Novel Approaches for the Treatment of Nonalcoholic Steatohepatitis

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December 15th, 2022

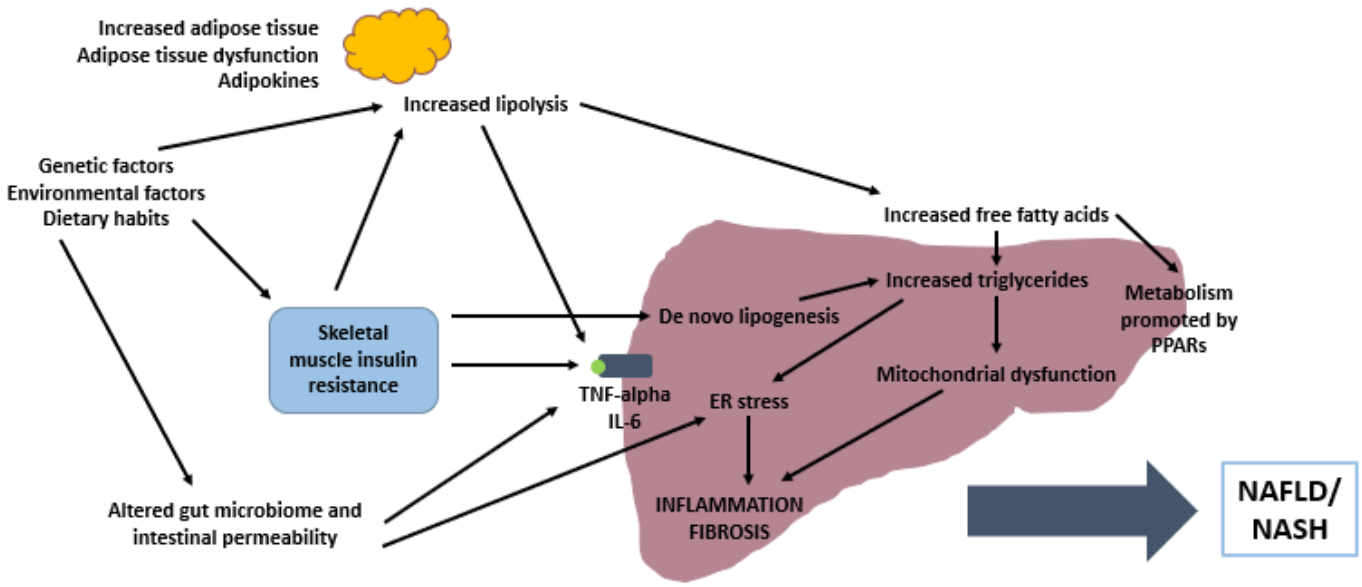
Learning Objectives:

1. Identify the risk factors associated with nonalcoholic steatohepatitis
2. Describe the mechanism of novel antidiabetic agents in relation to the pathophysiology of nonalcoholic steatohepatitis
3. Select appropriate pharmacologic treatment options for patients with nonalcoholic steatohepatitis

Background[1-4]

Nonalcoholic steatohepatitis (NASH) is the inflammatory subtype of nonalcoholic fatty liver disease (NAFLD) with steatosis and hepatocyte injury (with or without fibrosis)	**Presentation** • Often asymptomatic • Nonspecific symptoms • Often an incidental finding when abdominal imaging is completed for another reason	**Risk factors** • Obesity • Prediabetes or type 2 diabetes mellitus • Hypertension • Hypertriglyceridemia • Metabolic syndrome • Older age

Pathophysiology[5]



Current Guideline Recommendations[6-8]		
	EASL 2016	**AASLD 2017**
Lifestyle	• Diets including calorie restrictions and lower fats • Both aerobic and resistance training exercises	• Weight loss facilitated by low calorie diet +/- increased physical activity can reduce hepatic steatosis
Pharmacotherapy	• Should be reserved for patients with significant fibrosis or for those with high risk of disease progression • No firm recommendations made, but state pioglitazone +/- vitamin E can be used	• Metformin is not recommended • Pioglitazone can be used in biopsy-proven NASH, but a risk vs. benefit discussion must occur • Vitamin E can be used in biopsy-proven NASH, but not in patients with diabetes • GLP-1 agonists lack data

