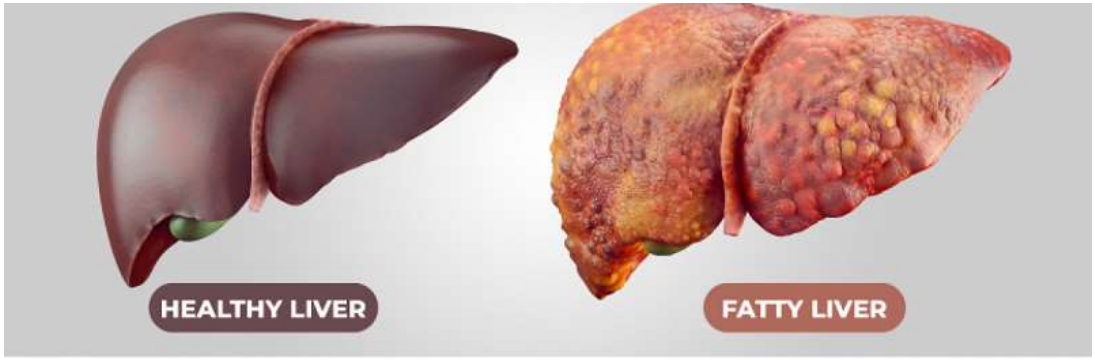


Non-Alcoholic Fatty Liver Disease (NAFLD)

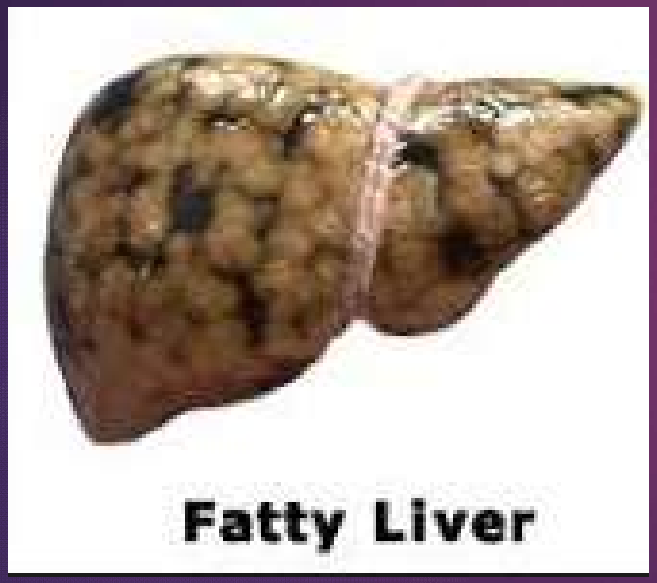
Non-Alcoholic Fatty Liver Disease: An Emerging Epidemic!

PROFESSOR MOHAMMAD ZAHIR UDDIN

DEPARTMENT OF MEDICINE

POPULAR MEDICAL COLLEGE

What is the most common liver disease in the world



25% of adults have NAFLD.

NASH prevalence: key figures

- non-alcoholic fatty liver disease (NAFLD) is growing to become the most common chronic liver condition in Western populations in relation to the obesity and type 2 diabetes epidemics, and the prevalence of NASH is also expected to increase by 63% between 2015 and 2030 (Estes 2018).

- In the United States, NASH is the leading cause of liver transplantation.

Prevalence :

