

Nonalcoholic Fatty Liver Disease (NAFLD) and Diabetes

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24th Annual Diabetes Symposium
November 14, 2018
Anahem Marriott - Anaheim, CA



Disclosure Statement

Today's faculty: *Heather Patton, MD* and the planners for this activity, as well as the CME staff, do not have any relevant financial relationships with commercial interests or affiliations to disclose.



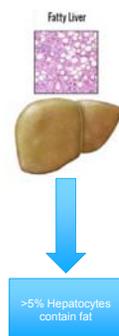
Learning Objectives

- Understand the full spectrum of NAFLD from simple steatosis to nonalcoholic steatohepatitis (NASH) to nonalcoholic cirrhosis
- Review estimated prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)
- Recognize at risk populations and diagnostic evaluation for NAFLD
- Review medical therapies for NAFLD
- Understand efficacy of lifestyle modification in treating NAFLD
- Understand health outcomes in NAFLD/NASH and the importance of NAFLD diagnosis on cardiovascular risk profile



Fatty Liver

- Alcoholic fatty liver**
- Nonalcoholic fatty liver**
 - Medications (amiodarone, methotrexate, tamoxifen, corticosteroids)
 - Hepatitis C genotype 3
 - Wilson Disease
 - Starvation
 - TPN
 - Acute fatty liver of pregnancy




Alcoholic vs. Nonalcoholic?



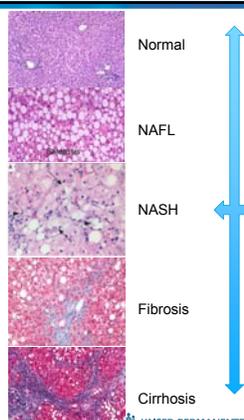
Standard drink = 14 grams alcohol

**>21 drink equivalents/week in Men
>14 drink equivalents/week in Women**



NAFLD Histology

- NAFL** = Simple Steatosis = Isolated steatosis ($\geq 5\%$), NO cellular injury
- NASH** = steatosis + inflammation + ballooned hepatocytes +/- fibrosis
- NASH Cirrhosis** = stage 4 fibrosis +/- residual histology from NASH




NAFLD Risk Factors

TABLE 3. Risk Factors Associated With NAFLD

Common Conditions With Established Association	Other Conditions Associated With NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
MetS*	Hypogonadism
Polycystic ovary syndrome	Pancreatoduodenal resection
	Psoriasis

*The Adult Treatment Panel III clinical definition of MetS requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) TG level 150 mg/dL or greater; (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.⁽²⁸⁷⁾

- Increasing age
- Male gender

HEPATOLOGY, Vol. 67, No. 1, 2018
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HEPATOLOGY
HEPATOLOGY, VOL. 64, NO. 3, 2016

Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes

Zohar M. Youniss,^{1,2} Aaron B. Keegan,³ Diana Abdillat,⁴ Yusef Fawzi,⁵ Linda Henry,⁶ and Mark Wilson^{1,2}

- 35 studies from North America, total of 8,016,928 people
- NAFLD prevalence is **12.89%** (95% CI: 8.32-19.44) by laboratory testing and **24.3%** (95% CI: 19.73-29.15) by imaging
- Estimated overall prevalence of **NASH 1.5-6.45%**
- Estimated **T2DM** prevalence in NAFLD **22%** and in **NASH 44%**

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NAFLD and DM: NHANES 2011-2014

Aliment Pharmacol Ther. 2017;46:974-980.

TABLE 2. Predictors of NAFLD overall and predictors of NAFLD-AF and NAFLD-SF among individuals with NAFLD