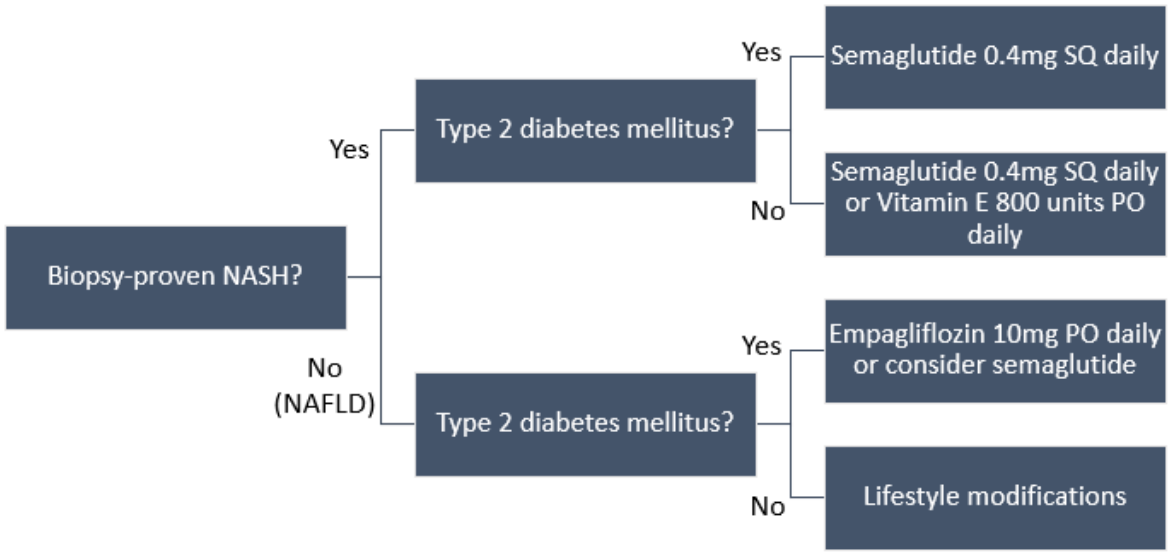
Select Trials for Antidiabetic Agents[9-13]

Trial	Design	Results
Cui J, et al. *J Hepatol*. 2016;65(2):369-376. Multicenter, randomized, double-blind, placebo-controlled trial N = 50	• **Sitagliptin** 100mg PO daily vs. Placebo • Adult patients with documented hepatic steatosis with prediabetes or well-controlled diabetes (A1c <8%) • 24 weeks	• No change in liver fat in the sitagliptin group from baseline to post treatment or when compared to placebo • No differences compared to placebo regarding liver enzymes, cholesterol, or fibrosis
E-LIFT Trial: Kuchay MS, et al. *Diabetes Care*. 2018;41(8):1801-1808. Single center, randomized, open-label trial N = 50	• **Empagliflozin** 10mg PO daily plus standard treatment vs. Standard treatment • Adult patients with documented hepatic steatosis with uncontrolled type 2 diabetes (A1c 7-10%) • 20 weeks	• Empagliflozin had a significant decrease in liver fat compared to standard treatment • ALT was significantly improved from baseline in the empagliflozin group compared to standard treatment
Newsome et al. *N Engl J Med*. 2021;384(12):1113-1124. Multicenter, randomized, double-blind, placebo-controlled trial N = 320	• **Semaglutide** 0.1mg, 0.2mg, or 0.4mg SQ daily vs. Placebo • Overweight, adult patients with histological evidence of NASH with or without type 2 diabetes • 72 weeks	• Semaglutide at any dose significantly increased resolution of NASH with no worsening of fibrosis • Semaglutide had larger decreases in body weight compared to placebo • Semaglutide 0.4mg SQ daily had the largest improvements in most outcomes

Summary of Data for Antidiabetic Agents

Characteristic	DPP-4 Inhibitors	SGLT-2 Inhibitors	GLP-1 Agonists
Histological outcomes	X	X	✓
Positive outcomes	X	✓	✓
Duration	24 weeks	20 weeks	72 weeks
T2DM?	Yes: Pre-diabetes or A1c <8%	Yes: A1c >8%	Mixed: With and without T2DM
NASH-specific patients	?	X	✓

Proposed Treatment Algorithm



Assessment Questions:

1. Which factor is associated with an increased risk of development of NASH?
    a. Younger age
    b. Low body fat
    c. Hypotension
    d. Obesity

2. How does improvement in blood glucose and hyperinsulinemia caused by antidiabetic agents improve NASH?
    a. Reduces fatty acid synthase
    b. Increases lipolysis
    c. Alters gut microbiome
    d. Agonizes PPARs

3. Which agent is most appropriate for a patient with biopsy-proven NASH with stage F2 fibrosis and without type 2 diabetes mellitus?
    a. Sitagliptin
    b. Semaglutide
    c. Empagliflozin
    d. Metformin

Abbreviations Used: TNF = tumor necrosis factor; IL = interleukin; ER = endoplasmic reticulum; PPAR = peroxisome proliferator-activated receptors; EASL = European Association for the Study of the Liver; AASLD = American Association for the Study of Liver Diseases; DPP-4 = dipeptidyl peptidase 4; SGLT-2 = sodium-glucose cotransporter 2; GLP-1 = glucagon-like peptide 1; T2DM = type 2 diabetes mellitus; PO = by mouth; ALT = alanine aminotransferase; SQ = subcutaneous; PO = by mouth

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