- **Worldwide prevalence (Younossi 2017):**

  NAFLD: ***25.2%***

  NASH: ***1,5 – 6.45%***

- **US prevalence (Kim 2013, Williams 2011):**

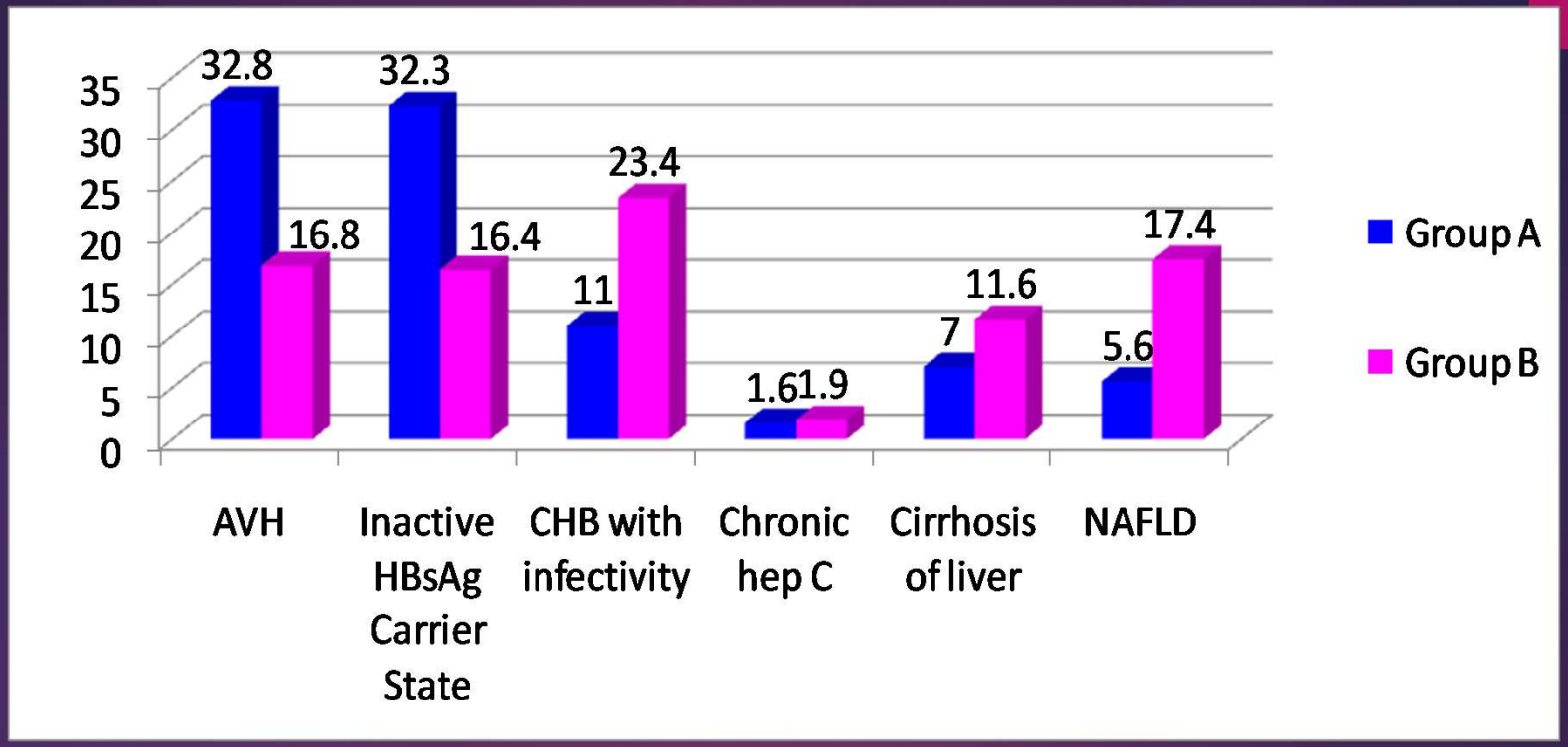
  NAFLD: ***34%***

  NASH: ***12%***

NASH prevalence in south asia

Source:Nonalcoholic Fatty Liver Disease: The Future Frontier of Hepatology for South Asia. Shahinul Alam, Thupten Kelsang Lama,Golam Mustafa, Mahabubul Alam andNooruddin Ahmad

Changing Pattern of Liver Diseases in Bangladesh



2000-2001 2009-2010 2012

Significantly **increased**: **fatty liver**, treatable hepatitis B

Significantly decreased: acute hepatitis, inactive hepatitis B

Prevalence of NAFLD among adults in Bangladesh by characteristics, Bangladesh 2017

	NAFLD prevalence, % (95% CI)
Gender	
Male	33.82 (31.6 – 36.11)
Female	33.91 (31.15 – 36.78)
Age group	
≤24	9.25 (7.33 – 11.61)
25–34	30.91 (27.95 – 34.04)
35–44	48.72 (44.56 – 52.9)
45–54	55.38 (50.4 – 60.25)
55+	48.37 (42.17 – 54.62)
Place of residence	
Urban	33.00 (31.03 – 35.03)
Rural	36.59 (33.01 – 40.33)

Prevalence of non-alcoholic fatty liver disease by age group and place of residence

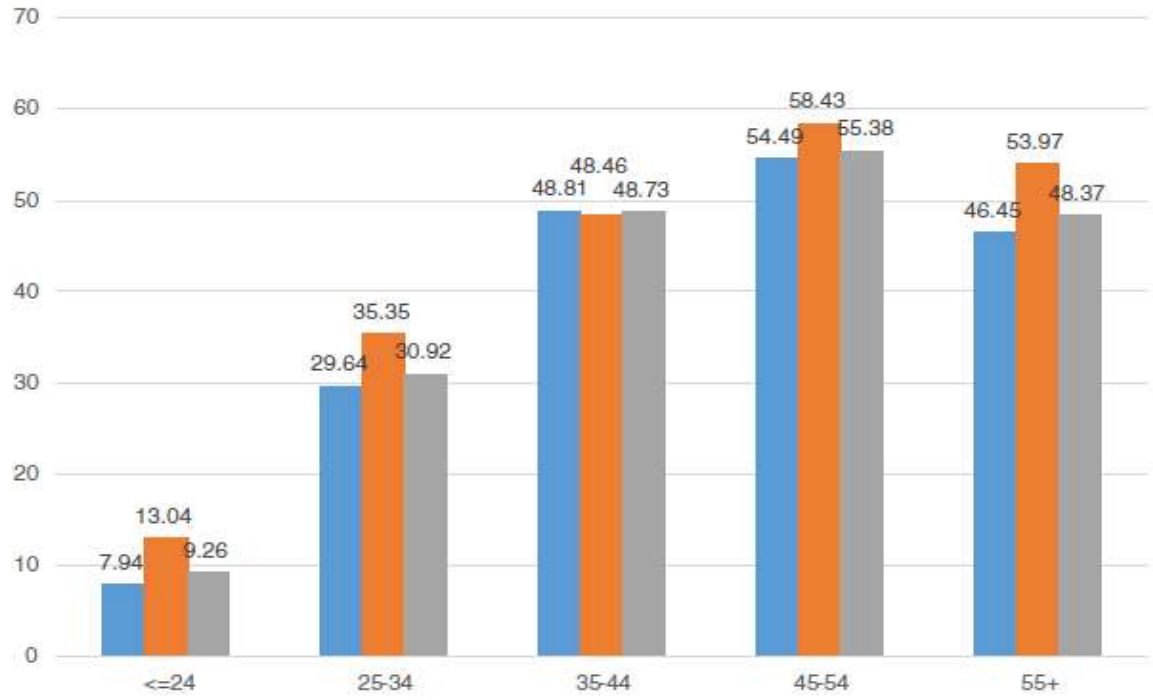


Figure 1 Prevalence of non-alcoholic fatty liver disease by age group and place of residence. Urban; rural; overall.

