Non-Alcoholic Fatty Liver Disease (NAFLD)

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Outline

- Criteria
- Magnitude
- Pathogenesis
- Diagnosis
- Management
- Evidence for therapeutic options

NAFLD Definition

- Evidence of hepatic steatosis (fatty liver) either by imaging or histology
- No other causes of secondary hepatic fat accumulation
- No significant alcohol consumption (<21 drinks/week for men, <14 drinks/week for women)

Epidemiology

- Most common liver disorder in world
- 10-24 % incidence in general population
- Mostly in 4^{th} -6^{th} decade of life
- F>M
- 75 % of type 2 diabetics have some form of NAFLD
- NASH – 5 % biopsy

NAFLD – low risk factors

Reference, Year	Country	Population (n)	NAFLD Diagnosis	Prevalence of NAFLD (%)	Prevalence of NASH/ Fibrosis (%)	Criteria	Alcohol/Viral Hepatitis Excluded
General population, imaging studies							
Zhou et al, 2007[29]	China	General population ($N=3543$)	US	15.0	NA	NA	Yes
Fan et al, 2007[30]	China	Employees ($N=14646$)	US	14.0	NA	NA	Yes
Lin et al, 2005[31]	China	Employees ($N=1581$)	US	28.9	NA	NA	Only alcohol
Fan et al, 2005[32]	China	General population ($N=3175$)	US	15.3	NA	NA	Yes
Shen et al, 2003[33]	China	Administrative officers ($N=4009$)	US	12.9	NA	NA	Yes
Zelber-Sagi et al, 2006[34]	Israel	General population ($N=326$)	US	30.0	NA	NA	Yes
Kagansky et al, 2004[35]	Israel	Non–liver related hospitalization, elderly ($N=134$)	US	46.0	NA	NA	Yes
Bedogni et al, 2005[36]	Italy	General population ($N=598$)	US	20.0	NA	NA	Yes
Hamaguchi et al, 2005[37]	Japan	General population ($N=4401$)	US	18.0	NA	NA	Yes
Jimba et al, 2005[38]	Japan	General population ($N=1950$)	US	29.0	NA	NA	Yes
Omagari et al, 2002[39]	Japan	General population ($N=3432$)	US	13.4	NA	NA	Yes
Kim et al, 2004[40]	Korea	General population ($N=768$)	US	23.4	NA	NA	Yes
Lizardi-Cervera et al, 2006[41]	Mexico	General population ($N=2503$)	US	17.1	NA	NA	Yes
Chen et al, 2006[42]	Taiwan	General population ($N=3245$)	US	11.5	NA	NA	Yes
Park et al, 2006[43]	Korea	General population ($N=6648$)	US	18.7	NA	NA	Yes
Lin et al, 2005[44]	Taiwan	Healthy workers, men ($N=2025$)	US	29.5	NA	NA	No
Church et al, 2007[45]	United States	Healthy men ($N=218$)	CT	19.7	NA	NA	Yes
Browning et al, 2004[46]	United States	General population ($N=2287$)	MRS	31.0	NA	NA	Only alcohol
General population, liver enzymes							
Pendino et al, 2005[47]	Italy	General population ($N=1050$)	AST or ALT or GGT	4.7	NA	NA	Yes
Suzuki et al, 2005[48]	Japan	General population ($N=1537$)	AST or ALT	9.3	NA	NA	Yes
Clark et al, 2003[49]	United States	Representative of the U.S. general population	AST or ALT	5.4	NA	NA	Yes
Ruhl et al, 2003[50]	United States	Non-diabetes general population ($N=5724$)	ALT	2.8	NA	NA	Yes
General population, histopathologic studies							
Amarapurkar et al, 2007[51]	India	Deaths, general population ($N=1230$)	Autopsy	15.8	30% Fibrosis	NA	No
Yamamoto et al, 2007[52]	Japan	Living liver donors ($N=263$)	Biopsy	17.9	1.1% NASH	Brunt et al[53]	NA
Halon et al, 2006[54]	Poland	Dead liver donors ($N=70$)	Biopsy	30.0	14% NASH	NA	No
Tran et al, 2006[55]	United States	Living liver donors ($N=70$)	Biopsy	38.5	18.5% NASH	Brunt et al[53]	Only hepatitis

NASH, nonalcoholic steatohepatitis; US, ultrasound; NA, not applicable; CT, computed tomography; MRS, magnetic resonance spectroscopy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase.

NAFLD – Risk factors

Reference, Year	Country	Population (n)	NAFLD Diagnosis	Prevalence of NAFLD (%)	Prevalence of NASH/Fibrosis/ Cirrhosis (%)	Criteria	Alcohol/Viral Hepatitis Excluded
High risk population, imaging studies							
Targher et al, 2007[61]	Italy	Type 2 diabetes patients ($N=2839$)	US	69.5	NA	NA	Yes
Angelico et al, 2005[62]	Italy	Metabolic clinic consultation ($N=308$)	US	95.0	NA	NA	Yes
Gupte et al, 2004[63]	India	Type 2 diabetes patients ($N=100$)	US	49.0	NA	NA	Yes
Roesch-Dietlen et al, 2006[64]	Mexico	Metabolic syndrome ($N=337$)	US	15.7	NA	NA	Yes
Gambarin-Gelwan et al, 2007[65]	United States	Policystic ovary syndrome ($N=88$)	US	54.5	NA	NA	NA
Weston et al, 2005[66]	United States	Chronic Liver Disease Registry ($N=742$)	US/CT	39.1	NA	NA	Yes
High risk population, liver enzymes							
Liangpunsakul et al, 2005[67]	United States	Metabolic syndrome ($N=4376$)	ALT	7.0	NA	NA	Yes
High risk population, biopsy studies							
Lima et al, 2005[68]	Brasil	Bariatric surgery patients ($N=112$)	Biopsy	99.1	55.7 NASH/21.6 fibrosis	Modified from Brunt[53]	Yes
de Oliveira et al, 2007[69]	Brasil	Bariatric surgery patients ($N=146$)	Biopsy	76.0	41.1 NASH	Other	Yes
Boza et al, 2005[70]	Chile	Bariatric surgery patients ($N=127$)	Biopsy	63.0	26.0 NASH/1.6 cirrhosis	Modified from Brunt[53]	Yes
Hamois et al, 2006[71]	France	Bariatric surgery patients ($N=92$)	Biopsy	98.0	9.8 NASH	Other	Yes
Wolf et al, 2005[72]	Germany	Bariatric surgery patients ($N=179$)	Biopsy	33.0	7.3 Fibrosis	Other	Yes
Gupte et al, 2004[63]	India	Type 2 diabetes + US positive ($N=32$)	Biopsy	12.5	NA	NA	Yes
Papadia et al, 2004[73]	Italy	Bariatric surgery patients ($N=1000$)	Biopsy	26.0*	8.0 Fibrosis	Other	Only alcohol and HCV
Sorrentino et al, 2004[74]	Italy	Bariatric surgery patients + metabolic syndrome ($N=80$)	Biopsy	72.0	72.5 NASH/32.5 fibrosis	Brunt et al[53]	Yes
Chavarria et al, 2005[75]	Mexico	Bariatric surgery patients ($N=35$)	Biopsy	82.9	NA	Brunt et al[53]	Yes
Liew et al, 2006[76]	Taiwan	Bariatric surgery patients ($N=160$)	Biopsy	33.8	33.8 NASH	NASH-CRN[77]	Yes
Gholam et al, 2007[78]	United States	Bariatric surgery patients ($N=100$)	Biopsy	86.0	36.0 NASH/25.0 fibrosis	NASH-CRN[77]	NA
Solga et al, 2005[79]	United States	Bariatric surgery patients ($N=189$)	Biopsy	88.0	45.0 NASH	Brunt et al[53]	NA
Kunde et al, 2005[80]	United States	Bariatric surgery patients ($N=233$)	Biopsy	97.0	32.6 NASH/31.3 fibrosis	NASH-CRN[77]	Yes
Abrams et al, 2004[81]	United States	Bariatric surgery patients ($N=195$)	Biopsy	99.0	36.4 NASH/33.3 fibrosis	Brunt et al[53]	Yes
Beymer et al, 2003[82]	United States	Bariatric surgery patients ($N=48$)	Biopsy	65.0	33.0 NASH/12.0 fibrosis	Ishak	Only alcohol
Spaulding et al, 2003[83]	United States	Bariatric surgery patients ($N=48$)	Biopsy	90.0	49.0 Fibrosis/2.0 cirrhosis	Others	NA
Ong et al, 2005[84]	United States	Bariatric surgery patients ($N=212$)	Biopsy	93.0	26.0 NASH/9.0 fibrosis	Other	NA
Albano et al, 2005[85]	UK	Liver unit referral ($N=167$)	Biopsy	47.3	44.0 NASH/8.0 cirrhosis	Modified from Brunt[53]	Yes

*70% or more hepatic steatosis.
NASH, nonalcoholic steatohepatitis; US, ultrasound; CT, computed tomography; NA, not applicable; ALT, alanine aminotransferase; HCV, hepatitis C virus; NASH-CRN, nonalcoholic steatohepatitis Clinical Research Network.

AFRICAN STUDIES

Nigeria - 20% and comparable to the prevalence of NAFLD in Asian countries.

Nigeria Type 2 DM :- NAFLD was identified in 16.7% (28 of 168) patients with T2DM compared with 1.2% (2 of 168) non-diabetic controls (Odds Ratio 16.6; $p < 0.001$)

Sudan - The overall prevalence of fatty liver among individuals with type 2 DM 50.3%.

Egypt - Fatty liver was prevalent in schoolchildren (15.8%)

Arab J Gastroenterol. 2014 Jun;15(2):76-81

Pan Afr Med J. 2016 May 6;24:20.

Arab J Gastroenterol. 2014 Mar;15(1):12-5.

ETHIOPIA

Ethiopian studies – risk factors

- Obesity :- 6.6 % (Females) and 1.5 % male

World data Atlas, 2014

- Jimma - overweight/obesity was 26.8 %.