	Overall NAFLD	Significant fibrosis AFG	Advanced fibrosis NFS	Advanced fibrosis NFS-4								
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value			
Male vs female	0.32	0.24-0.42	<.001	0.33	0.27-0.39	.044	0.32	0.23-0.39	.011	2.23	0.56-8.97	.258
Age	1.04	1.02-1.05	<.001	1.03	0.99-1.07	.443	1.08	1.02-1.13	.011	1.07	1.02-1.13	.011
White	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Black	0.40	0.43-0.65	<.001	0.45	0.28-0.71	.01	0.38	0.13-1.01	.052	0.44	0.31-0.61	.013
Hispanic	1.04	0.73-1.5	.796	0.49	0.23-1.02	.056	0.30	0.08-1.07	.063	0.7	0.32-1.94	.485
Age ≥ 50 years	2.70	2.02-3.59	<.001	0.99	0.82-1.16	.947	9.30	2.27-39.0	.001	1.66	0.57-4.72	.397
Diabetes	3.55	2.53-4.94	<.001	1.36	0.73-2.45	.344	38.30	4.7-301	<.001	2.63	0.54-12.9	.248
Hypertension	1.30	1.24-1.3	<.001	1.38	1.04-1.82	.029	1.30	0.96-1.7	.102	1.87	0.21-17.08	.37

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NAFLD Spectrum Prevalence Breakdown

Prevalence in the United States: 25% of adults (NAFLD), 5-6% of adults (NASH), 1-2% of adults (Cirrhosis/HCC).

N Engl J Med 2013;377:2063-72. DOI: 10.1056/NEJMe1305519
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HEPATOLOGY, VOL. 64, NO. 3, 2016

The Economic and Clinical Burden of Nonalcoholic Fatty Liver Disease in the United States and Europe

Zohar M. Youniss,^{1,2} Dinko Blazes,³ Robert Blazes,⁴ Linda Henry,⁵ Maria Ines,⁶ Yusef Fawzi,⁷ Zohar Youniss,⁸ Andras Kallai,⁹ Maria Hoss,¹⁰ and Rachel Beckman¹¹

- In the US >64 million people are projected to have NAFLD
- Annual direct medical costs approximately \$103 billion (\$1,613/patient)
- Costs are highest in patients aged 45-65

Trends in Outpatient Resource Utilizations and Outcomes for Medicare Beneficiaries With Nonalcoholic Fatty Liver Disease

J Clin Gastroenterol • Volume 49, Number 3, March 2015

- National outpatient claims for Medicare beneficiaries 2005-2010
- Mean yearly charge increased from \$2624 to \$5132

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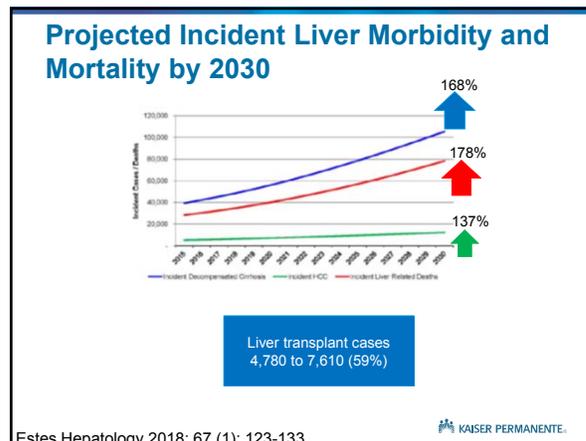
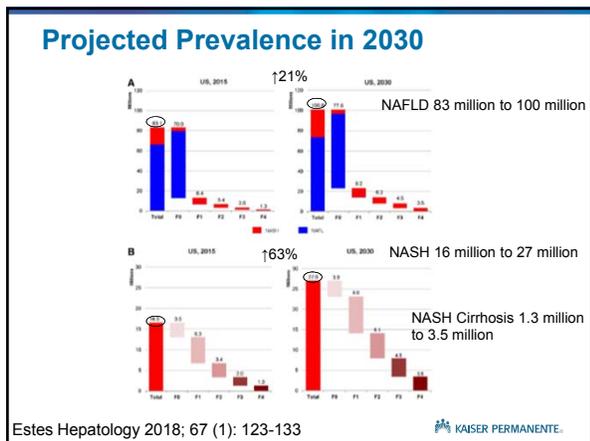
New Liver Transplant Waitlist registrations 2004-2013

Figure 1. Annual trends in new liver transplant waitlist registrations.

Trends in Etiology of Liver Disease in the US 2006-2014

Gastroenterology 2015;148:547-555.

