive metabolic panel and CBC to calculate Fib-4 or NAFLD Fibrosis score
  - Evaluate for excessive alcohol intake
  - Evaluate for other chronic liver and biliary diseases (HCV, chronic hep B, ETOH related liver disease and mass lesions)
  - Exclusion of secondary causes of hepatic steatogenic medications
    - Corticosteroids, Amiodarone, Methotrexate
  - Hereditary disorders
  - Viral infections

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al

RMF4

Fib-4

- Patients with low score are NOT requRMF3to undergo liver biopsy
- Patients with high scores MAY need to do biopsy to confirm liver disease diagnosis.
- Where a patient scores high AND has other clinical or imaging signs of progression to end-stage liver disease, biopsy may not be necessary anymore.

F1-F2 FIB 4 < 1.45 no cirrhosis

FIB 4 between 1.45 – 2.67 are deemed inconclusive

F3-F4 FIB 4 > 2.67 cirrhosis

Hepatology 2006, Sterling, et al.

Diabetes Care 2021, Kanwal et al.

Slide 19

RMF32 Mere
Ross, Meredith F., 10/11/2023

Slide 20

RMF33 Donita
Ross, Meredith F., 10/11/2023

Slide 21

RMF3 Low FIB4 has with a negative predictive value of 90% for advanced fibrosis
Ross, Meredith F., 8/15/2022

RMF4 High FIB4 has a positive predictive value of 65% for advanced fibrosis.
Ross, Meredith F., 8/15/2022

RMF18

Fib-4

- Score evaluates the degree of fibrosis in patients suspected of or already diagnosed with hepatic fibrosis.

$$FIB4 = \frac{(Age \times AST)}{(Platelet\ count \times \sqrt{ALT})}$$

RMF34

Step 3 Non-invasive testing for fibrosis

Fib-4 <1.3	Fib-4 1.3 – 2.67	Fib-4 >2.67
Low risk	Indeterminate risk	High risk
Liver Stiffness measurement (LSM) <8kPa	LSM 8 – 12 kPa	LSM > 12kPa
Repeat NIT in 2-3 years unless clinical circumstances change	Refer to GI or Hepatologist for liver biopsy or elastography or monitoring with re-evaluation of risk in 2-3 years.	Refer to GI or Hepatologist

Case Study # 1

- 52 year old male with elevated BMI at 36, poorly controlled T2DM, A1c 11.1% presents to establish care for Diabetes
- AST 25
- ALT 33
- Plt 256,000
- Fib 4=0.88

…..Do NOT refer to hepatology
Repeat Fib 4 in 2-3 years

Slide 22

RMF2 Ross, Meredith F., 8/15/2022

RMF18 Patient age is used because there is a direct correlation between age increase and progression of liver fibrosis. (Hep C and EtOH in particular)
AST and ALT Elevation suggests tissue injury.
Platelet count is used to identify whether there are sufficient clotting particle
Ross, Meredith F., 8/22/2022

Slide 23

RMF34 Donita
Ross, Meredith F., 10/11/2023

Case Study # 2

- 74 year old male with BMI 32, well controlled T1DM, A1c 6.5% presents to follow up for Diabetes
- AST 35
- ALT 33
- Plt 212
- Fib 4 2.13

.....Refer to hepatology

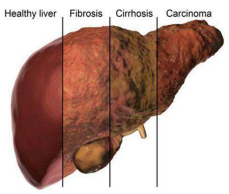
Fib-4 Interpretation

- Previous studies have shown that Fib-4 <1.3 (<2.0 for those older than 65) can reliably exclude advanced fibrosis in patients with MASLD, with a negative predictive value of ≥ 90%.
- Patients with Fib-4 >2.67 are at high risk for advanced fibrosis, with most studies reporting positive predictive values of 60%-80%.
- Recall that some other examples utilize a Fib-4 cutoff of 1.3 and some of 1.45*

Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al

Stages of liver injury/disease

- **F0**: No fibrosis
- **F1**: Portal fibrosis without septa
- **F2**: Few septa
- **F3**: Numerous septa without cirrhosis
- **F4**: Cirrhosis



Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease, Kanwal et al

Table 2—Initial evaluation in patients with suspected nonalcoholic fatty liver disease

History and medical review	Investigations
Obesity	Liver biochemistries (ALT, AST)
T2D	Exclude/identify other liver diseases[a]
Metabolic syndrome	HBV and HCV serology (and viral load)
Alcohol intake	Auto antibodies (ANA, AMA, ASMA)
<14 drinks/wk for women	Serum ferritin, A1AT
<21 drinks/wk for men	Liver ultrasound: increased echogenicity
No known pre-existing liver disease	—

A1AT, α1 antitrypsin; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; HBV, hepatitis B virus; HCV, hepatitis C virus. [a]NAFLD can coexist with other chronic liver diseases. Of note, 21% of patients with NAFLD may have elevations in autoantibodies in the absence of autoimmune hepatitis (85), and 20% may have high serum ferritin (>300 ng/mL in women and >450 ng/mL in men). Elevated serum ferritin is associated with advanced hepatic fibrosis (86) in patients with NAFLD.

Diabetes Care 2021, Kanwal et al.

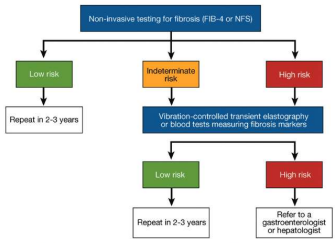


Figure 1—Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fibrosis score.

Diabetes Care 2021, Kanwal et al.

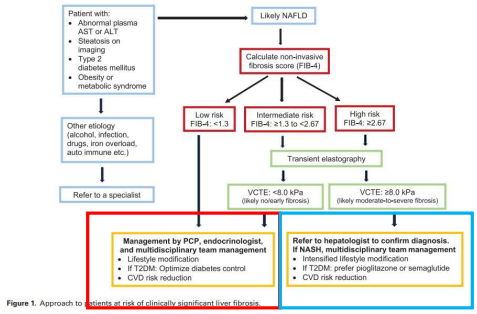


Figure 1. Approach to patients at risk of clinically significant liver fibrosis.

JCEM 2022, Chavez et al.

Fibroscan

- Acoustic radiation force impulse
- Ultrasound-based quantitative elastography technology
- Based on the principle that as liver fibrosis increases there is an associated increase in liver stiffness.
- Staging liver fibrosis helps determine initial degree of disease, continued surveillance, prioritization for treatment, and potential for reversibility of disease

Acoustic radiation force impulse

- Uses brief high-energy US pulses to excite a narrow region in liver parenchyma
- Results in minute displacements of tissue that results in shear waves that move laterally away from the line of the push pulse
- Shear waves are tracked by lower energy US beams which measure the speed of the propagating shear wave
- Shear wave velocity expressed in meters per second and/or kilopascals
- Velocity increases with liver stiffness and decreasing elasticity

Fibroscan measurements

- Fibrosis is measured in kilopascals (kPa)
- Normal range is between 2-6 kPa
- Steatosis is measured in decibels per meter

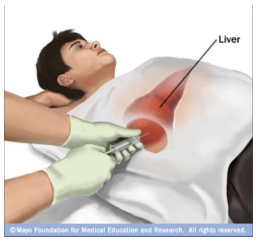
Considerations

- Fibroscan results can be overestimated
  - Liver inflammation (recent liver illness or alcohol)
  - Benign or cancerous liver tumors
  - Liver congestion (generally caused by heart failure)
- May be less accurate:
  - Ascites
  - Biliary obstruction
- Other considerations:
  - Fibroscan not appropriate for 5-7% of patients

How Fibroscan changes the game

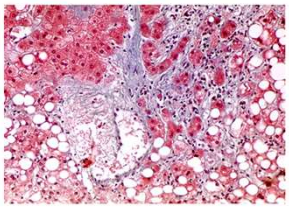
- Setting-in office
- Timing of results-immediate
- Non-invasive, as compared to liver biopsy

