The impact of alcohol in NAFLD

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Disclosures

• GILEAD

H. Sim. a 55 year old man



- Referred to your outpatient clinic for ALT, AST, GGT elevation known since several years
- Medical history: hypertension treated by amlodipine
- Last blood test shows: ALT 61 U/L (≤40), AST 62 U/L (≤ 40), GGT 250 U/L (≤ 50), ALP 120 U/L (≤120), total bilirubin 18 µmol/L, albumin 36 g/L, hemoglobin 12 g/dL, MCV 99 fl, platelets 145x109/L, glucose 10 mg/dL, cholesterol 300 mg/dL, triglycerides 300 mg/dL, normal renal function tests
- Clinical examination: palpable hepatomegaly, waist circumference 105 cm, weight 95 kg, high 172 cm, BMI 32
- Smoking stopped 10 years ago

How do you assess the alcohol use in your patients ?

- 1. By simple questions
- 2. By a self-reported questionnaire (AUDIT or AUDITc...)
- 3. By a structured interview

How to assess the alcohol use ?

HOW TO HELP PATIENTS: A CLINICAL APPROACH

How to Help Patients Who Drink Too Much: A Clinical Approach

STEP 1 Ask About Alcohol Use



AUDIT

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential, so please be honest.

For each question in the chart below, place an X in one box that best describes your answer.

NOTE: In the U.S., a single drink serving contains about 14 grams of ethanol or "pure" alcohol. Although the drinks below are different sizes, each one contains the same amount of pure alcohol and counts as a single drink:



Questions	0	1	2	3	4
 How often do you have a drink containing alcohol? 	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
 How many drinks containing al- cohol do you have on a typical day when you are drinking? 	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
 How often during the last year have you failed to do what was normally expected of you because of drinking? 	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
 How often during the last year have you had a feeling of guilt or remorse after drinking? 	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
 How often during the last year have you been unable to remem- ber what happened the night be- fore because of your drinking? 	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
 Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down? 	No		Yes, but not in the last year		Yes, during the last year
suggested you cut down:		A			

Score considered positive, optimal for identifying hazardous drinking or active alco use disorders:

- Men ≥ 8 •
- Women ≥ 4

1.5 oz. of

(about 40%)

alcohol)

AUDIT-C questionnaire

AUDIT-C Questi

Patient Name	Date of Visit

1. How often do you have a drink containing alcohol?

- 0 points 🗌 a. Never
- 1 points D. Monthly or less
- 2 points 🗌 c. 2-4 times a month
- 3 points 🗌 d. 2-3 times a week
- 4 points e. 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day?

0 points _____ a. 1 or 2 1 points _____ b. 3 or 4

- 2 points 🔲 c. 5 or 6
- 3 points 🔲 d. 7 to 9
- 4 points 🗌 e. 10 or more

3. How often do you have six or more drinks on one occasion?

- 0 points 🔲 a. Never
- 1 points 📋 b. Less than monthly
- 2 points 🗌 c. Monthly
- 3 points 🗌 d. Weekly
- 4 points 🗌 e. Daily or almost daily

Score considered positive, optimal for identifying hazardous drinking or active alcohol use disorders:

- Men ≥ 4
- Women ≥ 3

Bush K et al. Arch Internal Med 1998/Bradley KA et al. Arch Internal Med 200

What's a Standard Drink?

• In the U.S., a standard drink is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons).



What's a Standard Drink?

In France, a standard drink is any drink that contains about 10 grams of pure alcohol



AUDIT-C questionnaire of Mr HS



AUDIT-C Questionnaire

Patient Name	HS	Date of Visit _	14 jan2019	
1 How often do v	ou have a drink conta	ining alcohol?		

0 points	a.	Never
1 points	b.	Monthly or less
2 points	C.	2-4 times a month
3 points	d.	2-3 times a week
4 points	e.	4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day?

0 points a. 1 or 2 1 points b. 3 or 4 2 points c. 5 or 6 3 points d. 7 to 9 4 points e. 10 or more

3. How often do you have six or more drinks on one occasion?

0 points a. Never 1 points b. Less than monthly 2 points c. Monthly 3 points d. Weekly 4 points e. Daily or almost daily

H. Sim. a 55 year old man



- Alcohol consumption: 60 g/day and more during the WE, bier essentially
- Etiologic investigation: no viral infection, no auto-immune diseases, no hemochromatosis (high ferritin but normal TSC)
- Fibroscan 17 kPa, FIB-4: 3
- Abdominal ultrasound: homogeneous hepatomegaly, severe steatosis, nodular surface, PV diameter 12 mm
- Gastroscopy: no varices or signs of PHT
 - ≻You ask the patient to:
 - Stop alcohol
 - Reduce his caloric intake
 - Reduce sugar and fat intake
 - Favour mediterranean diet
 - Have a regular physical activity

Would you perform a liver biopsy in this patient ?