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NAFLD Diagnosis/Staging

- **NAFLD Diagnosis:** (1) hepatic steatosis by imaging or histology, (2) no significant alcohol consumption*, (3) no competing etiologies for steatosis, and (4) *no coexisting causes of chronic liver disease*
 - Recommend to assess for common comorbidities
 - Variable impact on ALT, AST, GGT
 - Steatosis imaging: US, CT, MRI
- **NASH Diagnosis:** Liver Biopsy
- **Staging:** Noninvasive versus Liver Biopsy

*>21 drinks/week in Men
>14 drinks/week in Women*

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Liver Fibrosis

Normal 0-1 2 3 4 Cirrhosis

"severity of liver fibrosis is the only histologic measure that independently predicts liver-related illness, liver transplantation, and liver-related death in patients with nonalcoholic fatty liver disease"

New England Journal of Medicine 377:21 nejm.org November 23, 2017 KAISER PERMANENTE.

Noninvasive Assessment Tools

- Fibrosis Scoring systems
 - NAFLD Fibrosis Score (NFS)
 - FIB-4
 - APRI
- US Elastography (FibroScan®)
- MR Elastography

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Using NAFLD Fibrosis Score in KPSC

Use order panel to gather components

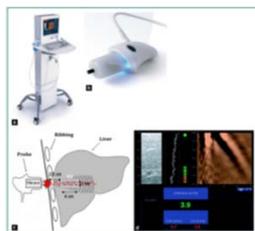
Can cut and paste results into medical documentation

Use AURA to launch embedded med calculators

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Transient Elastography

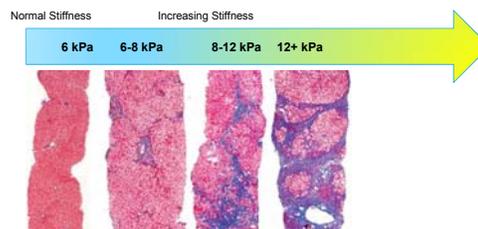
- Probe delivers mechanical impulse which delivers a shear wave through the liver
- Shear wave velocity if measured by ultrasound and reflects elasticity of the liver tissue



Tapper Clinical Gastroenterol Hepatol 2015
Diagnostic and Interventional Imaging (2013) 94, 515–534

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Transient Elastography Results



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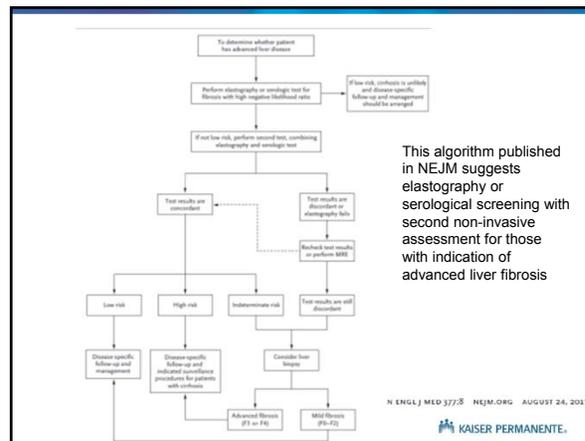
Assessment of Liver Fat Content



Figure 1 Controlled attenuation parameter (CAP) assessment using the FibroScan®.

Clinics and Research in Hepatology and Gastroenterology (2012) 36, 13–20

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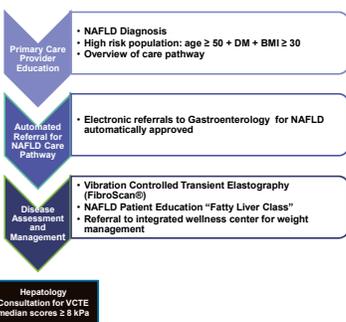


This algorithm published in NEJM suggests elastography or serological screening with second non-invasive assessment for those with indication of advanced liver fibrosis

N ENGL J MED 377:37 NEJM.ORG AUGUST 24, 2017

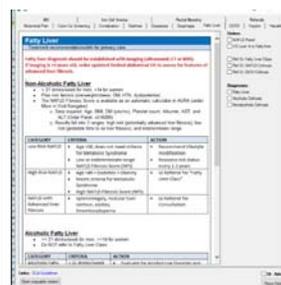
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NAFLD Care Pathway in San Diego