Liver biopsy



- Invasive
- High risk scores on noninvasive tests
- Diagnostic doubt
- Indeterminate, unreliable, or conflicting noninvasive assessments
- Differentiate between MASLD and MASH
- Look for inflammation, hepatocyte balloon degeneration, pericellular fibrosis

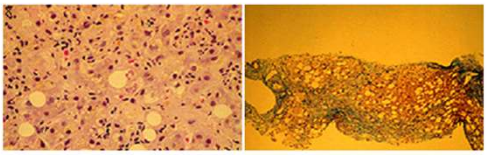
Nonalcoholic steatohepatitis liver biopsy



Liver biopsy showing steatosis, hepatocyte balloon degeneration, mixed acute and chronic inflammation, and pericellular fibrosis.

Courtesy of Marshall M. Kaplan, MD.

Nonalcoholic steatohepatitis on biopsy



Histologic changes in nonalcoholic steatohepatitis (NASH). Left panel: The hepatocyte in the center contains a large vacuole of fat and deeply staining eosinophilic strands of cytoplasmic hyalin. Numerous neutrophils and phagocytic cells containing golden brown pigmented material (bile components and cellular debris) are present in the sinusoids. Right panel: NASH with cirrhosis. Trichrome stain shows regenerating nodules with fat surrounded by fibrous tissue.

RMF30
RMF31

Case Study # 3

- 48-year-old male
- PMH: Alcoholism, ascites, cirrhosis
- Past alcohol treatment programs and RRTP admissions
- Two paracenteses 3L, 4.5L
- Sober 4 years
- Referred to GI, 2023
- Fibroscan done – Median kPa – 4.6. Mean CAP score 194 dB/m. IQR 19%

Slide 39

RMF30 You're doing such a nice job with this but let's cut out a ton of detail :)

Ross, Meredith F., 10/9/2023

MD4 For sure, was doing this at the end of the day and throwing stuff in!

Mariegard, Donita, 10/10/2023

RMF31 You're a rockstar!

Ross, Meredith F., 10/10/2023


FibroScan
CAP (dB/m)
E (kPa)
MEAN
MEDIAN
IQR/Med
SD
12
194
4.6
19%
Measurement conditions
Thick subcutaneous tissues
Patient positioning
Choice of measurement position
Intercostal Space
Axillary Line
Unknown
echosens


FibroScan
CAP (dB/m)
E (kPa)
MEAN
MEDIAN
IQR/Med
SD
5
161
11.9
15%
Measurement conditions
Thick subcutaneous tissues
Patient positioning
Choice of measurement position
Intercostal Space
Axillary Line
Unknown
echosens


FibroScan
CAP (dB/m)
E (kPa)
MEAN
MEDIAN
IQR/Med
SD
13
271
3.6
12%
Measurement conditions
Thick subcutaneous tissues
Patient positioning
Choice of measurement position
Intercostal Space
Axillary Line
Unknown
echosens

You found MAFLD...now what?

Received: 20 October 2021 | Revised: 25 January 2022 | Accepted: 21 February 2022
DOI: 10.1111/liv.15209

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes

Patrizia Carrieri[1] | Abbas Mourad[1] | Fabienne Marcellin[1] | Aldo Trylesinski[2] | José Luis Calleja[3] | Camelia Protopopescu[1] | Jeffrey V. Lazarus[4,5]

Perception gaps

- 2020 study to understand the perception gap between patients and providers on how MASLD/MASH is detrimental to health. 1411 participants.
- 2 major findings:
  - Those with severe obesity were those who most frequently reported not knowing their fibrosis stage.
  - Poor adherence to lifestyle changes more frequent in those unaware of their fibrosis stage and in those with obesity

Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes, Carrieri et al.

How does knowledge improve lifestyle change adherence?

- Life-style interventions are an effective first-line approach for MASLD management and prevention of MASH
- Weight loss can reverse liver disease
- Following a Mediterranean diet has been shown to be successful in reducing liver fat content, even without weight loss.
- Coffee and green tea can potentially slow the progression of both MASLD and MASH.

Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes, Carrieri et al.

Study conclusion

- Fibrosis staging is becoming the main predictor of MASLD progression.
- Improving communication between patient-provider about liver fibrosis stage and liver disease progression may facilitate better adherence to lifestyle changes.
- Need training for healthcare professionals and promoting patient educational programs to support behavioral changes to prevent MASLD progression.

Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes, Carrieri et al.

Management strategies

This Photo by Unknown Author is licensed under CC BY-SA

- Impact of weight loss
- Impact of managing diabetes
- Pharmacotherapy
  - Many medications are in development for the treatment of MASH but currently no treatment is US FDA approved.
  - Vitamin E, Pioglitazone, Glucagon-Like Peptide-1 Receptor Agonists

Uptodate NASH article.

Table 3—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFL	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

[a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. [b]Among GLP-1 receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. [c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution.

Diabetes Care 2023, Kanwal et al.

MASH treatment: Weight loss

- Weight loss is the primary therapy for most patients with MASLD
- Magnitude of weight loss correlates with decreases in intrahepatic triglyceride (IHTG) content, hepatocyte ballooning, and hepatic inflammation
- Improvement in liver tests and histology, and quality of life
- Goal loss of ≥5% of body weight
- 7% weight loss decreases IHTG by 40%!
- Hepatic fibrosis is more resistant and requires ≥10% of body weight
- Not meeting weight loss goals at 6 months? Discuss bariatric surgery
- Of note the Atherosclerotic CVD risk calculator recommends statin for patients with MASLD

Diabetes Care 2023, Kanwal et al.

MASH treatment: Vitamin E

- For patients with biopsy-proven MASH and F2-F4 who do NOT have diabetes mellitus: first treatment option is vitamin E 800 IU/day
- Some studies suggest that vitamin E induces liver histological benefit by reducing steatosis and inflammation
- Potential benefit that vit E is antioxidant
- Data is more mixed in patients WITH T2D
- Potential safety concerns with high-dose vitamin E
- One retrospective study showed longer transplant free survival

Uptodate NASH article.

Vitamin E: PIVENS Trial

- Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH (sic), large RCT did suggest a benefit with vitamin E.
- 247 adults with MASH WITHOUT T2D who were randomly assigned to pioglitazone 30 mg daily, vitamin E 800 international units daily, or placebo for 96 weeks.
- Patients treated with vitamin E were more likely to have improvement in their global histology score compared with patients who received placebo (43% vs 19%).
- Improvement in ALT was more common in patients receiving vitamin E (48%) than placebo (16%).

Uptodate NASH article.

Risks of Vitamin E

- High-dose Vitamin E supplementation is ≥400 IU/day and has been inconsistently associated with an increase in all-cause mortality
- Underlying comorbidities or use of alternative high dose supplements may have confounded the results, making their interpretation uncertain
- Avoid Vitamin E in male patients with either a personal history or strong family history of prostate cancer

Diabetes Care 2023, Kanwal et al.

MASH treatment: Pioglitazone

- Improves steatohepatitis and to a lesser extent fibrosis in patients with and without T2D
- TZD, activation of proliferator-activated receptor-gamma and alpha agonism
- 5 RCT show that it reverses steatohepatitis in patients with and without diabetes
- PIVENS Trial, pioglitazone led to resolution of steatohepatitis in 47% of patients compared with 21% of patients in placebo group
- Follow up 3 year studies have shown reported benefit from pioglitazone treatment

Diabetes Care 2023, Kanwal et al.

JCEM 2022, Chavez et al.

Treatment of MASH in patients with T2D

- Pioglitazone
- GLP1 receptor agonists
  - Liraglutide
  - Semaglutide
  - Dulaglutide
  - Tirzepatide

JCEM 2022, Chavez et al.