POPULATIONS AT RISK:

PREVALENCE IN POPULATION WITH OBESITY

- NAFLD → 70% or more
- NASH → 25-30%

POPULATIONS AT RISK:

PREVALENCE IN POPULATION WITH TYPE 2 DM

- NAFLD → 65 to 70%
- NASH → 25-30%

PEDIATRIC NAFLD AND NASH

- NAFLD has become a leading cause of chronic liver disease in children and adolescents from developed countries.
- prevalence of NAFLD ranging from 3% to 10% in a general pediatric population

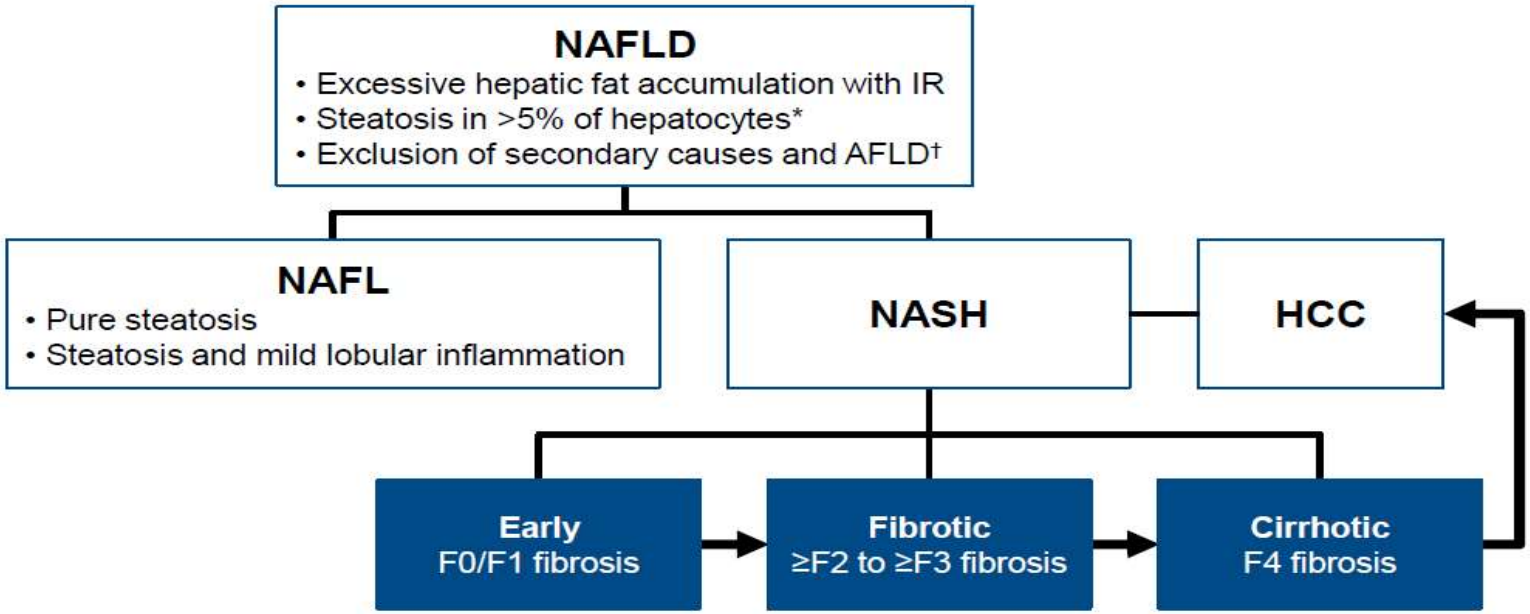
Outline of Presentation

- INTRODUCTION & DEFINITIONS
- PATHOGENESIS & RISK FACTORS
- DIAGNOSIS
- PROGNOSIS & COMPLICATIONS
- MANAGEMENT
- SUMMARY

INTRODUCTION

- Most common among all liver disorders & the cause of CLD.
- Commonest cause of asymptomatic abnormal LFTs.
- Most common cause of End stage liver disease requiring liver transplantation.
- NAFLD exists as a spectrum from simple steatosis to cirrhosis.
- Hepatic steatosis describes accumulation of fat >5% of liver weight.
- Commonest cause of death in patient with NAFLD,NAFL & NASH is cardiovascular disease.

Definitions of NAFLD, NAFL and NASH



Definitive diagnosis of NASH requires a liver biopsy

*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

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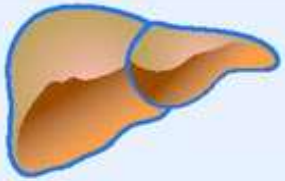
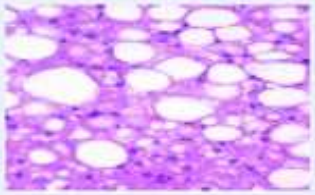
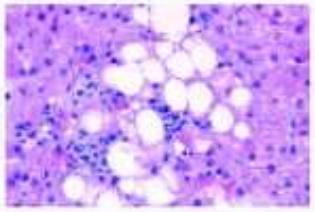
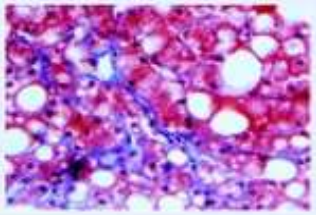
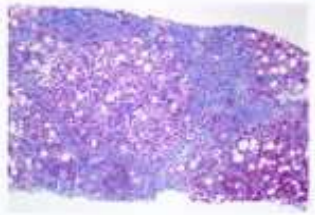
NAFLD— Spectrum of Disease

	Image	Histopathology	Pathophysiology
Non-alcoholic fatty liver (hepatic steatosis)			Accumulation of fat in liver (when excessive alcohol consumption is ruled out).*
Non-alcoholic steatohepatitis (NASH)			Accumulation of fat in liver is combined with inflammation and cell damage.
Fibrosis			Scarring (excess fibrous tissue) in an inflamed liver. Categorised into stages 0 to 4 (or mild, moderate and advanced) based on extent and distribution of scarring.
Cirrhosis			Late stage of chronic liver disease marked by nodules of damaged liver cells surrounded by scarring.