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Next Iteration to Care Pathway



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Pharmacotherapy: Insulin Sensitizers

- **Metformin** is not recommended for treating NASH in adult patients.
- **Pioglitazone** may improve liver histology in patients with and without DM with biopsy-proven NASH. Risks and benefits should be discussed with each patient before starting therapy.
- Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.
- It is premature to consider (glucagon-like peptide-1) **GLP-1 agonists** (liraglutide) to specifically treat liver disease in patients with NAFLD or NASH.

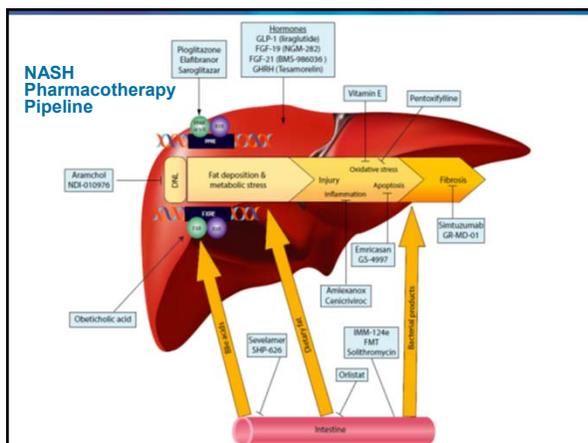
HEPATOLOGY, Vol. 67, No. 1, 2018



Pharmacotherapy: Vitamin E

- Vitamin E administered at a daily dose of 800 IU/day may improve liver histology in nondiabetic adults with **biopsy-proven NASH** and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.
- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

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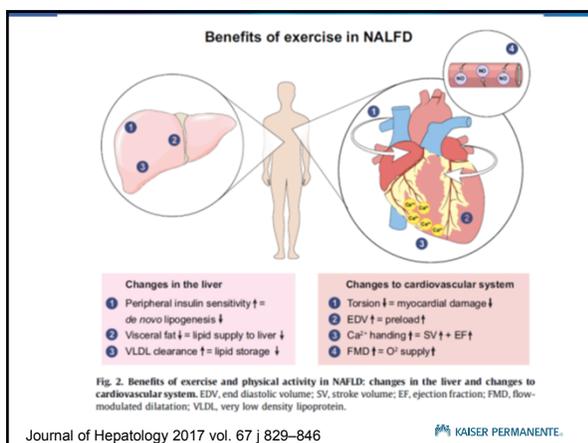
Exercise and NAFLD

- Meta-analysis of 28 randomized trials of exercise-based lifestyle interventions
 - Physical activity, *independent of diet change*, was associated with a significant reduction in intrahepatic lipid content and reduction in ALT and AST

Orci Clinical Gastroenterology and Hepatology 2016;14:1398–1411

- BOTH aerobic and resistance training are effective at reducing liver fat
 - 40-45 minutes, 3 x a week appears sufficient