Hailemichael et. al., 2010

- School children, Diredawa 14.7 and 5.8 % Alemnesh, 2016
- Type 2 DM 3.1% (1980) to 7.1%(2014) in WHO African report
- There were over 1.33 million cases of diabetes in Ethiopia in 2015.

IDF, 2015

Risk Factors for NAFLD

Major Co-morbidities

- Type 2 Diabetes
- Dyslipidemia
- Obesity
- Metabolic Syndrome

Other Associations

- Sleep Apnea
- Polycystic Ovary Syndrome
- Hypothyroidism
- Hypopituitarism

Metabolic Syndrome (≥ 3 of following: NCEP/ATP III criteria)

i. Impaired fasting glucose and DM
ii. Central obesity: (waist circumference > 35 inches in women and 40 inches in men)
iii. Elevated Triglyceride (≥ 150 mg/dl)
iv. Low HDL Cholesterol (< 50 mg/dL in females and 40 mg/dL in males)
v. HTN

Lonardo A, et al. J Hepatol 2006;44:1196
McCullough A et al. J Clin Gastroenterol 2002;34:255

Spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD)

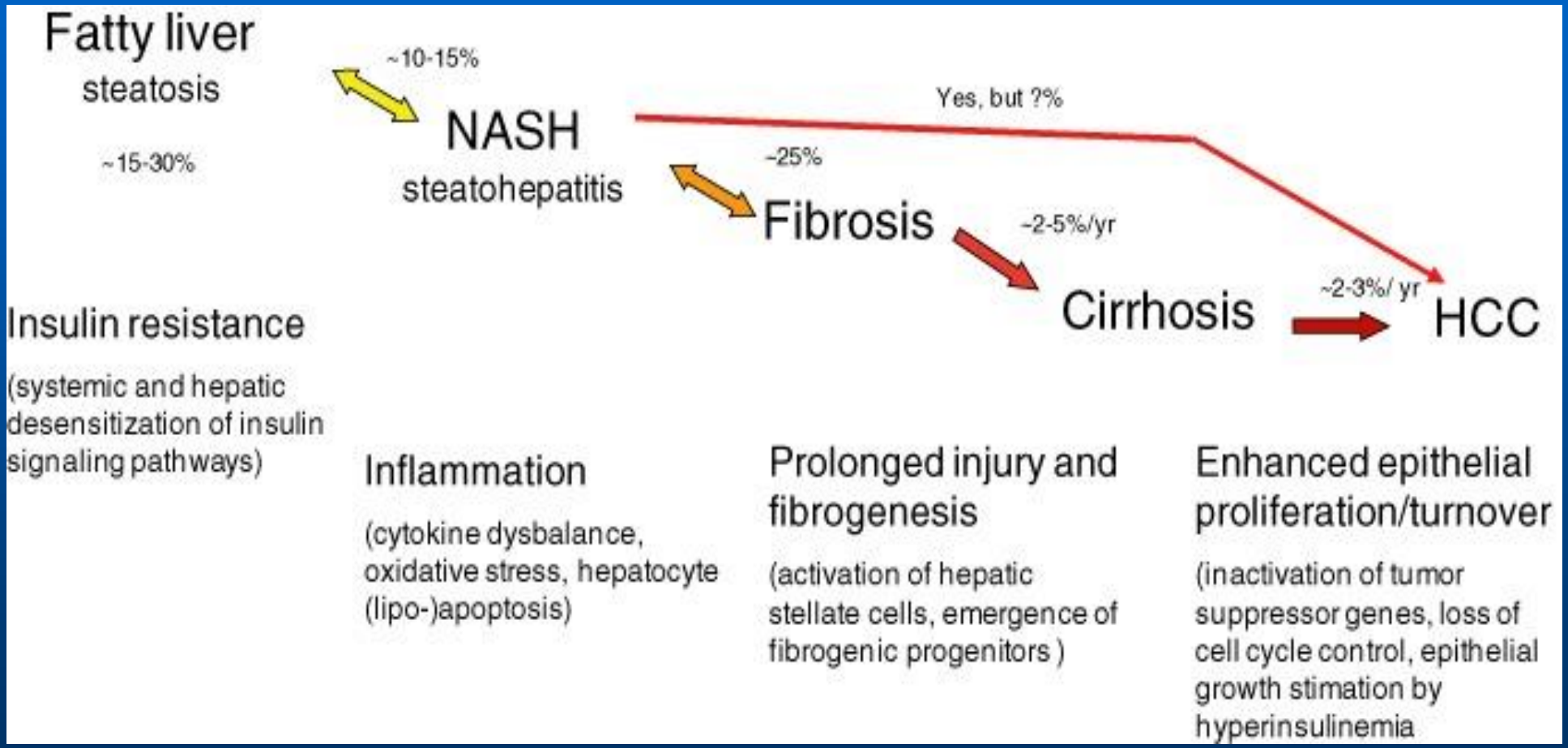
NAFL

(Fat/Steatosis only)

Steatohepatitis (NASH)

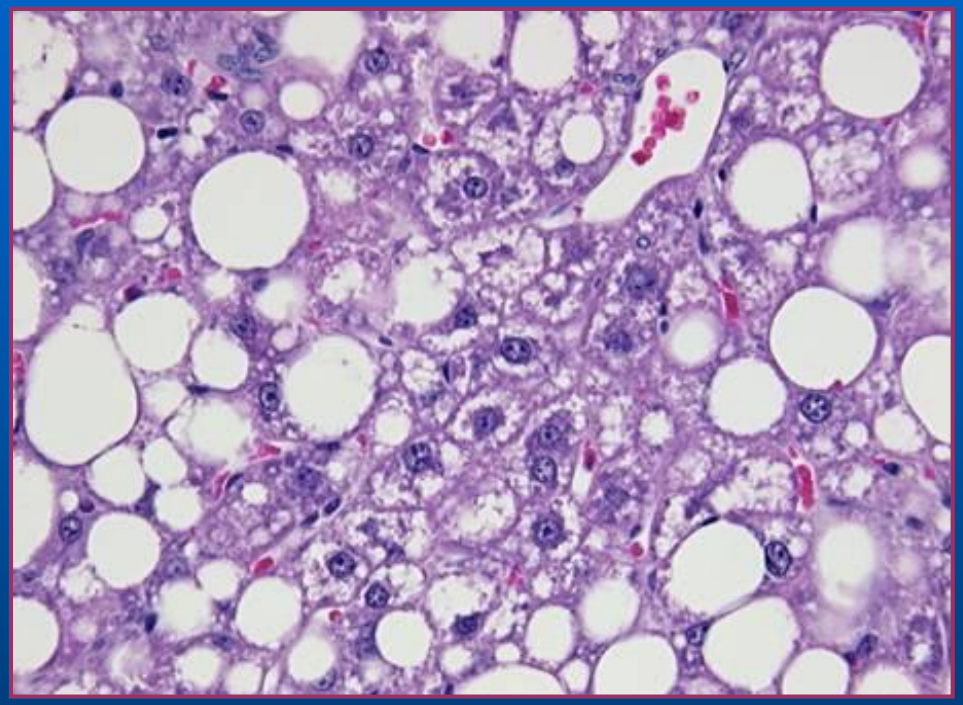
(Steatosis, inflammation, ballooning degeneration, +/- fibrosis)

NAFLD Spectrum

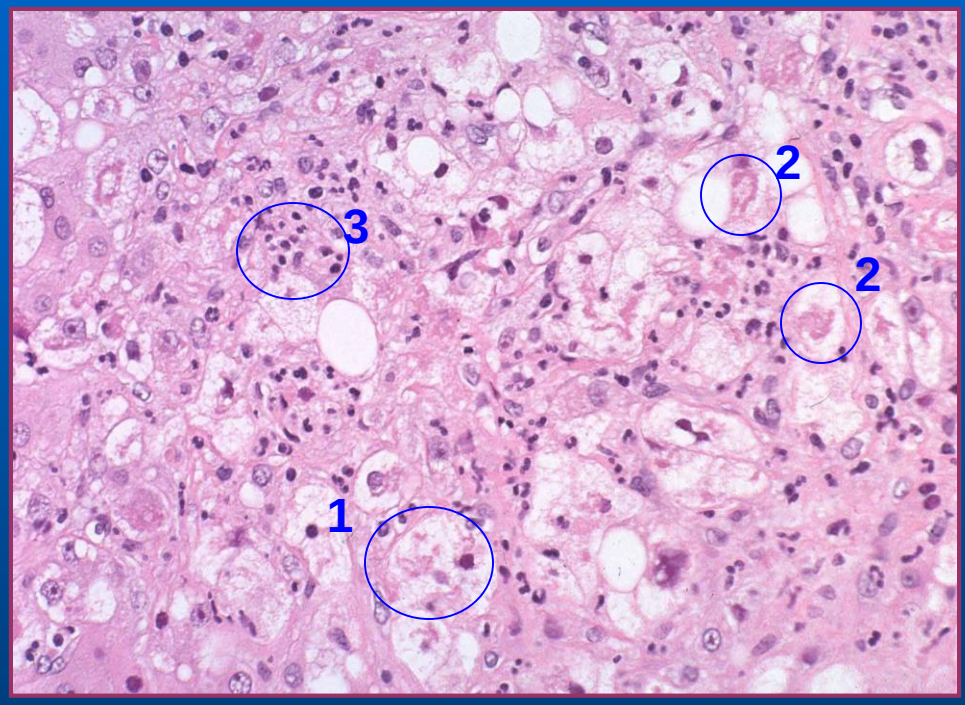


Spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD)