Secondary HS

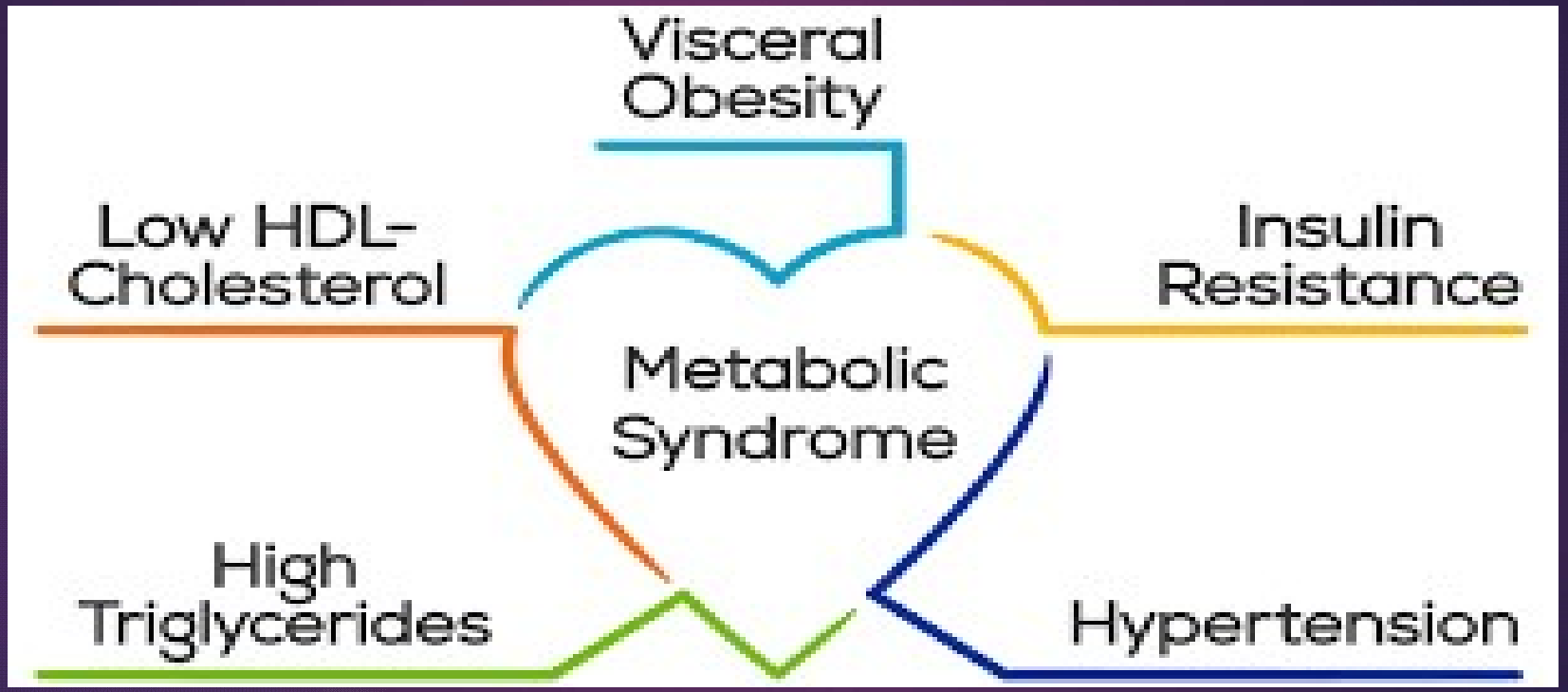
Macrovascular steatosis	Microvascular steatosis
Excessive alcohol consumption	Reye's syndrome
Hepatitis B, C	Medication(valproate, antiretroviral)
Wilson's disease	Acute fatty liver of pregnancy
Lipodystrophy	HELLP syndrome
Starvation and Parenteral nutrition	Inborn error of metabolism
Medication(amiodarone, MTX, tamoxifen, corticosteroid)	
Abetalipoproteinemia	

Risk Factors Associated with NAFLD

Condition with established association

- Obesity
- Type-2 DM
- Dyslipidemia
- Metabolic syndrome
- Polycystic ovary syndrome
- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreato-duodenal resection