Hashida Journal of Hepatology 2017 vol. 66 | 142–152

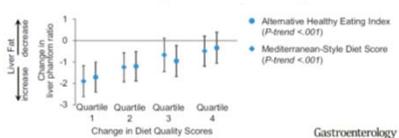


Journal of Hepatology 2017 vol. 67 | 829–846



Dietary Composition/Quality and NAFLD

Association Between Change in Diet Quality and Change in Liver Fat

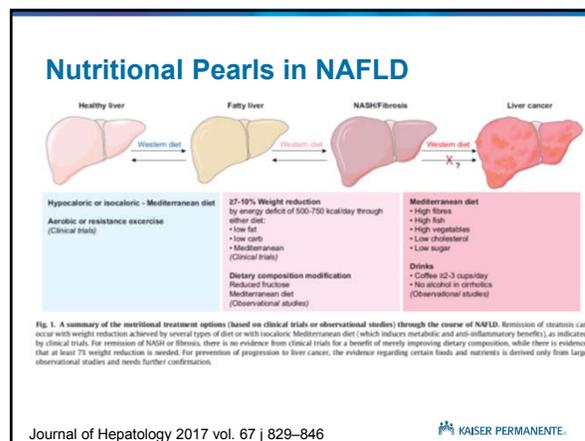
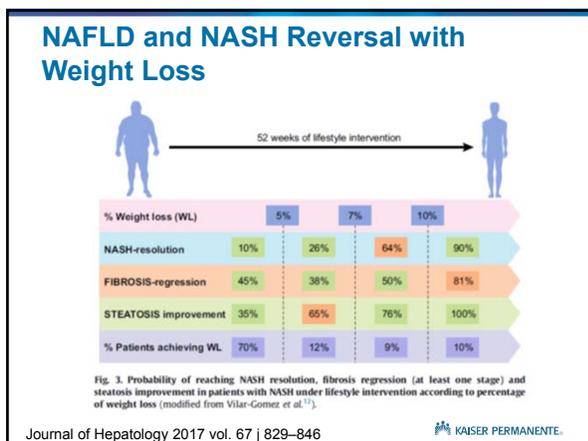


Supplement	Table 1. Comparison of NASH and AMLD
Vitamin E	✓
Pioglitazone	✓
GLP-1 (liraglutide)	✓
Metformin	✓
Amantadine	✓
Obeticholic acid	✓
Semaglutin	✓
Liraglutide	✓
BMS-1244 (FMT)	✓
Sofosbuvir	✓
Oxidative stress	✓
Injury, inflammation	✓
Apoptosis	✓
Fibrosis	✓
Sarcosumab	✓
GR-MD-01	✓
Emericasan (GS-4997)	✓
Amlexanox	✓
Caracitabine	✓
Metabolic products	✓
Orlistat	✓

1521 Participants from Framingham Heart Study
Fatty Liver assessed with CT scan, 6 year interval
Improved dietary scores associated with decreased liver fat
Higher dietary scores had decreased incident NAFLD

Gastroenterology 2018;155:107–117





Healthy Balance

Healthy Balance: A Weight Management Program
 10 Steps for a new way of thinking about weight loss.

Convenient and developed by professionals, the Healthy Balance program is based on three basic ideas for success.

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Bariatric Surgery

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

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Outcomes in NAFLD/NASH

- NAFLD **increased mortality** versus no NAFLD
- **Cardiovascular disease** is #1 cause of death
- **Non-liver cancers** #2 cause of death
- NASH, *especially with fibrosis*, increases risk for **cirrhosis** and **liver-related mortality** (#3 cause of death)
- NAFLD is 3rd leading cause of **HCC**
 - Diagnosed older & with shorter survival time vs. other etiologies
- Most **cryptogenic cirrhosis** is “burned out” NAFLD
- Predicted #1 indication for **liver transplant** in US by 2020

HEPATOLOGY, Vol. 67, No. 1, 2018 KAISER PERMANENTE.

NASH and Mortality: LIVER

- **Differentiate NAFL from NASH:** only NASH requires resource intensive, liver-targeted interventions to reduce risk for liver related morbidity and mortality
- **Fibrosis assessment matters:** both liver-related and all cause mortality increase with fibrosis stage ≥ 2
 - Risk of death from liver disease increased 50-80 X in NASH with stage 3-4 fibrosis

N ENGL J MED 377:21 NEJM.ORG NOVEMBER 23, 2017 KAISER PERMANENTE.

T2DM Increases Risk for Mortality in NAFLD

Table 1 Summary of studies reporting mortality in patients with non-alcoholic fatty liver disease with and without Type 2 diabetes mellitus.

