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Gastroenterology & Hepatology
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Can Statins Be Used Safely?

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Disclosures

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Disclosures

Corrie Berk, DNP, MBA

Speaker’s Bureau: Gilead - HCV, Salix - HE

Jordan Mayberry, MPAS, PA-C

No financial relationships to disclose.

Case Study #1

64yo Mexican male

DM, HLD, obesity, CAD with history of MI

Normal liver enzymes

Cholesterol 299, Trigs 928, HDL 30

Why This “Normal” Case Study?

Helps focusing illusion as we often tend to focus on risks

Benefits of statins (Chou et al 2016):

- NNT to prevent CV event? 72
- NNT to prevent one death? 250

Liver-Related Risks in the General Population

- Liver injury, if it occurs, usually happens 3-4 months into therapy
- Up to 3% occurrence of persistent transaminitis (dose dependent)
- **Incidence of hepatic failure in patients taking statins is no different from incidence of hepatic failure in the general population**[1]
- Idiosyncratic liver injury is rare but can be severe[2]
  - Atorvastatin associated with cholestatic/mixed injury
  - Simvastatin hepatocellular injury

1. Cohen et al, 2006; Bjornsson et al, 2012.

Recommendations in Gen Pop

- LFTs recommended prior to starting statin but do not need to be checked routinely unless clinically significant side effects develop
- Stop statin if ALT or AST >3x ULN with evidence of cholestasis (TB >2x ULN)
  - Work up for DILI & presence of underlying CLD before blaming statin
- DILI & ALF are incredibly rare (1 in 100,000 and 1 in 1,000,000 respectively)
- Statins contraindicated in ALF