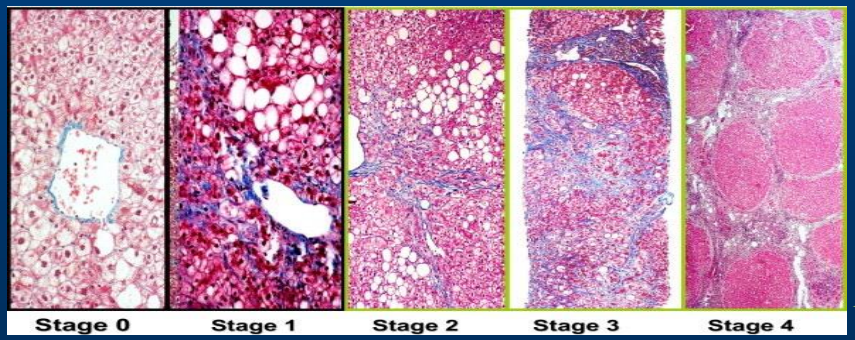
NAFL



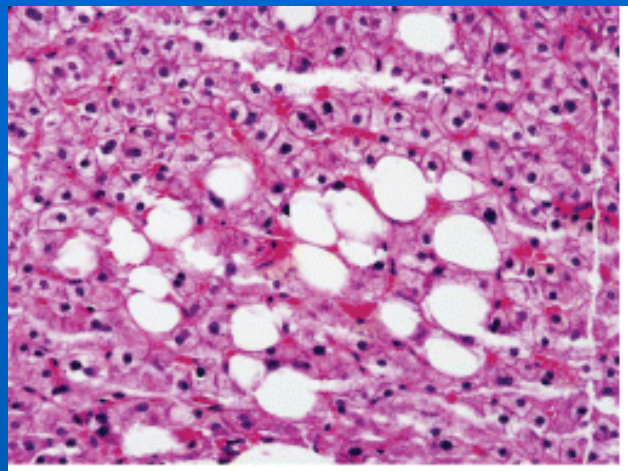
NASH



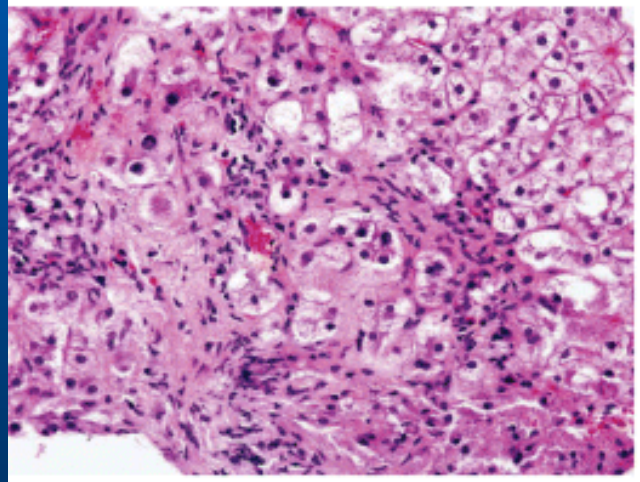
- Hepatocyte Injury (Ballooning[1], Mallory Bodies[2], Dead cells)
- Inflammatory Cell (Infiltration[3])



- Fibrosis[4]



Fatty Liver



NASH

Fatty Liver

↓

NASH

↓

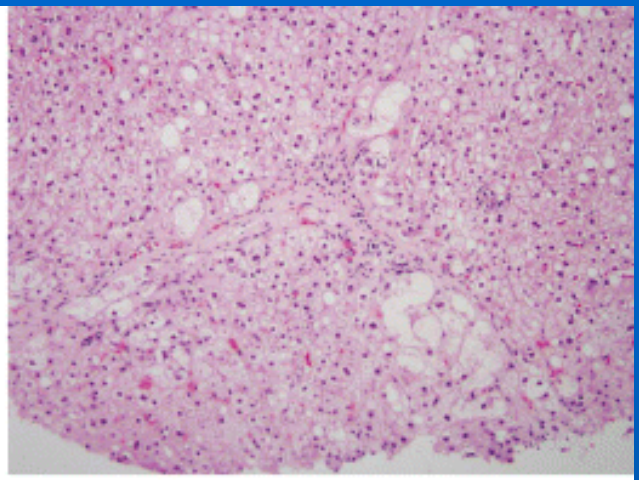
NASH
with Fibrosis

↓

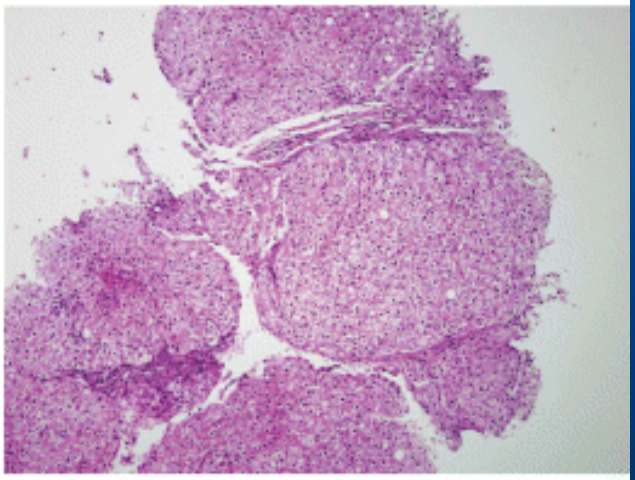
Cirrhosis

↓

Decompensated
Cirrhosis



NASH with Fibrosis



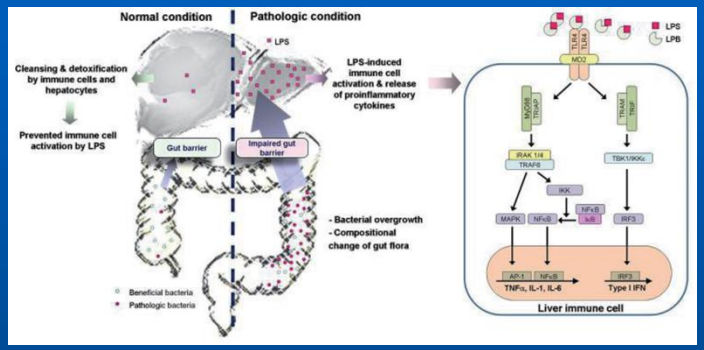
Cirrhosis

http://www.nature.com/ajg/journal/v101/n3/images/ajg2006121f1.gif

Gut Microbiome on Obesity, IR, NAFLD Progression

Intestinal microbiota

GI Tract



First Hit

- Endotoxemia
- Insulin Resistance
- ↑ calorie extraction
- Hyperlipidemia
- Altered choline metabolism

Second Hit

- Bacterial Translocation
- Elevated levels of PAMPs in portal V

Healthy Liver

Steatosis

TLR4 & TLR9 activation

Steatohepatitis

Inflammation

Fibrosis/Cirrhosis

Adapted from: Henao-Meja J et al. Journal of Autoimmunity 2013

Henao-Meja J et al. Nature 2012;482:179-185

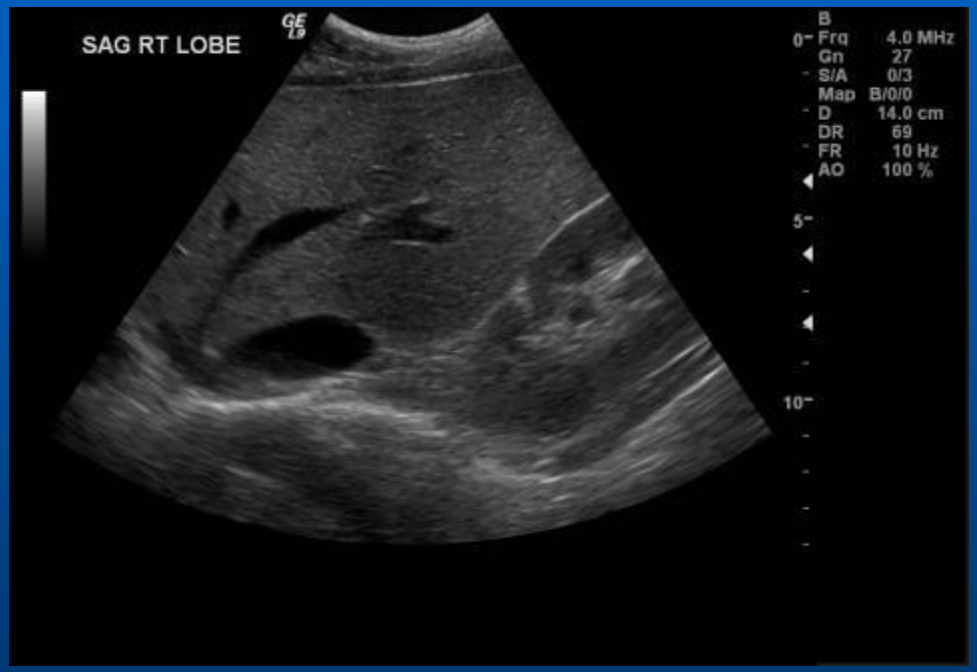
Frasinariu OE et al. Digestive and Liver Disease 2013;45:543– 551