Metabolic Syndrome



Obesity prediction of NASH

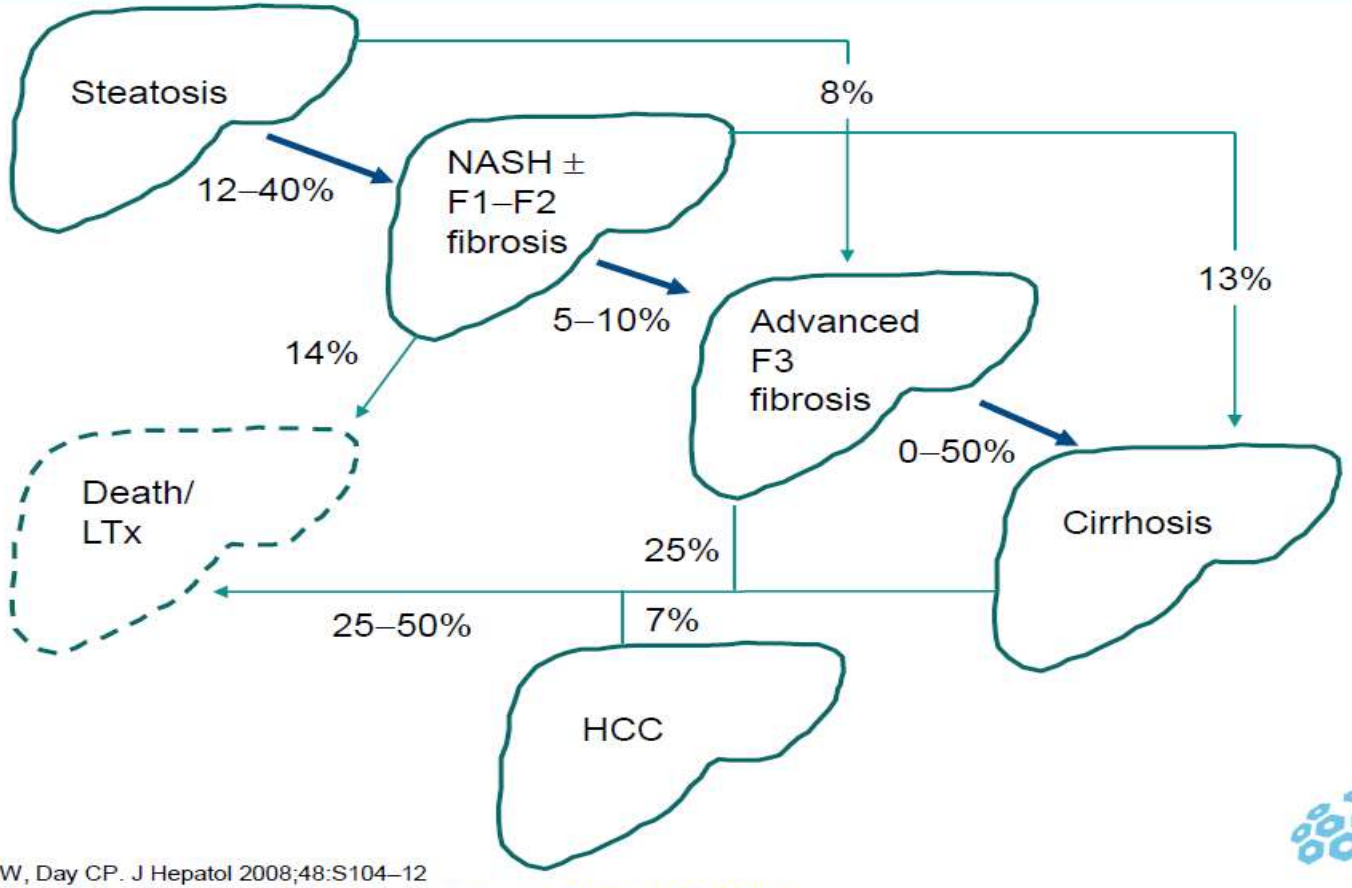
NASH SCORING SYSTEM IN MORBID OBESITY

FACTOR	POINTS
HTN	1
Type 2 DM	1
AST ≥ 27 IU/L	1
ALT ≥ 27 IU/L	1
Sleep apnea	1
Non black	1

Risk prediction

Point Total	Risk of NASH
0-2	Low
3-4	Intermediate
5	High
6-7	Very high

Natural history of NAFLD over 8–13 years



de Alwis NMW, Day CP. J Hepatol 2008;48:S104–12

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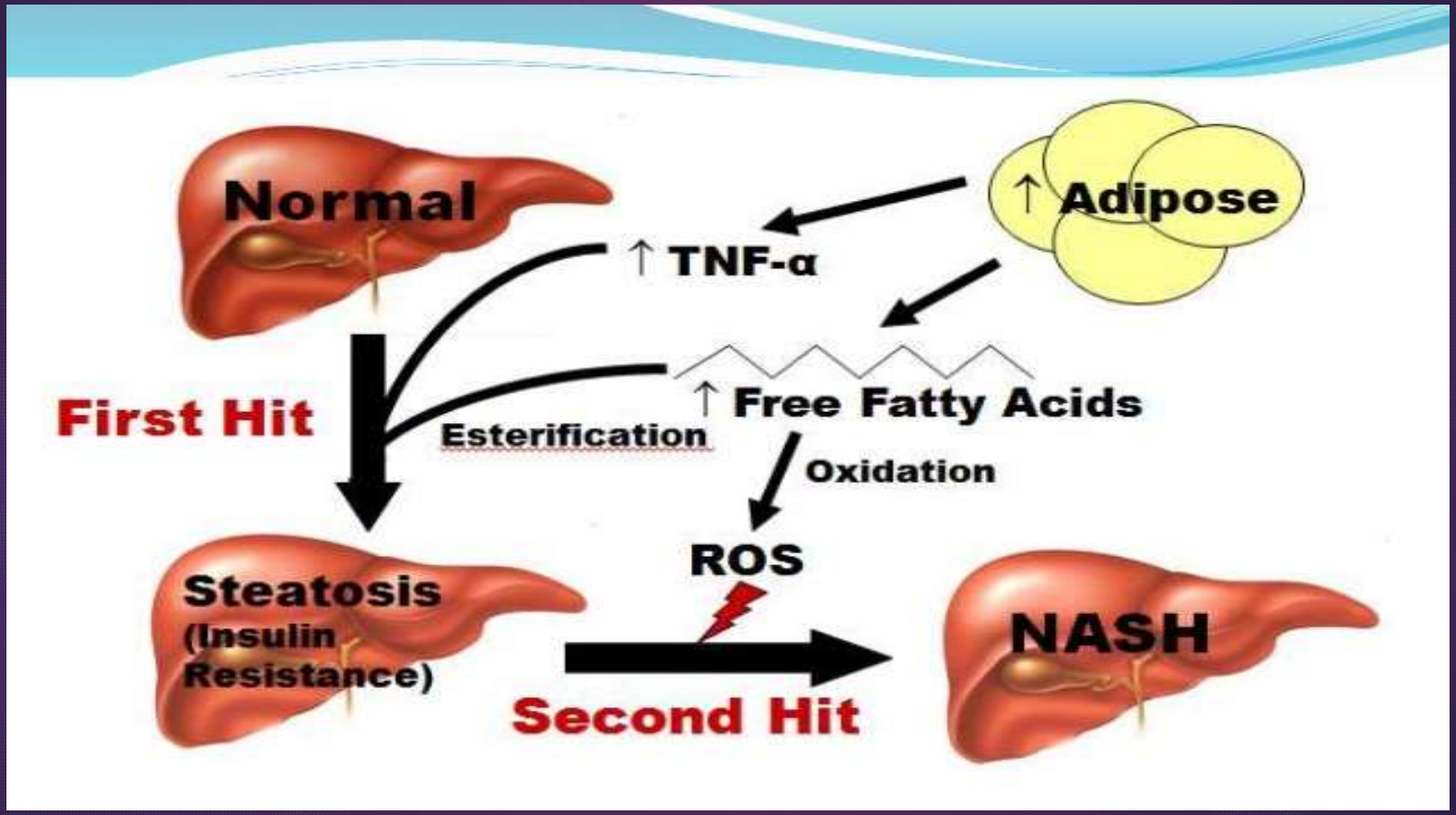
Pathogenesis