- No, it is not necessary because the probability of cirrhosis is high
- Yes, it will be useful to confirm the existence of cirrhosis and his etiology
- Yes, but only if I have the opportunity to include the patient in a clinical trial

ASH and NASH: similar pathophysiological pathways





Phenotype	nenotype Disease Activity Disease Stage		Etiology/Associations		
Steatosis Steatohepatitis Indeterminate	NAS - Steatosis - Lobular inflammation - Ballooning SAF - Steatosis - Lobular inflammation - Ballooning - Fibrosis	Fibrosis - Stage 0: No fibrosis - Stage 1a: Mild perisinusoidal - Stage 1b: Moderate perisinusoidal - Stage 1c: Portal/periportal - Stage 2: Perisinusoidal and portal/periportal - Stage 3: Bridging - Stage 4: Cirrhosis	Insulin resistance Alcohol Lean NASH PNPLA3 ⁺ Drugs Inherited disorders (e.g., Weber-Christian, hypobetalipoproteinemia) Lipodystrophy Short bowel TPN		

- - -

Jejunoileal bypass

ASH vs NASH



Mallory bodies



If you see large number of ballooned cells with Mallory bodies, it is more likely to be ASH

Sanyal A-Brunt E. Paris Nash Meeting 201

ASH vs NASH: features of ASH

Obliterative venulitis



Fibro-obliterative disease



Central to portal fibrosis





Sanyal A-Brunt E. Paris Nash Meeting 201

ASH vs NASH :when can we call it steatohepatitis of mixed etiology ?



Glycogen nuclei common Infrequent ballooning Loss of glycogen nuclei Frequent ballooning Increasing Mallory bodies Cholestasis Rosettes Central vein obliteration Biliary proliferation

H. Sim. a 55 year old man, 3 months later



- Patient has reduced the intake of fat, sugar, calories, he walks every day (30 mn per day), he
 has reduced the alcohol consumption to 20 g/day even during the WE → 5 kg weight loss
- Recent blood test shows: ALT 61 U/L (≤40), AST 50 U/L (≤ 40), GGT 150 U/L (≤ 50), ALP 110 U/L (≤120), total bilirubin 15 µmol/L, albumin 36 g/L, hemoglobin 12 g/dL, MCV 94 fl, platelets 150x109/l, glucose 115 mg/dL, Hb A1c 8 %, cholesterol 265 mg/dL, HDL 35 mg/dL, LDL 190 mg/dL, triglycerides 230 mg/dL, normal renal function tests
- A liver biopsy is performed:



➤He asks you if it is risky for him to continue to drink small amount of bier every day

What is your answer ?

- 1. Yes, because it may increase the risk of liver decompensation
- 2. Yes, because it may increase the risk of HCC
- 3. Probably this moderate alcohol consumption will have no effect of the outcome of cirrhosis

NASH cirrhosis: short term outcome



Impact of alcohol intake on the incidence of HCC in cirrhotic patients

Incidence of HCC according to etiology of cirrhosis Incidence of HCC according to alcohol consumption

Incidence of HCC: Social alcohol intake vs no alcohol intak



HCC annual incidence:

- HCV 4%
- NASH 2.6 %

Social alcohol intake= ≤ 2 drinks/d or ≤ 6 drinks/d on WE

Ascha MS et al. Hepatology 2010

Outcome in patients with advanced NASH



Outcome in patients with advanced NASH



Vilar-Gomez E et al. Gastroenterology 2018

Impact of moderate alcohol consumption in cirrhotic patients



Moderate alcohol intake: 1-70 g/week women, 1-140 g/week men

Vilar-Gomez E et al. Gastroenterology 2018

H. Sim. a 55 year old man, 3 months later



 Recent blood test shows: ALT 61 U/L (≤40), AST 50 U/L (≤ 40), GGT 150 U/L (≤ 50), ALP 110 U/L (≤120), total bilirubin 15 µmol/L, albumin 36 g/L, hemoglobin 12 g/dL, MCV 94 fl, platelets 148x109/l, glucose 115 mg/dL, hemoglobine A1C 8 %, cholesterol 265 mg/dL, HDL 35 mg/dL, LDL 190 mg/dL, triglycerides 230 mg/dL, normal renal function tests

How will you manage the diabetes ?