NAFLD Diagnosis

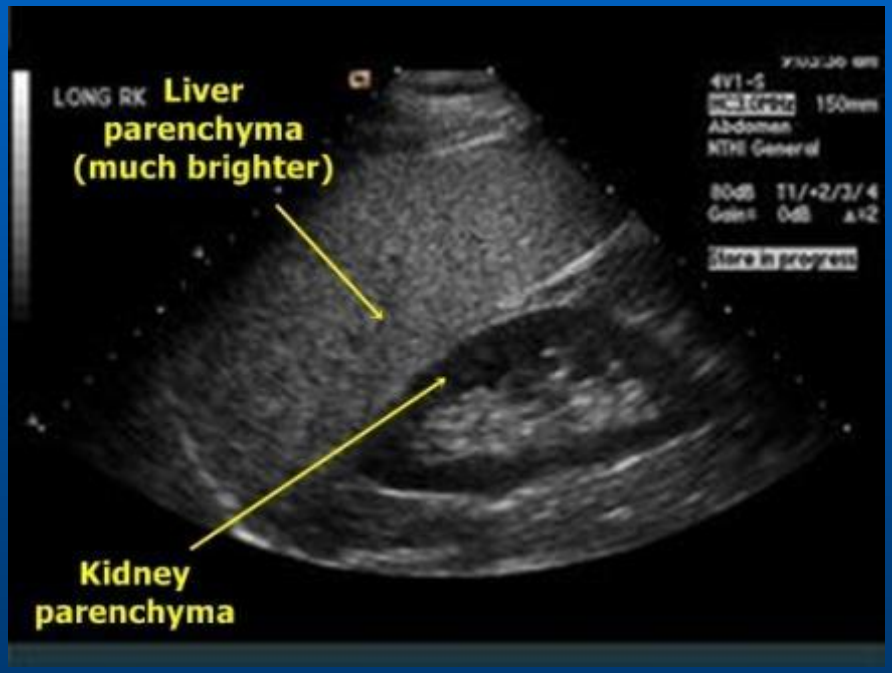
- Evidence of hepatic steatosis (fatty liver) either by imaging or histology
- No other causes of secondary hepatic fat accumulation
- No significant alcohol consumption (<21 drinks/week for men, <14 drinks/week for women)
- Elevated liver enzymes (*predominantly ALT and AST, Alkaline Phosphatase in a small percent of cases*) – can be normal in about 10%
- Imaging: US, CT, MRI
  - Cannot distinguish NAFL vs. NASH, degree of fibrosis

Ultrasound

Normal Liver



Fatty Liver



Ultrasound

Pros

Quick test

Inexpensive

No radiation

Painless

Cons

Sensitivity: 93% when steatosis is >33%, but poor when steatosis <30%

Changes of hepatic steatosis on ultrasound (increased brightness, vascular blurring) can also be seen in fibrosis or early cirrhosis

Limited by body habitus

Liver biopsy

Assessing Histological Severity NAFLD

- **Liver Biopsy**: remains the gold standard
  - NAFL (Steatosis) vs. NASH

- **Non-Invasive Methods of assessing severity**
  - Presence of **Metabolic Syndrome**
  - **Serum Markers** (clinical//biochemical) and **Imaging Modalities**
    - Serum Biomarkers (NAFL vs. NASH): **CK-18**

→ Blood cytokeratin-18 fragment (CK-18) reflects the degree of apoptosis, a characteristic feature of NASH

→ Limited sensitivity for NASH, fibrosis

    - Fibrosis Markers/Liver Fibrosis Panel: ELF, Fibrometer, FIB-4, Hepascore, Fibrotest
    - **NAFLD Fibrosis Score** (http://nafldscore.com): age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio
    - Elastography (liver stiffness): US/MR

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)

BMI (kg/m²)

IGF/diabetes ☐

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

calculate score

BMI: body mass index
IGF: impaired fasting glucose

Assessing Histological Severity NAFLD

NAFLD Fibrosis Score (http://nafldscore.com):

age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio

-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

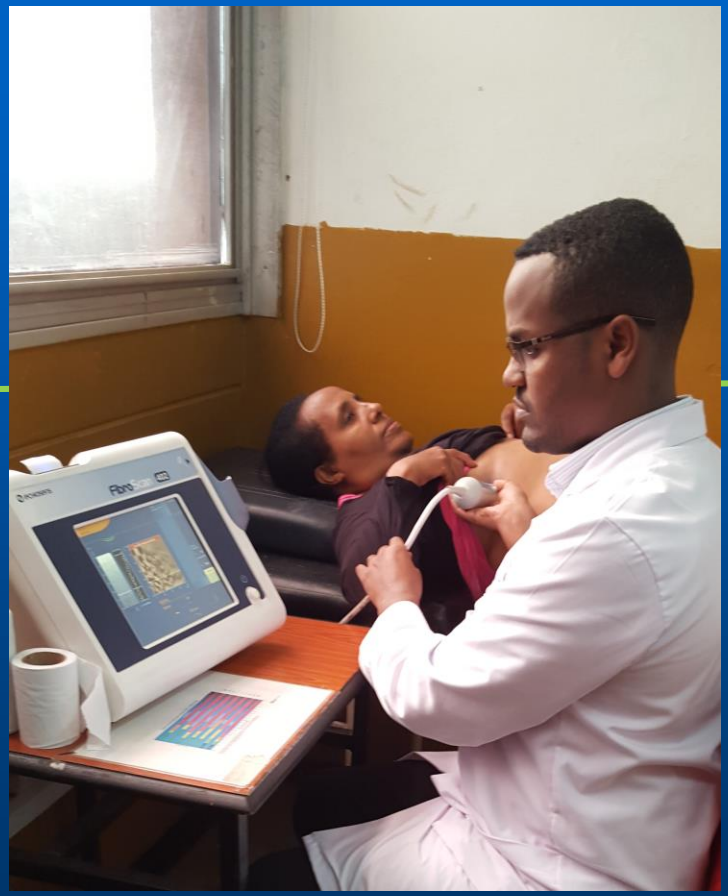
NAFLD Score < -1.455 = F0-F2 (none-mild fibrosis)
NAFLD Score -1.455 – 0.675 = Indeterminate score
NAFLD Score > 0.675 = F3-F4 (bridging/cirrhosis)

NAFLD Fibrosis Score – An Independent Predictor of Mortality

Angulo P, et al. Hepatology. 2007 Apr;45(4):846-54
Younossi Z et al. AASLD 2013 Abstract #634

Imaging Tests Measuring Stiffness: Elastography

Fibroscan



Point SWE ("ARFI quantification") (Siemens, Phillips)

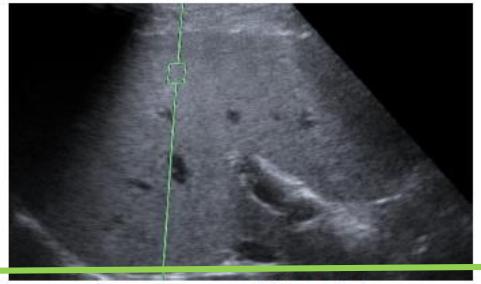
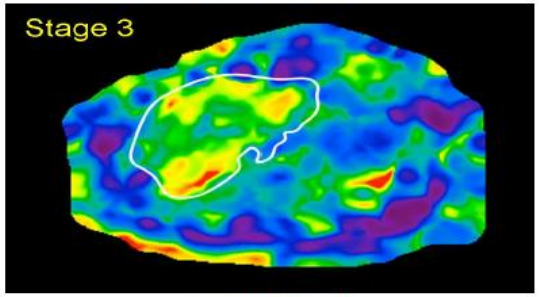


Image courtesy of Elhamy Heba

MR Elastography (G.E.)