Study design and setting	Country	Method of diagnosis	N	DM %	Follow-up (median, years)	Mortality in patients with NAFLD and Type 2 diabetes (HR compared with patients without diabetes)	
						Overall (CI)	Liver-related (CI)
Stepanova et al. 2013 [84]	USA	Retrospective hospital	289	26.0	12.5	2.09 (1.39-3.14)	2.19 (1.03-4.81)
Rafiq et al. 2019 [85]	USA	Retrospective hospital	173	28.9	10.5 ^a , 11 ^b	2.7 (P = 0.0013)	6.7 (P = 0.0238)
Adams et al. 2005 [84]	USA	Retrospective community	420	26.0	7.6	2.6 (1.3-5.2)	Not reported
Younossi et al. 2004 [89]	USA	Retrospective hospital	132	33.0	10.0 ^c	3.3 (1.76-6.18)	22.8 (2.97-175.03)

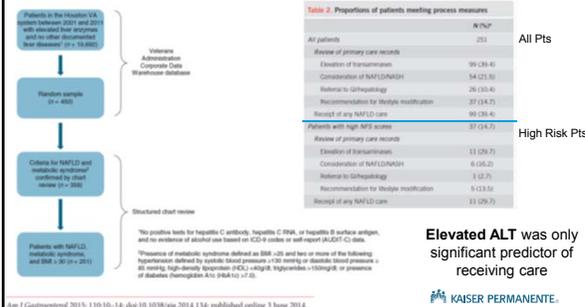
HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. ^aNon-NASH patients, ^bNASH patients, ^cMean. The study by Stepanova et al. included 176 patients previously reported by Rafiq et al. in addition to 113 new patients.

Diabet. Med. 32, 1121-1133 (2015)

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Nonalcoholic Fatty Liver Disease is Underrecognized in the Primary Care Setting

Pierre Blais, MD¹, Nisreen Husain, MD², Jennifer R. Kramer, MPH, PhD^{3,4}, Marc Kowalkowski^{5,6}, Hashem El-Serag, MD, MPH^{1,3} and Faisla Kanwal, MD, MSHS^{1,7}



Elevated ALT was only significant predictor of receiving care

Am J Gastroenterol 2015, 110:10-14, doi:10.1038/ajg.2014.134, published online 3 June 2014

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HEPATOLOGY
PRACTICE GUIDANCE | HEPATOLOGY, VOL. 47, NO. 1, 2018

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

- “Routine Screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics is *not advised* at this time 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 and NASH in patients with *type 2 diabetes*. Clinical decision aids such as NFS or fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis).”

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THE NEW ENGLAND JOURNAL OF MEDICINE

REVIEW ARTICLE

Don L. Longo, M.D., Editor

Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis

- “Dedicated efforts are necessary to identify persons with NASH because neither a diagnosis of the disorder nor the severity of associated liver fibrosis is predicted simply on the basis of obesity, insulin resistance, or hepatic steatosis.”
- “Overweight or obese persons with the metabolic syndrome, elevated serum aminotransferase levels, and a negative noninvasive workup for other causes of liver disease are likely to have NASH.”
- “Those who are 45 years of age or older and who have type 2 diabetes are particularly likely to have advanced fibrosis and an increased risk of bad liver outcomes.”

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Screening for NAFLD in DM Clinics

72.8% had elevated liver fat by CAP
11% cirrhosis with M probe
22% cirrhosis with XL probe

Duration DM, BMI, increased ALT, low HDL, spot urine albumin:Cr associated with fibrosis

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How can healthcare providers managing T2DM help in addressing NAFLD?

- When you identify a fatty liver**
 - Get the alcohol history
 - Evaluate for features of metabolic syndrome
 - Look for features of advanced fibrosis (platelets, spleen size, AST>ALT)
 - Use a non-invasive calculator like NFS
 - Advanced Fibrosis refer to specialty care
 - Indeterminate risk consider another non-invasive calculator or repeat NFS
 - Educate your patients and promote lifestyle modification
- When you are seeing a patient with multiple risk factors for NAFLD/NASH/Advanced Fibrosis**
 - ALT > 20 in woman and >30 in men is abnormal
 - GGT can help identify fatty liver
 - Low threshold to get a limited abdominal US
 - If liver is fatty, see above

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What is a Primary Care Physician To Do?

- **Know your specialty resources**
 - GI/Hepatology
 - Access to FibroScan or MRE
 - Weight management programs, bariatric surgery
- **Consider clinical trials/research**
 - Clinicaltrials.gov
- **Recognize NAFLD as a CV risk**
 - No increased risk for liver injury from statins
- **Give your patients *specific recommendations and resources* for lifestyle modification**

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