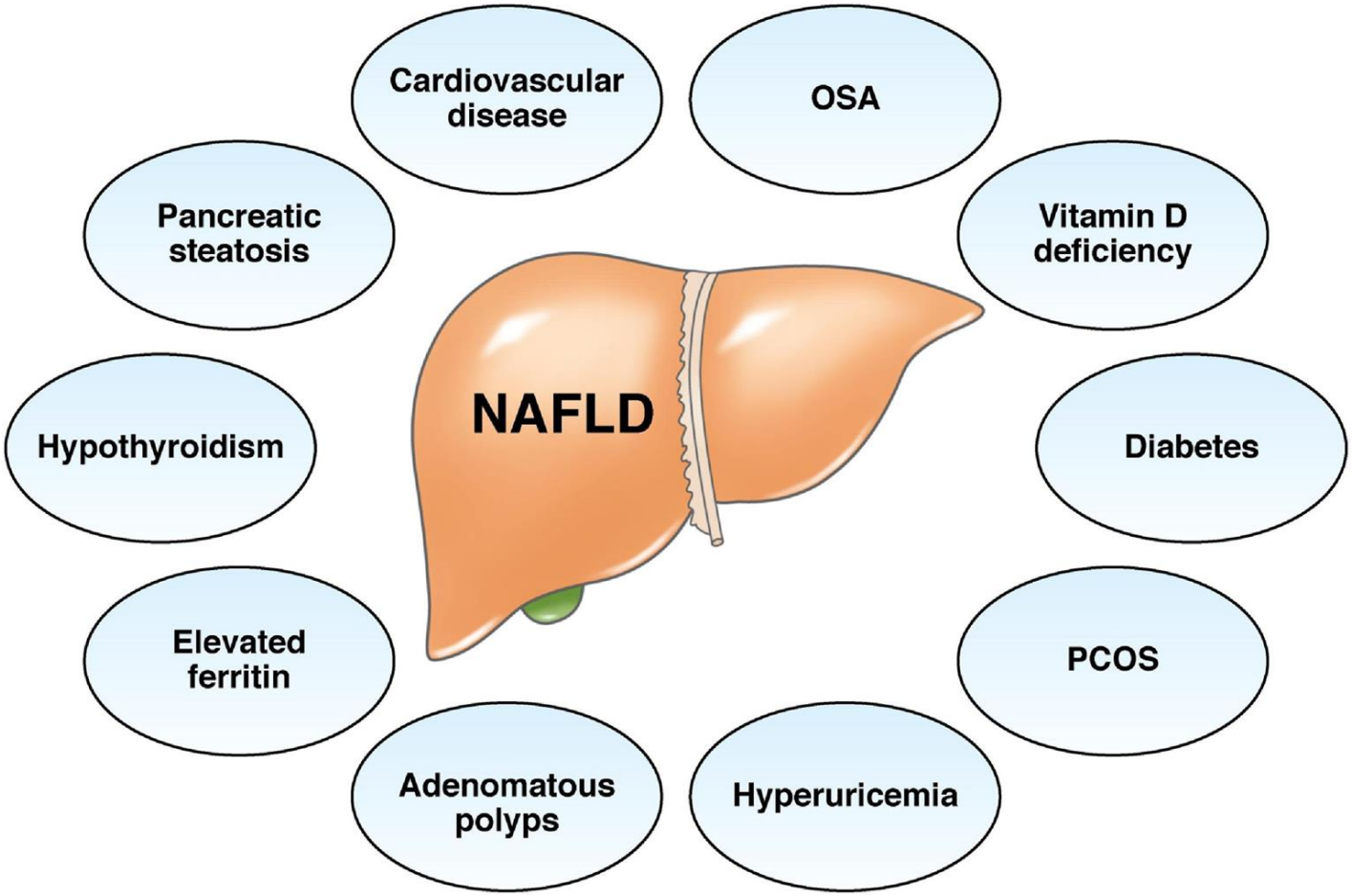
Case Study #2

- 64 y/o Hispanic male PMHx obesity, hypertension, DM2, hyperlipidemia, CAD hx of MI who is referred to your clinic by PCP for elevated LFTs. Recently had an ultrasound showing steatosis
- **Presenting Symptoms:** occasional abdominal discomfort
- **Which tests/labs should be offered?**
  - Viral Hepatitis labs
  - Autoimmune liver disease (ANA, AMA, Smooth muscle antibody)
  - Genetic liver disease (Alpha-1, Ceruloplasmin, Iron studies)

Results of Tests/Labs

- Results (List results from previous labs and procedures.)
  - Ultrasound- steatosis
  - Chronic liver disease work-up
    - HAV Ab positive
    - HBsAg negative
    - HBsAb negative
    - ANA,AMA, Smooth Muscle Ab- negative
    - Ceruloplasmin, Alpha-1- normal
    - AST/ ALT 64/72
    - CBC- normal
- Discuss differential diagnosis
  - NAFLD vs NASH
- Is any further workup necessary?
  - Fibrosure
  - Fibroscan
  - Liver biopsy?
  - Lipids, HgbA1c

Clinical Associations With NAFLD



Torres DM et el. *Clin Gastro Hepatol*. 2012;10:837-858.

Beware of Normal Liver Enzymes

- 103 Type II DM with normal liver enzymes had MR Spectroscopy
- Prevalence of NAFLD was 50%
- Prevalence of NASH among those with NAFLD was 56%
- BMI, gender, duration of diabetes or its control were not associated with NASH
- Serum triglycerides were significantly higher in NASH

Portillo Sanchez P, et al. *J Clin Endocrinol Metab*. 2015;41:292-400.

NAFLD vs. NASH

- NAFLD = hepatic steatosis without evidence of significant inflammation
  - U.S. prevalence 10-46%
- NASH = hepatic steatosis associated with hepatic inflammation → cirrhosis
  - U.S. prevalence 3-5%
- ACC/AHA guidelines should be used to assess CV risk in NAFLD patients