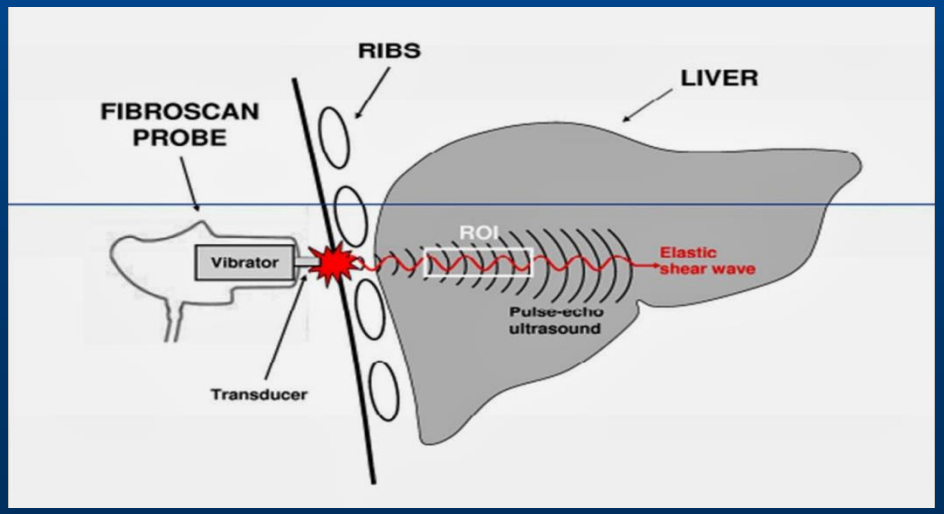


Loomba DDW 2013

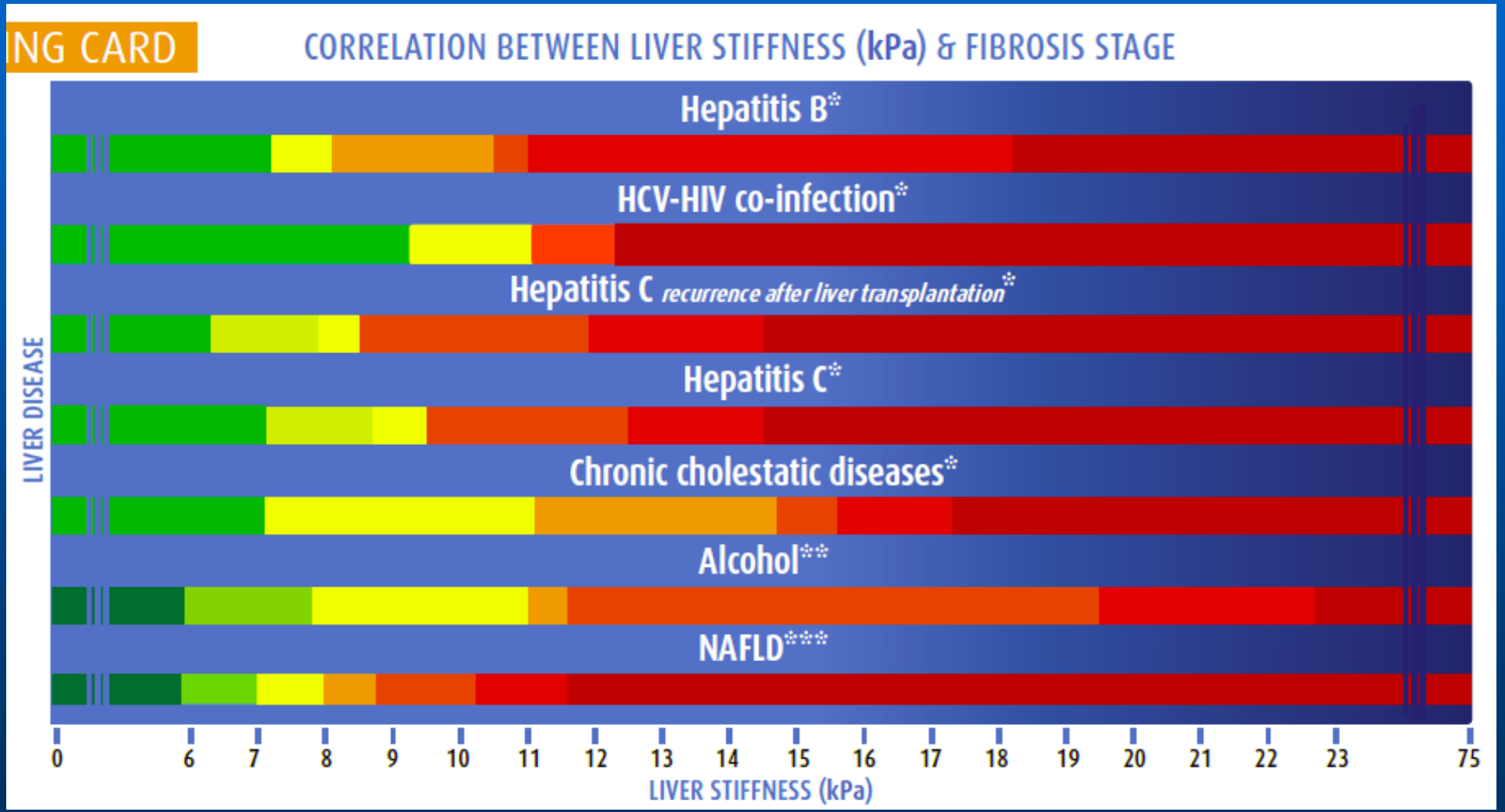
Courtesy of **Loomba R**

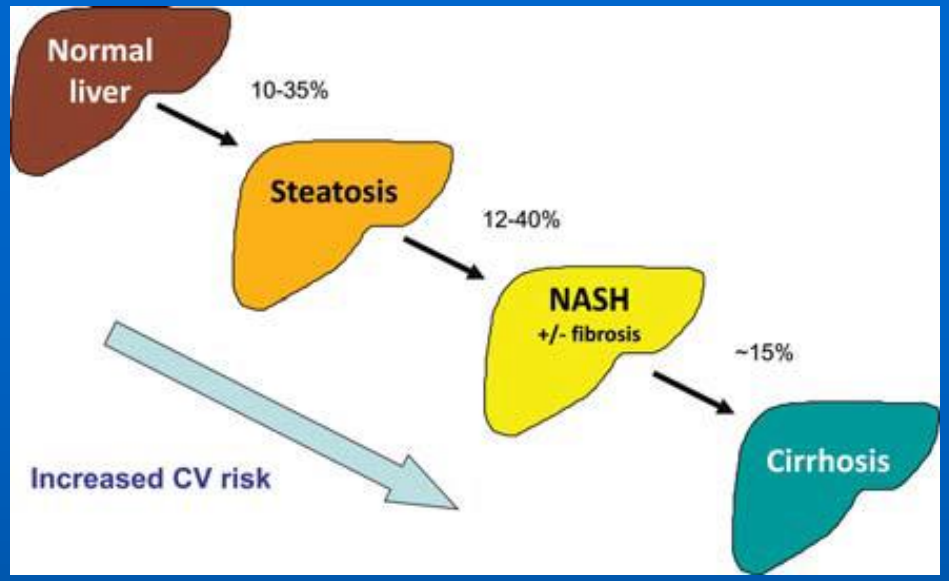
Fibroscan: US Elastography

- Non-invasive way to measure liver stiffness, which correlates with fibrosis
- Measures shear wave velocity by passing a 50-MHz wave into the liver and then a transducer measures the velocity of the shear wave
- Shear wave velocity then gets converted into liver stiffness and is expressed as kilopascals



Fibroscan: US Elastography





NAFLD: a new and important cardiovascular risk factor

- Elevated levels of plasma biomarkers of inflammation
- Endothelial dysfunction
- Early carotid changes
- Early myocardial dysfunction

- There is a graded relationship between the histological severity of NAFLD and atherosclerosis.
- Increased CVD risk seen even after adjustment for traditional risk factors and components of the metabolic syndrome.

NAFLD: Not just a biomarker but an early mediator of atherosclerosis

Bhatia LS et al. European Heart J 2012;33:1190
Targher G et al. Diabetologia 2008, 51:1947

AASLD/ACG/AGA - Work up NAFLD

- Look for metabolic risk factors and alternate etiologies in pts with steatosis
- NASH cirrhosis - screen for varices, HCC screening
- Uncertainities - screening not recommended
- Exclude competing etiologies
- NAFLD fibrosis score - predict likelihood of bridging fibrosis/cirrhosis
- Liver biopsy - exclude coexisting CLD, high autoantibodies, persistently high ferritin

Management

Management of NAFLD: NAFL/NASH

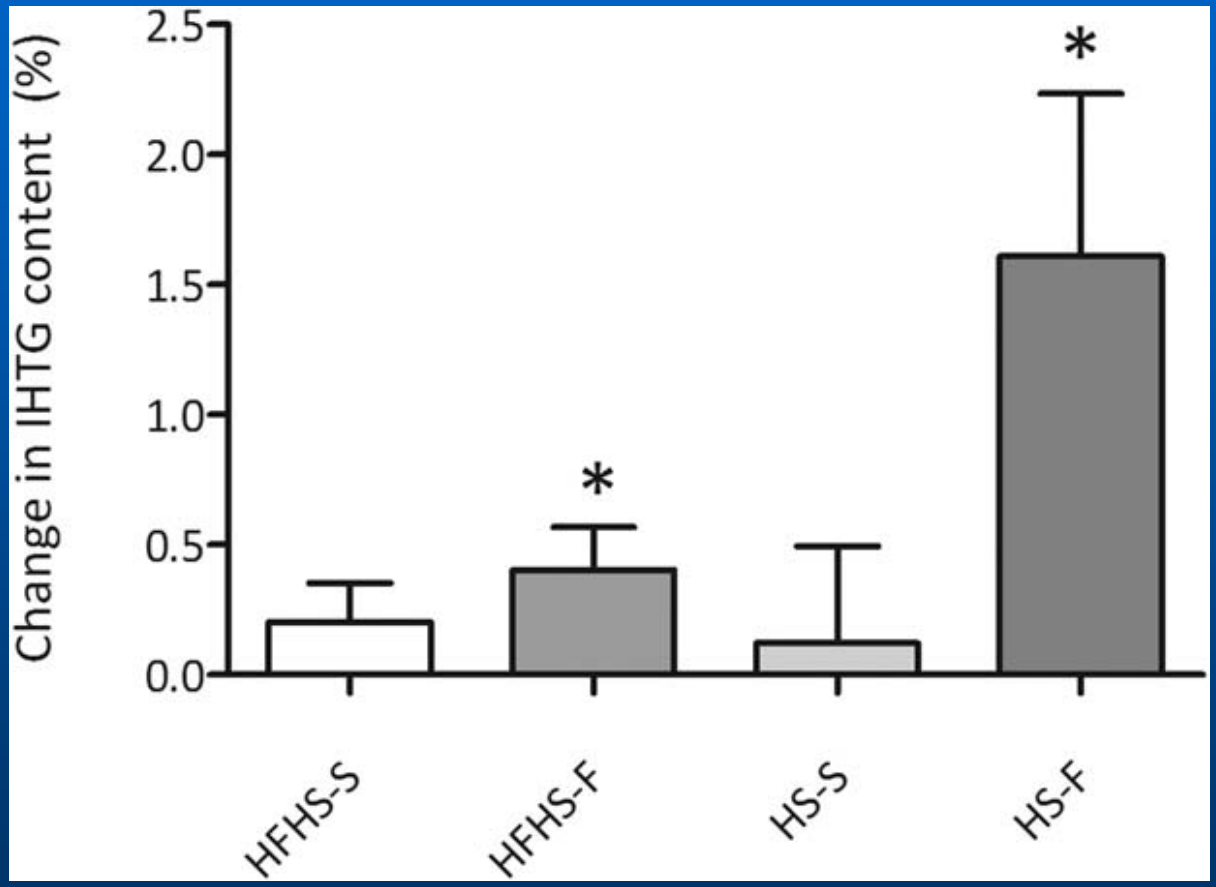
- Improving underlying risk factors
  - Correct metabolic syndrome
  - Life-style changes (Dietary modification, Weight loss, Physical exercise)
  - Surgical [Bariatric] therapy
- Ameliorating insulin resistance, intra-hepatic lipids and oxidative stress
  - Life-style changes (Dietary modification, Weight loss, Physical exercise)
  - Medical Therapy (Drugs)
  - Surgical [Bariatric] therapy

Dietary Modification

- **Total calorie restriction:** *most important goal for improving steatosis*
  - Leads to weight loss
- **Macronutrient modification:** *provides additional benefit*
  - **Low carbohydrate diet vs. Low Fat diet**
    - Both similar to lower liver fat and serum ALT
    - Both similar to induce wt. loss, improve insulin sensitivity (IS), TGL
  - **Low carbohydrate diet**
    - Better in improving IS in pts. with glucose intolerance
    - Significantly reduces waist circumference, more consistent changes in LDL-C and HDL-C
  - **Low fat diet:** less saturated fat, more Polyunsaturated Fat (PUFA)

Musso G et al. Diabetologia 2012; 55:885
McCarthy EM, Rinella M. JADA 2012;112:401
Finelli C, Tarantino G. J Gastrointestin Liver Dis 2012; 21:293