- 1. Only lifestyle intervention
- 2. Insulin
- 3. Metformin
- 4. GLP-1 receptor analogues
- 5. Sulphonyureas

Therapy	Mechanism of action	Useful in type 2 DM	Useful in patients with cirrhosis and DM	Side-effects/risks
Lifestyle interventions Low fat diet Physical exercise	Decrease liver and adipose fat Increase insulin sensitivity	Very useful	Potentially useful	Malnutrition frequent in patients with cirrhosis Physical exercise may not be feasible in patients with advanced cirrhosis (edema_ascites)
Metformin	Increase insulin sensitivity	Very useful	Very useful	Contraindicated in patients with renal dysfunction
Thiazolidinediones	Increase insulin sensitivity	Useful	No available data	Reported hepatotoxicity Usefulness in patients with NASH has not been demonstrated
Secretagogues Sulphonyureas Glinides	Increase endogenous production of insulin	Useful	Not useful	Contraindicated in patients with advanced cirrhosis because of the risk of hypoglycaemia
Incretins GLP-1 receptor analogues DPP-4 inhibitors	Increase insulin sensitiviy	Very useful Obese patients (weight loss)	No available data	
Alpha-glucosidase inhibitors	Decrease carbohydrate absorption in the bowel	Useful	May be useful in patients with HE	Benign digestive side-effects
Insulin	Substitutive treatment	Often necessary	Often necessary	Risk of hypoglycaemia

Table 2. Therapeutics options for treatment of diabetes mellitus in patients with cirrhosis

DM, diabetes mellitus; NASH, non-alcoholic steatohepatitis; GLP-1, glucagon-like peptide-1; DPP-4, dipeptyl peptidase-4; HE, hepatic encephalopathy.

Impact of metformin on the outcome of cirrhosis

ffect of antidiabetic treatment on HCC in diabetic HCC subjects (n=610) vs control (n=1696) vs liver cirrhosis

	Univariate analysis			Multivariate analysis of metformin vs sulphonylureas or insulin		
	Odds ratio	95% CI	Р	Odds ratio	95% CI	Р
HCC vs Controls						
Metformin	0.33	0.10-0.61	0.0005	0.15	0.04-0.50	0.005
Sulphonylureas or insulin	3.06	1.61-5.70	0.005			
HCC vs LC						
Metformin	0.15	0.09-0.28	< 0.0001	0.16	0.06-0.46	0.0006
Sulphonylureas or insulin	6.44	3.58-11.6	< 0.0001			

Effect of metformin continuation on survival after discovery of cirrhosis



Donadon V et al. Liver Int 2010/Zhang X et al. Hepatology 202

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H. Sim. a 55 year old man, 6 months later



- Patient is now alcohol abstinent
- Recent blood test shows: ALT 58 U/L (\leq 40), AST 42 U/L (\leq 40), GGT 99 U/L (\leq 50), ALP 110 U/L (\leq 120), total bilirubin 15 µmol/L, albumin 36 g/L, hemoglobin 12 g/dL, MCV 93 fl, platelets 152x109/l, glucose 99 mg/dL, Hb A1c 7 %,

➢He asks you if there is a treatment available for NASH

What can you propose ?

- 1. Only lifestyle interventions
- 2. Vitamin E
- 3. Other strategy

Vitamin E in NASH: PIVENS

<u>ctudv</u>

Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.						
Variable	Placebo	Vitamin E	Pioglitazone	PV	alue☆	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo	
Primary outcome†						
No. of subjects randomly assigned	83	84	80			
Subjects with improvement (%)	19	43	34	0.001	0.04	
Changes from baseline in histologic features						
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70			
Steatosis						
Subjects with improvement (%)	31	54	69	0.005	< 0.001	
Mean change in score	-0.1	-0.7	-0.8	< 0.001	< 0.001	
Lobular inflammation						
Subjects with improvement (%)	35	54	60	0.02	0.004	
Mean change in score	-0.2	-0.6	-0.7	0.008	<0.001	
Hepatocellular ballooning						
Subjects with improvement (%)	29	50	44	0.01	0.08	
Mean change in score	-0.2	-0.5	-0.4	0.03	0.01	
Total NAFLD activity score (mean change)	-0.5	-1.9	-1.9	<0.001	<0.001	
Fibrosis‡						
Subjects with improvement (%)	31	41	44	0.24	0.12	
Mean change in score	-0.1	-0.3	-0.4	0.19	0.10	
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001	

Sanyal A et al. N Engl J Med 2010

Impact of vitamin E in NASH with severe fibrosis



70% cirrhosis

Vilar-Gomez E et al. Hepatology 2018

Conclusion

We need knew therapeutic strategies for severe NASH