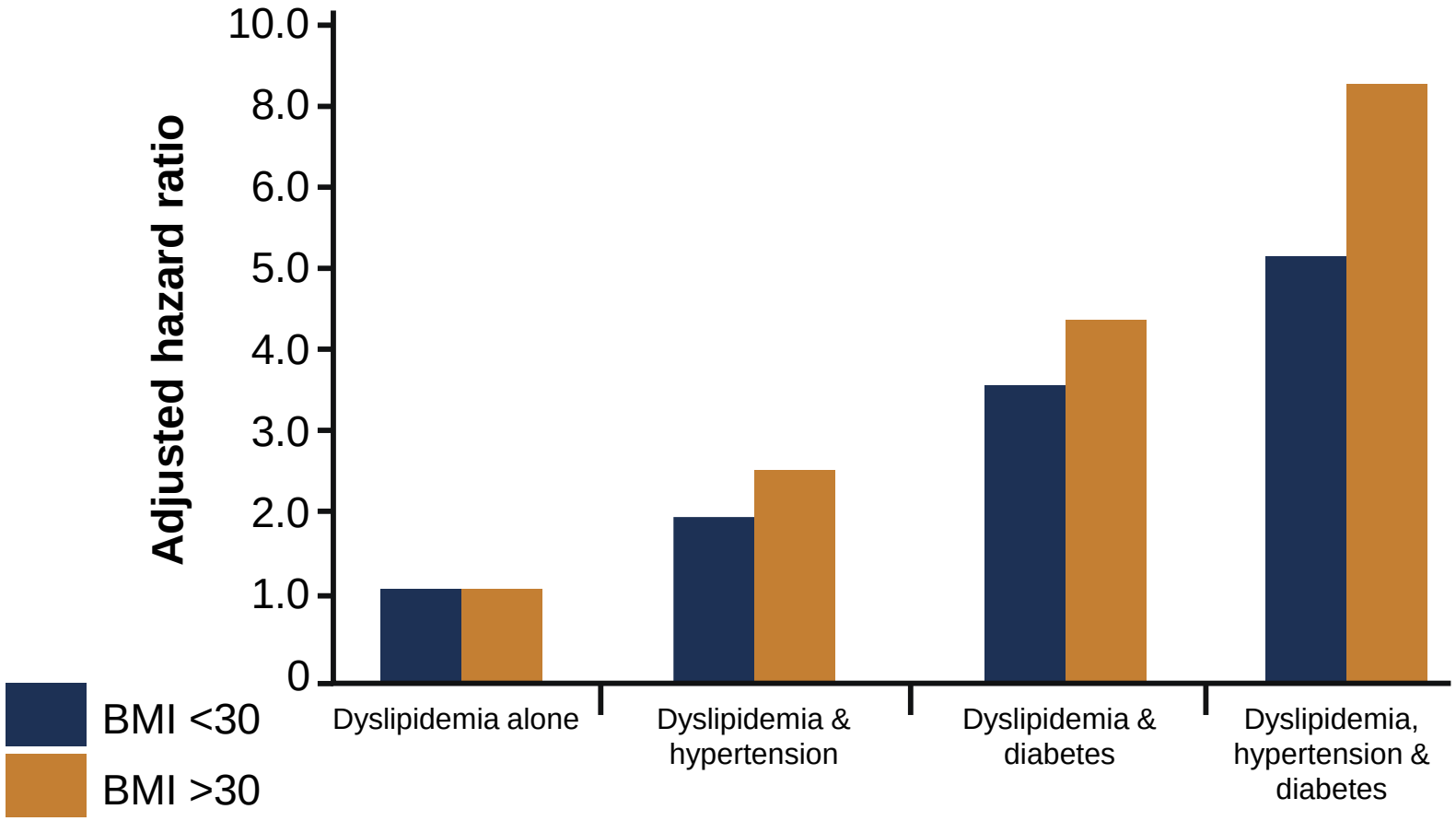
Prevalence of NASH Within NAFLD

			% steatosis	% NASH
Ekstedt	N=129	Tertiary	45	55
CYTOL 2002	N=248	Tertiary, multicentric	45	55
Soderbergh	N=118	Tertiary care	57	43
NASH CRN	N=679	Tertiary, multicentric	20	59
Campos	N=125	Bariatric surgery	45	55