Hypercaloric Diets With Increased Meal Frequency, but Not Meal Size, Increase Intrahepatic Triglycerides: A Randomized Controlled Trial



HF = High Fat High Sugar; HS= High Sugar
S = Size
F = Frequency

Koopman KE et al. Hepatology 2014;60:545-553

Weight Loss

- **~ 10% loss in body weight may lead to histological improvement (target for weight loss)**
  - Improves IS, fasting glucose, glucose tolerance, plasma lipids
  - **≥5%** weight loss improves hepatic steatosis
  - **≥7%** weight loss also improves NAS (NASH Activity Score)
  - **>10%** weight loss also predicts **'fibrosis regression'**
- **Less than 50% achieve goal despite multi-disciplinary approach**
- **Avoid rapid and dramatic weight loss and weight cycling**

Musso G et al. Diabetologia 2012;55:885
Huang MA, Conjeevaram H. Am J Gastroenterol 2005;100:1072
Promnat K et al. Hepatology 2010;51:121
Glass LM et al. AASLD 2012 Abstract #378

Weight Loss

Weight Loss for NASH

- Design: Prospective cohort study of 293 patients with biopsy-proven NASH followed over 12 months
- "Intervention":
  - Given recommendations to consume a low-fat diet of 750 kcal/day less than their estimated daily energy needs (64% carbs, 22% fat, 14% protein)
  - Encouraged to walk 200 minutes/week
  - Liver biopsies obtained pre-and post study
- Primary Outcome: Resolution of NASH with no worsening of fibrosis

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis
Vilar-Gomez, Eduardo et al. Gastroenterology , 2015, Volume 149 , Issue 2 , 367 - 378.e5

Weight Loss Results

Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	*P* value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis[a]	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01
NAS improvement[b]	138 (47)	66 (32)	21 (62)	22 (88)	29 (100)	<.001
Change in NAS from baseline	−1.58 ± 0.27	−0.89 ± 0.13	−1.94 ± 0.36	−3.84 ± 0.29	−4.10 ± 0.23	<.001
Steatosis improvement[c]	142 (48)	72 (35)	22 (65)	19 (76)	29 (100)	<.001
Change from baseline	−0.63 ± 0.10	−0.36 ± 0.07	−1 ± 0.13	−1.40 ± 0.19	−1.69 ± 0.12	<.001
Lobular inflammation improvement[c]	147 (50)	72 (35)	24 (71)	22 (88)	29 (100)	<.001
Change from baseline	−0.49 ± 0.15	−0.29 ± 0.05	−0.53 ± 0.22	−1.32 ± 0.09	−1.21 ± 0.11	<.001
Ballooning improvement[c]	115 (39)	54 (26)	14 (41)	21 (84)	26 (90)	<.001
Change from baseline	−0.45 ± 0.17	−0.24 ± 0.04	−0.41 ± 0.13	−1.12 ± 0.13	−1.34 ± 0.08	<.001
Fibrosis status[d]						<.01
Regression	56 (19)	33 (16)	6 (18)	4 (16)	13 (45)	
Stabilized	191 (65)	129 (63)	25 (74)	21 (84)	16 (55)	
Worsened	46 (16)	43 (21)	3 (8)	0 (0)	0 (0)	
Change from baseline	−0.01 ± 0.02	0.09 ± 0.07	−0.02 ± 0.03	−0.17 ± 0.12	−0.86 ± 0.20	<.001**
Portal inflammation improvement[c]	44 (15)	27 (13)	3 (9)	5 (20)	9 (31)	.049
Change from baseline	0.02 ± 0.02	0.06 ± 0.01	0.09 ± 0.03	−0.07 ± 0.01	−0.31 ± 0.08	<.01**
NAS status						<.001
NAS ≤2	119 (41)	48 (23)	20 (59)	22 (88)	29 (100)	
NAS 3–4	79 (27)	74 (36)	2 (6)	3 (12)	0 (0)	
NAS ≥5	95 (32)	83 (41)	12 (35)	0 (0)	0 (0)	

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis
Vilar-Gomez, Eduardo et al. Gastroenterology , 2015, Volume 149 , Issue 2 , 367 - 378.e5

Weight Loss Results

- At least a 5% weight loss increases the odds of resolution of NASH.
- The more weight lost, the greater the odds of resolution of NASH.
- **Weight loss of ≥10%** resulted in:
  - Resolution of NASH in 90% of patients
  - Regression of fibrosis in 45% of patients
  - Reduction in NAS to ≤2 in 100% of patients

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis
Vilar-Gomez, Eduardo et al. Gastroenterology , 2015, Volume 149 , Issue 2 , 367 - 378.e5

Exercise

- Aerobic exercise with or without weight training improves insulin resistance (IR)
  - Moderate exercise (expending 400 kcals/session) 3 x per week is sufficient to improve IR
- Overall energy expenditure achieved per workout is very important
- More recently, exercise intensity has also been shown to improve liver histology in NASH

Rector RS, et al. Am J Physiol Gastrointest Liver Physiol 2008;294:G619
Mikus CR, et al. J Appl Physiol 2010;109:1203
Laye MJ, et al. J Physiol 2009;587:3729
Vieira VJ, et al. Am J Physiol Endocrinol Metab 2009;296:E1164
Bradley RL, et al. Am J Physiol Endocrinol Metab 2008;295:E586
Robol R, et al. PNAS USA 2011;108:13705

Potential Medical Therapeutics for NASH

- **Ursodiol**
- **Antioxidants**
  - **Vitamin E**
  - SAM-E
  - Betaine
- **Insulin Sensitizers**
  - **Metformin**
  - **TZDs (PPAR© agonists)**
- **Anti-lipemics**
  - Clofibrate
  - Gemfibrozil
  - Atorvastatin
  - Fenofibrate (PPAR〈 agonist)
- **Losartan**
- **Anti-Fibrotics**
  - **Galectin-3, Simtuzumab**
- **TNFα inhibitors**
  - **Pentoxifylline**
- **Omega-3 Fatty Acids**
- **Capsase Inhibitor**
  - **GS-9450**
- **GLP-1 receptor agonist**
  - **Liraglutide, Exenatide**
- **FXR agonist**
  - **Obeticholic acid (OCA)**
- **Orlistat (Xenical)**
- **CAM: Sylimarin**
- **Growth Hormone**
- **Rimonabant** (CB1 receptor antagonist)

A Randomized controlled trial of Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis (PIVENS)

- A placebo-controlled trial with 3 arms (Rx for 96 weeks):
  - **Pioglitazone 30 mg/d (n, 80)**
  - **Natural Vitamin E [rrr 〈 -Tocopherol] 800 IU/d (n, 84)**
  - **Placebo (n, 83)**
- Inclusion criteria: NAFLD Activity Score (NAS) ≥ 4 within 6 months prior to randomization
  - NAS = steatosis (0-3) + ballooning (-02) + lobular inflammation (0-3)
- Exclusion criteria:
  - Presence of diabetes
  - Presence of cirrhosis
  - History of bariatric surgery

Sanyal A, et al. N Engl J Med 2010;362:1675-85

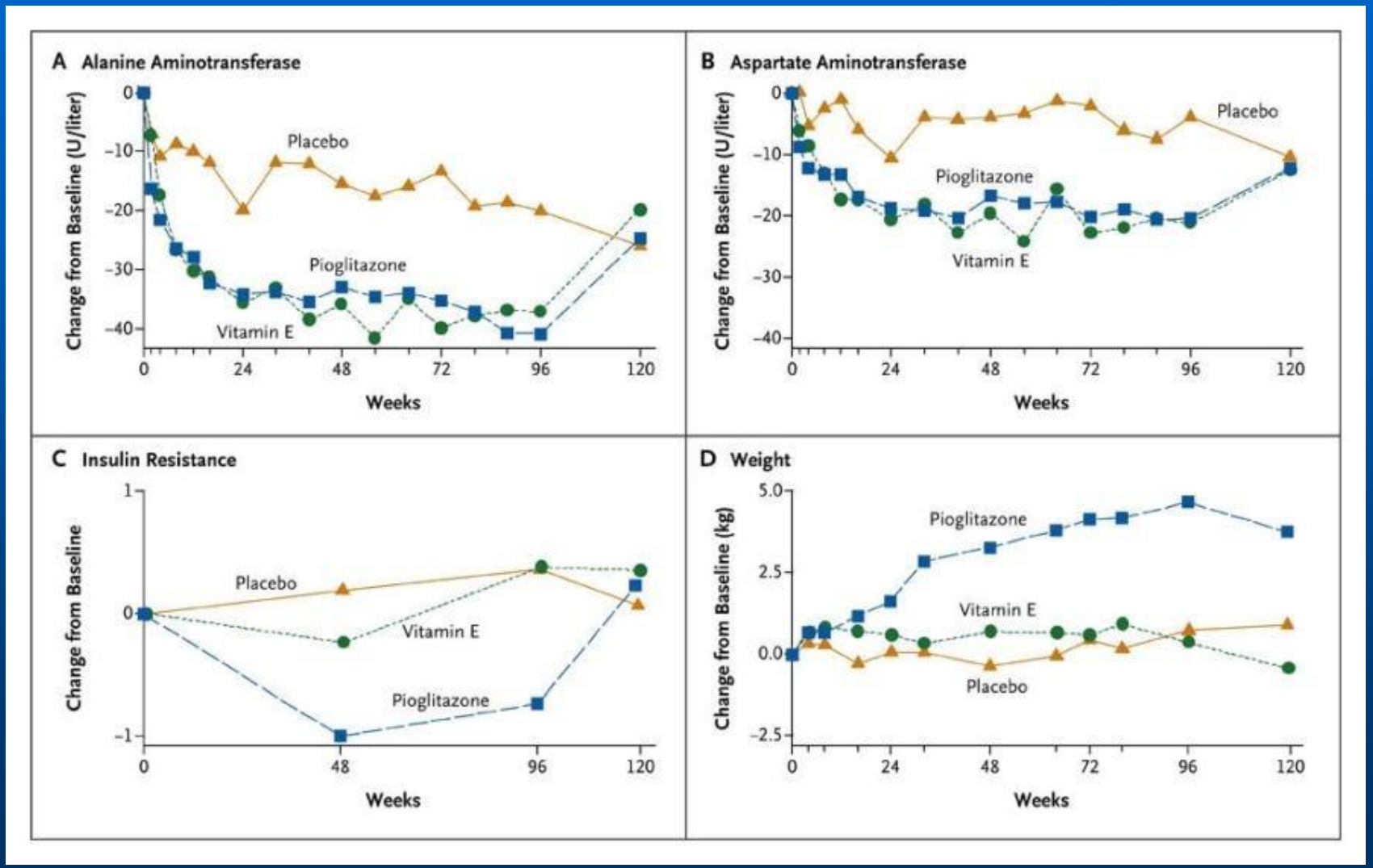
A Randomized Controlled Trial of Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis (PIVENS)