GLP-1RAs in patients with T2DM

- LEADER trial Liraglutide
- SUSTAIN-6 Semagultide
- REWIND Dulaglutide
- PIONEER Oral Semaglutide
- SURPASS-3 Tirzepatide

GLP-1RA Benefits

- A systematic review of Cardiovascular outcomes trials includine 56,000+ participants concluded that treatment with GLP-1RAs:
- ↓ fatal or non-fatal stroke by 16% (p=0.0001)
- ↓ cardiovascular death by 12% (p<0.003)
- ↓ fatal or non-fatal myocardial infarction by 9% (p=0.043)
- ↓ Hospital admission for heart failure by 9% (p= 0.028)
- ↓ Composite of kidney outcomes by 17% (p<0.0001)
- ↓ All cause mortality by 12% (p= 0.001)

JCEM 2022, Chavez et al.

GLP-1RAs Risks

- Mild to moderate gastrointestinal side effects
- In Cardiovascular outcomes trials severe hypoglycemia, pancreatitis, and pancreatic cancer were not observed
- There was an increased risk of cholelithiasis (odds ratio 1.3, p=0.041)

JCEM 2022, Chavez et al.

GLP-1RA Cardiovascular Benefits

- ADA recommends GLP-1RAs for glycemic control and reduce CVD in patients with T2DM, and this is reassuring to support their use in MASLD and MASH.
- Cardiovascular disease is the number 1 cause of death in T2DM, MASLD, and MASH.

JCEM 2022, Chavez et al.

GLP-1RA for Weight Loss

- Liraglutide for weight loss
  - Weight loss with liraglutide led to >50% reduction in the risk of progression from PreDM to T2D
- Semaglutide for weight loss
  - Patients in the STEP 1-4 trials patients with obesity WITHOUT T2D treated with 2.4mg/wk vs placebo for 20 weeks, data pooled shows that semaglutide patients lost **-7.9% to -16%** of body weight whereas placebo was +6.9% to -5.7%
  - Approval of semaglutide as Wegovy 2.4mg weekly in June 2021

JCEM 2022, Chavez et al.

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Table 1. Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]

Author	GLP1-RA	n	Study design	Weight change[b]	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	71	RCT	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	87	Open label	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	68	Open label	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	72	RCT	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	52	Open label	↓ 2.6%	↓ 20%

Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]

Author	GLP1-RA	n	Study design	Weight change[b]	NASH resolution
Armstrong et al, 2016	Liraglutide	52	RCT	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	320	RCT	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial.
[a] Placebo or comparator subtracted change in hepatic steatosis.
[b] Placebo or comparator subtracted weight loss.
[c] Placebo-subtracted change in number of patients with resolution of NASH.

JCEM 2022, Chavez et al.

Liraglutide

- Armstrong et al liraglutide 1.8mg per day or placebo for 48 weeks
- Resolution of MASH was found in 39% of patients with liraglutide compared to 9% on placebo (p=0.019)
- Progression of fibrosis was less on liraglutide (9% compared to 36% respectively with p=0.04)
- Provocative enough data to inspire interest in use of this drug class

JCEM 2022, Chavez et al.

Semaglutide

- More potent for weight loss than liraglutide
- Weight loss >10%
- Study randomized 320 patients with biopsy proven MASH and fibrosis to receive either injectable daily semaglutide at 3 different doses (0.1mg, 0.2mg or 0.4mg) or placebo for 72 weeks
- Strengths of study: 62% of patients had T2D
- Dose dependent metabolic improvement and reduction in liver enzymes with mean weight loss of 13% in 0.4mg per day group compared to 1% in placebo group
- Resolution of steatohepatitis without worsening of fibrosis with highest dose was 59% with semaglutide compared to 17% placebo (p<0.001)

JCEM 2022, Chavez et al.

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GLP-1RA MASH

- Thus far, trials with GLP-1RAs for MASH outcomes have been similar in patients WITH or WITHOUT T2D as well as similar in patients who are overweight OR with severe obesity
- No clear correlation between A1c levels over time and liver histology or other clinical outcomes
- Still these trials hint at potential role for these medications for treatment for MASH and a larger phase 3 trial is under development

JCEM 2022, Chavez et al.