Diagnosis

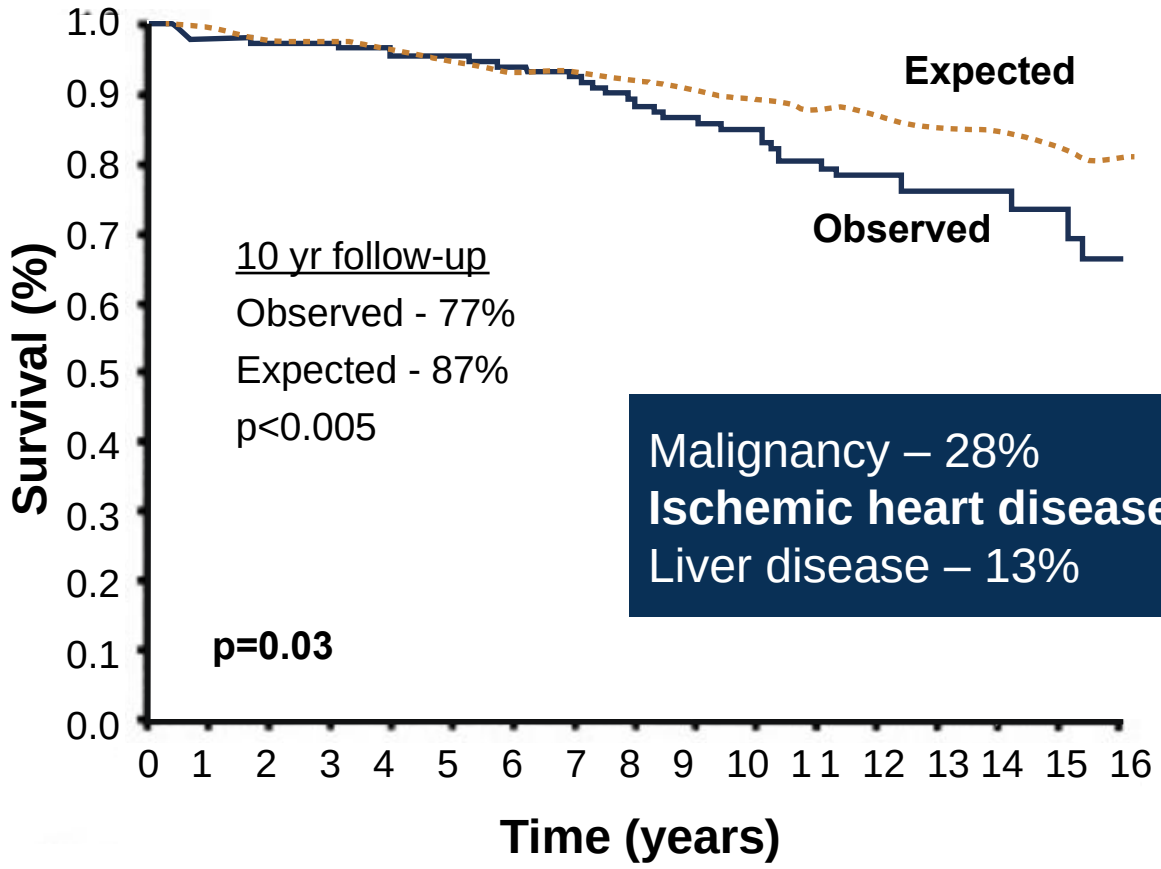
- NASH
  - Fibroscan done revealing
    - 10.3 kPa
    - CAP 323
- Which management options are available for this patient?

Effect of Metabolic Traits on NAFLD Progression



Kanwal F et. al. *Gastroenterology*. 2018.

NAFLD and Mortality



Malignancy – 28%
Ischemic heart disease – 25%
Liver disease – 13%

Adams et al. *Gastroenterology.* 2005.

Lifestyle Modification

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake

- Avoid fructose-containing food and drink

Coffee consumption

- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women

Macronutrient composition

- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity

- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

Treatment

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH-defining lesions accepted as surrogate endpoint
- Safety and tolerability are prerequisites
  - Extensive comorbidities associated with significant polypharmacy and increased likelihood of DDIs

Treatment

- Insulin sensitizers
  - Little evidence of histological efficacy with metformin
  - PPARγ agonist pioglitazone better than placebo
    - Improved all histological features except fibrosis
    - Achieved resolution of NASH more often
- Antioxidants
  - Vitamin E may improve steatosis, inflammation and ballooning and resolve NASH in some patients
    - Concerns about long-term safety exist

Statins

- Lipid-lowering agents
- Statins have not been adequately tested in NASH
- Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease
- Similarly, n-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH

Statin Safety in Patients With Liver Disease

- Unlikely to be harmful, actually seem to improve survival
- Decreases risk of decompensation in patients with cirrhosis[1]
- Decreases all cause mortality
- All statins metabolized in the liver
  - Little evidence supports one agent's use over another, however pravastatin

1. Kumar et al. 2014.

Antifibrotic Effects of Statins

- Favorable impact on hepatic inflammation, fibrosis, and vascular tone
- 41% lower risk of HCC

Patient Follow-Up

- Patient Care
  - Short-term plan
    - RTC in 6 months to follow-up on weight loss
  - Long-term plan
    - Due to elevated kPa on fibroscan recommend follow-up every 6 months

Post-Liver Transplant Use of Statins

- OK and, in fact, absolutely necessary due to increased risk of CV event!
- Dyslipidemia common post-OLT[1]
- Elevated pre-transplant cholesterol → hypercholesterolemia post[2]
- Pravastatin preferred due to least amount of interaction with immunosuppressants
  - Not metabolized by CYP3A4
- Starting doses
  - Pravastatin 10-20mg QD
  - Atorvastatin 5-10mg
    - Max 10mg with cyclosporine; increases concentrations of sirolimus & everolimus

1. Liu & Schiano, 2007; 2. Gisbert et al, 1997

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Q&A

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