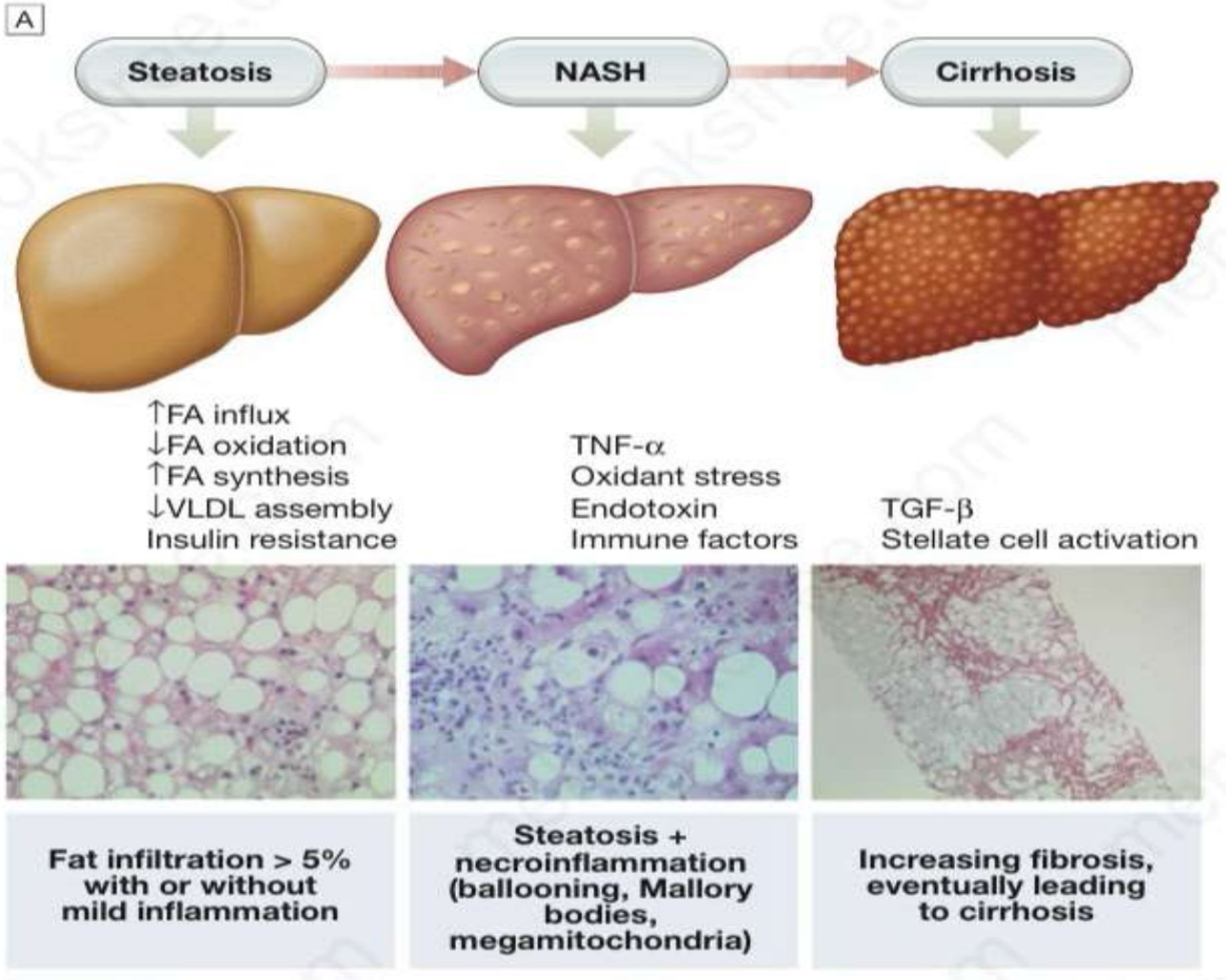
- Proposed by DAY and JAMES in 1998.
- Described by “two hit hypothesis”
- First hit: Deregulation of fatty acid metabolism leads to steatosis.
- Second hit: “ Oxidative stress”

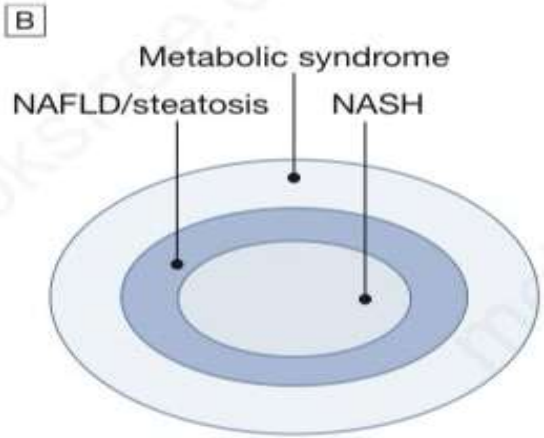
- May be environmental or genetic factors.

Pathogenesis: CONT.