- **Primary end-point: Decrease in NAS by ≥ 2 points (at least 1 point decrease in ballooning) and no increase in fibrosis**
  - **A p-value of < 0.025 considered significant when comparing groups**

- **Secondary end-points:**
  - Individual features of NASH
  - No NASH after treatment
  - Improvement of Insulin Resistance
  - Quality of Life

Sanyal A, et al. N Engl J Med 2010;362:1675-85

Effects of Pioglitazone, Vitamin E and Placebo on ALT, AST, IR, Body Weight



Sanyal A, et al. N Engl J Med 2010;362:1675-85

Results

- **Primary end-point (Histological):**
  - **Placebo** — **19%**
  - **Vitamin E** — **43% (p= 0.001 vs. Placebo)***
  - **Pioglitazone** — **34% (p= 0.04 vs. Placebo)**

- Compared to Placebo:

	Vitamin E	Pioglitazone
Improved steatosis	yes	yes
Improved inflammation	yes	yes
Improved ballooning	yes	yes
Improved fibrosis	no	no
Improved serum ALT	yes	yes

*P < 0.025 considered significant

Sanyal A, et al. N Engl J Med 2010;362:1675-85

Potential Problems/Risks with TZDs and Vitamin E

- **TZDs:**
  - Weight gain
  - Congestive heart failure
  - Increased heart attacks with rosiglitazone
  - Bone loss
  - Discontinuation of therapy leads to worsening of histology
- **Vitamin E:**
  - Increased in total mortality, heart failure, and hemorrhagic stroke in certain high risk patients[#]

[#]Saremi A and Arora R. American J Therapeutics 2010;17:56-65

AASLD Practice Guidelines 2012

(i) Vitamin E (a-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.

(ii) 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.

Chalasani N et al. Gastroenterology. 2012;142:1592-1609

AASLD Practice Guidelines 2012

(i) **Metformin** has no significant effect on liver histology and is **not recommended** as a specific treatment for liver disease in adults with NASH.

(ii) **Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH.**

However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established.

Chalasani N et al. Gastroenterology. 2012;142:1592-1609

Newer Potential Therapies in the Horizon

Liraglutide

- A Glucagon-like peptide-1 analogue – licensed for use in Type 2 DM.
- Increases insulin secretion and insulin sensitivity.
- Up to 26 weeks of liraglutide (dose = 1.8 mg) has been shown to be safe, well tolerated and improve liver enzymes in patients with type 2 diabetes.
  - Effect appears to be mediated by its action on weight loss and glycemic control.

Zhang L et al. Liver International 2013;
Armstrong MJ et al. Aliment Pharmacol Ther 2013; 37: 234–242

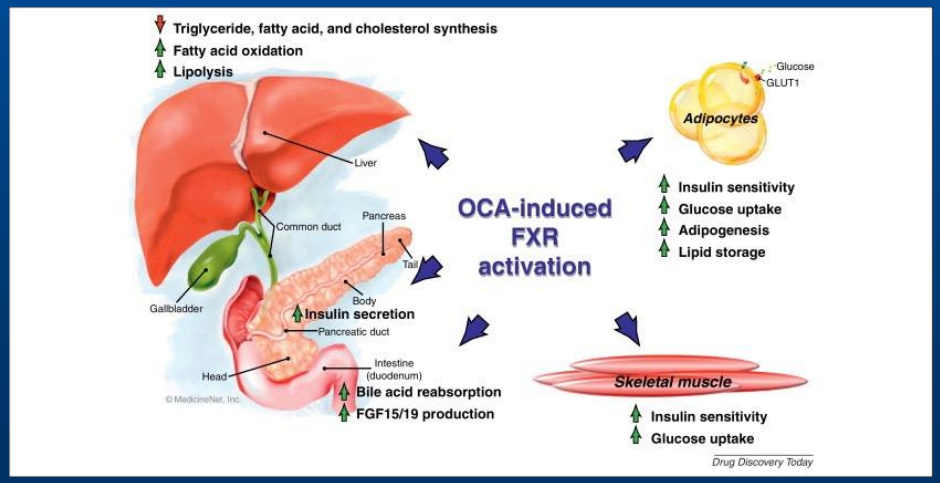
A Pilot Study of Liraglutide in NAFLD/NASH Patients with glucose intolerance

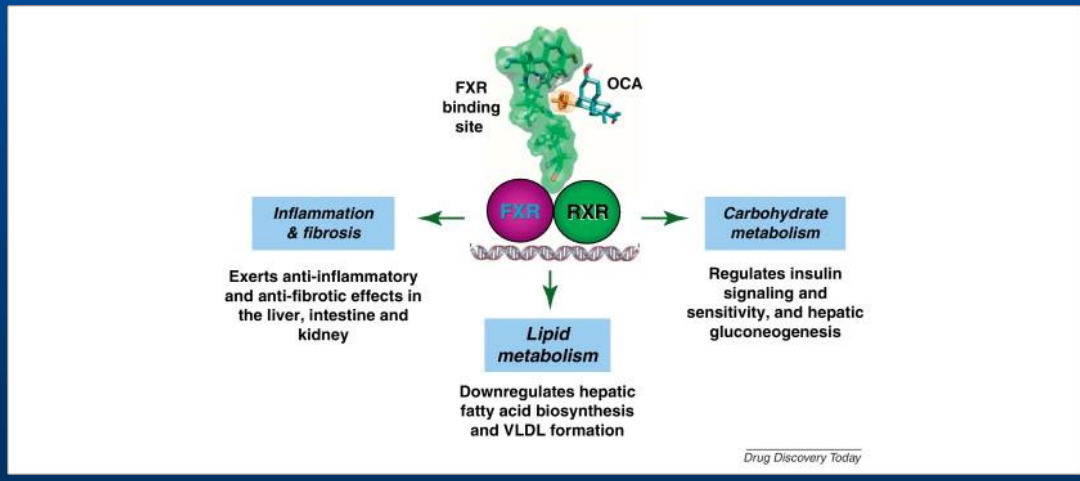
- Patient Inclusion Criteria: After lifestyle modification intervention for 24 weeks, subjects whose hemoglobin A1c levels failed to improve to less than 6.0% and/or whose ALT levels were not lower than baseline.
  - 19/26 patients met the criteria
- Liraglutide dose: 0.9 mg/body per day for 24 weeks.
- 10 patients continued therapy for 96 weeks – repeated liver biopsy performed in these patients.
- **Results**:
  - 6 patients had decreased inflammation as determined by NASH activity score (NAS) and stage of fibrosis; 3 had no change and one patient had worsening of both findings.
  - No significant adverse events during therapy with liraglutide.

Eguchi Y et al. Hepatology Res 2014

Obeticholic acid (OCA)

- OCA: 6a-ethyl-chenodeoxycholic acid is a semisynthetic derivative of the primary human bile acid chenodeoxycholic acid, the natural agonist of the farnesoid X receptor, which is a nuclear hormone receptor that regulates glucose and lipid metabolism.
- First-in-class **agonist of the farnesoid X receptor (FXR)**.
- In animal models, OCA has been shown to decrease insulin resistance and hepatic steatosis.