Tirzepatide

- Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1R agonist
- Promising implications for management of T2D, MASLD, and obesity
- Weekly doses 5-15mg induce weight loss from 8-13%
- Improvement in glucose metabolism and cardiometabolic risk factors
- Benefits exceed those of semaglutide 1mg per week but did not compare 2.4mg/weekly dose
- In the SURPASS-3 MRI substudy, 296 people underwent magnetic resonance imaging at baseline and at week 52
- Average liver fat content was 15.7% at baseline, but during treatment this decreased by 6.35%, 8.21%, and 7.78%, on average, in people taking the 5, 10, and 15 mg tirzepatide doses. All of these changes were significant relative to the average 3.19% reduction in the degludec group. P<0.0006.

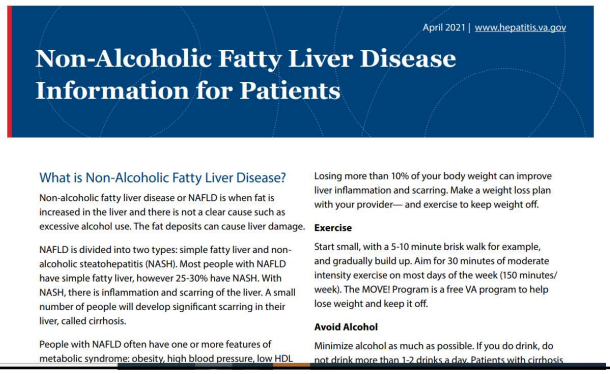
JCEM 2022, Chavez et al.
The Lancet, 2022, Gastaldelli, et al.

What's next for MASLD and MASH?

- Tirzepatide (GIP and GLP1R agonists) promising data for MASLD, obesity and T2D
- Artificial intelligence use to perform noninvasive tests
- Multidisciplinary approach: RDN/CDCES, primary care, gastroenterology, endocrinology, hepatology, obesity management
- Clear consistent guidelines

What should we do next?

- Start screening at risk patients. Consider which patients are at risk and start with a Fib4 or NAFLD Risk score calculator
- Follow guidance of when to refer to gastroenterology/hepatology, and when to refer to RDN/CDCES for weight loss
- Consider pharmacotherapy: Vitamin E, Pioglitazone, GIP/GLP1-RA
- Educational resources for patients



April 2021 | www.hepatitis.va.gov

Non-Alcoholic Fatty Liver Disease Information for Patients

What is Non-Alcoholic Fatty Liver Disease?

Non-alcoholic fatty liver disease or NAFLD is when fat is increased in the liver and there is not a clear cause such as excessive alcohol use. The fat deposits can cause liver damage.

NAFLD is divided into two types: simple fatty liver and non-alcoholic steatohepatitis (NASH). Most people with NAFLD have simple fatty liver, however 25-30% have NASH. With NASH, there is inflammation and scarring of the liver. A small number of people will develop significant scarring in their liver, called cirrhosis.

People with NAFLD often have one or more features of metabolic syndrome: obesity, high blood pressure, low HDL

Losing more than 10% of your body weight can improve liver inflammation and scarring. Make a weight loss plan with your provider— and exercise to keep weight off.

Exercise

Start small, with a 5-10 minute brisk walk for example, and gradually build up. Aim for 30 minutes of moderate intensity exercise on most days of the week (150 minutes/ week). The MOVE! Program is a free VA program to help lose weight and keep it off.

Avoid Alcohol

Minimize alcohol as much as possible. If you do drink, do not drink more than 1-2 drinks a day. Patients with cirrhosis

Pearls

- See if your EMR can autofill a Fib-4 into your notes
- Talk to your patients!
- Form a referral pattern to a gastroenterologist for screening
- Form a referral pattern to RDN/CDCES to assist with lifestyle changes if needed
- Utilize endocrinologist for prescription of medications to assist with treatment of fatty liver and possible overlap with obesity and diabetes management
- Watch for future treatments/drug indications to come!

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