Pathogenesis of NAFLD





CLINICAL FEATURES

COMMON

- Symptoms

  None (48 to 100%)

- Signs:

  Hepatomegaly

UNCOMMON

- Symptoms :
  - Vague pain
  - Fatigue
  - Malaise
- Signs:
  - Splenomegaly
  - Spider angiomata
  - Palmar erythema & ascites

DIAGNOSIS

DIAGNOSIS:

- NAFLD/NASH is a diagnosis of exclusion, and liver biopsy will often be required to confirm the diagnosis, stage the disease ,rule out other liver disease and determine the need for and urgency of aggressive therapy.

Diagnosis
When to suspect NAFLD ??

- History: No symptoms, fatigue, malaise and abdominal discomfort.
- The presence of any of the following, especially with a history of abnormal AST/ALT, should lead to a work up for NAFLD/NASH:

1. 1.Presence of obesity, especially morbid obesity .(BMI >35)
2. Diagnosis of Type 2 DM
3. Diagnosis of metabolic syndrome
4. H/O Obstructive sleep apnea
5. Presence of insulin resistance
6. Chronic elevation of AST/ALT, otherwise unexplained.

Diagnosis : Laboratory test

- Elevated ALT and AST :

  In 10% of NASH patients, ALT and AST may be normal, especially with simple steatosis.

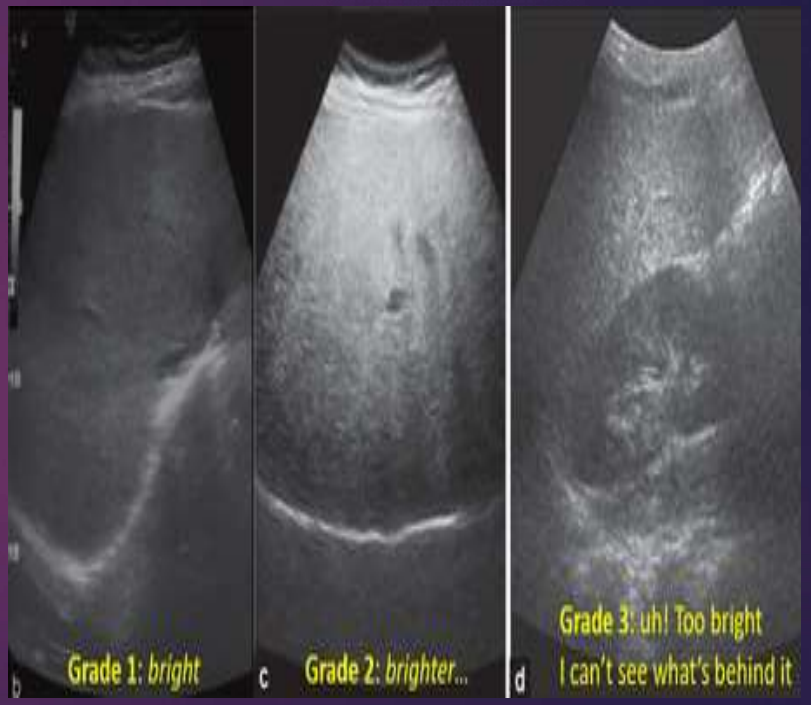
- An abnormal ferritin level in the presence of normal transferrin saturation should always suggest a need to rule out NASH.
- AST/ALT ratio <1 – this ratio is usually >2 in alcoholic hepatitis.

Imaging Tests:

- Ultrasound is the usual screening test for fatty liver.
- The MRI test has a quantitative value but can not distinguish between NASH and ASH.
- No imaging study can identify fat accurately if it is <33% or distinguish NASH from ASH.

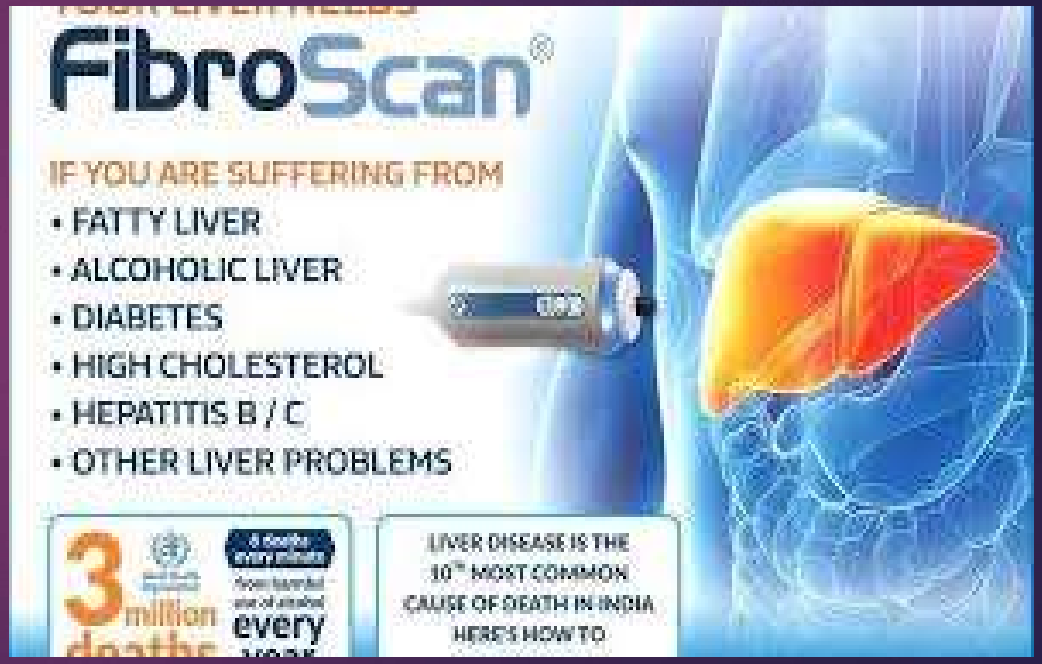
What is the grading of fatty liver on USG

- Grade I: Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.
- Grade II: Increased hepatic echogenicity with imperceptible periportal echogenicity without obscuration of diaphragm.
- Grade III: Increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm.