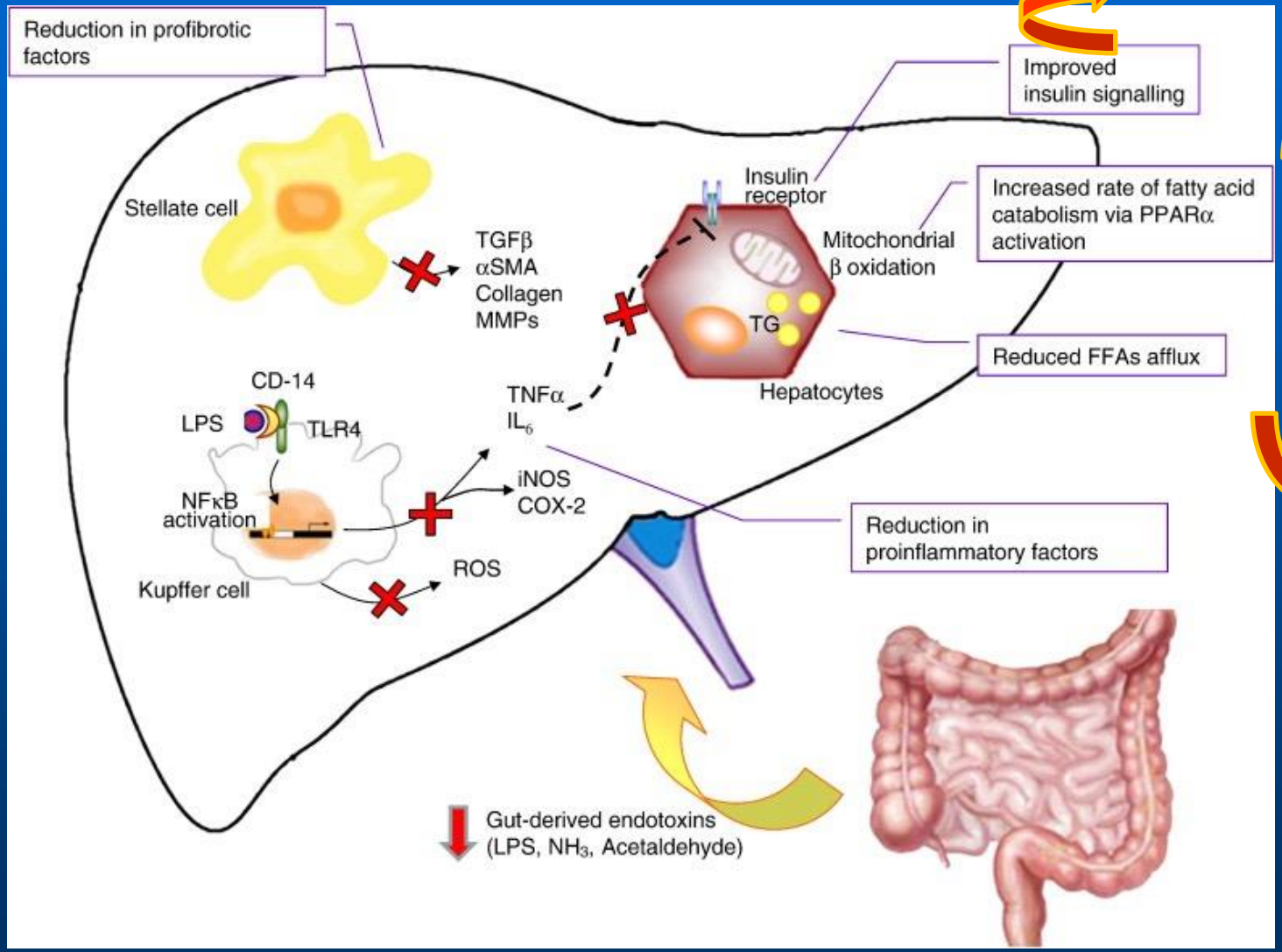
Adorini L et al. Drug Discovery Today 2012;17:988-997

Obeticholic acid (OCA) For Treatment of NASH: FLINT TRIAL

- A multi-center, double-blind, placebo-controlled clinical trial to assess safety and efficacy of obeticholic acid (OCA) 25 mg daily in adult patients (n= 283) with biopsy proven NASH x 72 weeks.
- An Interim Analysis demonstrated that OCA treatment resulted in a significant improvement in primary histological endpoint (defined as a decrease in the NAFLD Activity Score (NAS) of $\geq$ 2 points with no worsening of fibrosis, as compared to placebo: 45 vs. 21 % (*p=0.0024 on an intention-to-treat [ITT] basis*).

  Increased pruritus (23% vs. 6%) and increased LDL
- Study stopped prematurely by the Data Safety Monitoring Board (DSMB) as the pre-defined threshold of statistical significance for stopping FLINT was $p < 0.0031$.

Probiotics Treatment in Liver Diseases: Evidence for Role of Gut Microbiota in NAFLD



Kirpich IA, McClain CJ. J Am Coll Nutr 2012;31:14-23

Probiotics in Treatment of NAFLD

- **Animal Studies:**
  - Reduced liver oxidative stress and insulin resistance
  - Reduced hepatic total fatty acid content
  - Decreased aminotransferase levels
  - Improved hepatic steatosis and inflammation; amelioration of fibrosis

- **Human Studies:**
  - Improved plasma levels of lipid peroxidation (VSL#3)[1]
  - Decreased serum levels of aminotransferases [2,3]
  - Increased liver fat (VSL#3)[4]

Kelishadi R et al. Hepat Mon 2013;13:e7233
[1]Loguercio C et al. J Clin Gastroenterol 2005;39:540-3
[2]Loguercio C et al. Am J Gastroenterol 2002;97:2144-6
[3]Aller R et al.Eur Rev Med Pharmacol Sci 2011;15:1090-5
4Ejtahed HS et al. J Dairy Sci 2011;94:3288-94

Bariatric Surgery in the Severely Obese

- Improves insulin resistance, glucose and lipid levels
- Improves liver enzymes and liver histology (steatosis, inflammation and fibrosis) with controlled weight loss
- Should not be done in decompensated cirrhotics or those with portal hypertension (CT showing collaterals or even small esophageal varices)
- Experienced surgeon, careful consent, and avoidance of long-limb bypass
- Identifying factors associated with favorable outcomes and the independent roles of wt. loss and other metabolic changes after bariatric surgery on improvements in obesity-associated diseases is important

Kral JG et al. Surgery 2004; 135: 48
Mattar SG et al. Annals of Surgery 2005; 242: 610
Clark JM, et al. Obesity Res 2005;13:1180
Barker KB, et al. Am J Gastroenterol 2006;101:368
deAlmeida SR, et al. Obesity Surgery 2006;16;270
Liu X, et al. Obesity Surgery 2007;17:486
Furuya CK, et al. J Gastroenterol Hepatol 2007;22:510
Rabl C and Campos GM. Semin Liver Dis 2012;32:80–91

SUMMARY

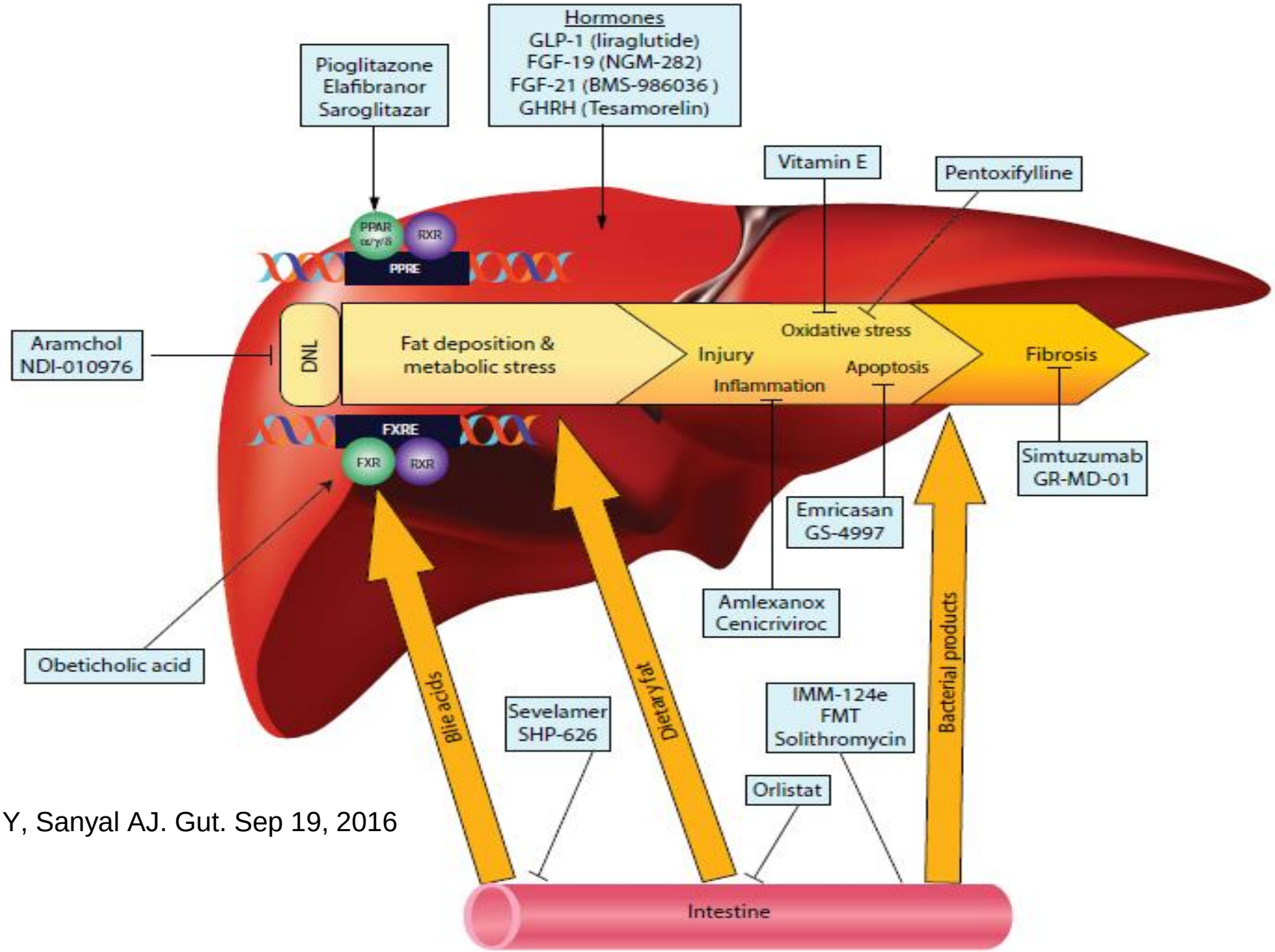
- ? Next epidemic
- No clear definitive diagnosis
- U/S lacks sensitivity with degree of steatosis
- Non-invasive fibrosis assessment
- No pharmacological therapy is approved for NAFLD or NASH.
- Emphasise the importance of lifestyle changes, weight loss and exercise as the mainstay of treatment.
- Orlistat can be safely used as an adjunct to weigh loss and may provide additional benefit.
- Treat other components of the metabolic syndrome, including hypertension, dyslipidemia and insulin resistance or diabetes

- Statins can be safely used to treat hypercholesterolaemia in patients with NAFLD or NASH.

- For patients with biopsy-proven NASH, currently available medications with proven benefit, although for off-label use, include
  - liraglutide, pioglitazone, vitamin E and pentoxifylline

Summary of Management

- Treatment should be targeted against liver pathology as well as co-morbidities
  - In patients with simple steatosis (NAFL): focus should be on co-morbidities
  - In patients with NASH: focus on treating liver pathology and co-morbidities



Rotman Y, Sanyal AJ. Gut. Sep 19, 2016