Non- invasive assessment of steatohepatitis and advanced fibrosis

- NAFLD fibrosis score(NFS)
- FIB-4 index
- AST to platelet ratio index(APR)
- Fibroscan
- MRE



NAFLD fibrosis score(NFS)

- NFS is based on **six variable** – age, BMI, platelet count, hyperglycemia, albumin and AST/ALT ratio
- **NFS< -1.455** exclude advanced fibrosis and **>.676** identify the presence of advance fibrosis.

- FIB-4 INDEX: Based on age, platelet, AST and ALT.

In FIB-4 INDEX score<1.45 are unlikely and>3.25 are likely to have advance fibrosis.

- FIBROSCAN: To detect advanced fibrosis have 95% sensivity and 77% specificity.

- In patient with NAFLD, Mets predicts the presence of SH and it's presence can be used to target patients for live biopsy.
- NFS or FIB-4 INDEX are clinically useful tools for indetifying NAFLD patient with higher likelihood of having bridging fibrosis (Stage -3) or Cirrhosis (stage 4)
- Fibroscan or MRE are clinically useful tools for identifying advanced fibrosis in patient with NAFLD

Indication of liver biopsy in patient with NAFLD
AASLD Recommendations

- Liver biopsy is the **gold standard** in patient with NAFLD
- Liver biopsy should be considered in patient with NAFLD who are at **risk of having SH and/or advanced fibrosis**
- The presence of **mets, NFS, FIB-4 or liver stiffness measured by Fibroscan or MRE may be used for identifying patient** who are at risk for SH and/or advanced fibrosis
- Liver biopsy should be considered in patient with suspected NAFLD in whom **competing etiologies for HS and the presence and/or severity of coexisting CLD** cannot excluded without liver biopsy.

Fibrosis Staging

Scale ranging from F0 to F4

- F0- No fibrosis
- F1 – Portal fibrosis without septa
- F2 – Portal fibrosis with few septa
- F3 – Bridging septa between central and portal veins
- F4– Cirrhosis

- Liver fibrosis can be expected to worsen by one class each decade i.e, F2 will progress ti cirrhosis in 20 years.

TEST	SENSITIVITY	SPECIFICITY	REMARKS
Histology , liver biopsy	Gold standard	Can not reliably distinguish between ASH and NASH	Significant variability between pathologists reading of the same sample.
Liver enzymes	Low	Low	AST/ALT usually <1; values may be normal.
Ultrasound	Limited	Limited	Insensitive unless steatosis > 33%
MRI,MRS,CT Scan	Result are variable	Not well verified	Test are costly,less available,insensitive.

NAFLD fibrosis Score Online Calculator

Age (years)	
BMI (Kg/m^2)	
IGF / Diabetes	
AST	
ALT	
Platelet	
Albumin Calculate Score	

MANAGEMENT OF PATIENT WITH NAFLD

Management

- Targets for therapy: Insulin resistance and oxidative stress.
- Goals of treatment: Reduce the histologic features and improve insulin resistance and liver enzyme levels.
- General Approach to the patient:

1. Weight loss
2. Vaccination
3. Treatment of risk factors for cardiovascular disease
4. Avoid alcohol consumption

Treatment modalities in NAFLD

- **Lifestyle modification**

- **Pharmacological management**
  - insulin sensitizer
  - GLP-1 analogue
  - UDCA
  - Thiazolidinediones
  - vitamin E
  - Omega 3 fatty acid

- **Newer agent**: obeticolic acid, elafibrinor

- **Surgery** : - Bariatric surgery
  - Liver transplantation

- **Management of CVD and dyslipidemia**

Lifestyle modification

- Weight loss generally reduce HS, achieved either by hypocaloric diet (daily reduction by 500- 1000 kcal)alone or in combination with increased physical activity(moderate intensity exercise) is the best method in sustaining weight loss overtime.

- Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss 7%-10% is needed to improve NASH including fibrosis.
- Exercise alone in adult in NAFLD may prevent or reduce HS, but its ability to improve other aspects of liver histology remains unknown.

No Fatty Liver

ফ্যাটি লিভার রোগ প্রতিরোধে

শুধুমাত্র শারিরীক ব্যায়মই যথেষ্ট নয়, খাগ্যাভ্যাসের নিয়ন্ত্রণ ও অত্যন্ত জরুরী

ফ্যাটি লিভার রোগ প্রতিরোধে কার্যকর ভূমিকা পালন করে

যদি টিভি দেখার সময় হয়

যদি ইন্টারনেট ব্রাউজ করার সময় হয়

তাহলে ব্যায়াম করার সময়ও অবশ্যই করা যায়

Preventive measures for Fatty liver disease

- Eat a healthy diet
- Avoid fast food, junk food, oily food & energy drink
- Avoid alcohol and smoking
- Exercise regularly
- Maintain a healthy weight
- Lose weight, if you are overweight or obese
- Lower your cholesterol and triglycerides
- Control your diabetes
- See a doctor who specializes in the liver regularly
- Talk to your doctor about ways to improve your liver health
- Only take medicines that you need and follow dosing recommendations.

Pharmacotherapy

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

- A recent meta analysis conducted that 6-12 months of metformin plus lifestyle intervention did not improve aminotransferase or liver histology, compared with lifestyle intervention alone, independently of metformin dose or the presence of diabetes

June 2012 AGA 1597.

Pharmacotherapy

Pioglitazone

- Pioglitazone can be used to treat steatohepatitis with biopsy –proven NASH.
- A recent meta-analysis that included 5 RCTs showed that Pioglitazone significantly improved steatosis and inflammation but not fibrosis.
- Side effects of pioglitazone: weight gain, osteoporosis, bladder cancer
- Rosiglitazone : Improved enzymes and steatosis but not inflammation.

GLP-1 ANALOGUE (Liraglutide)

- Liraglutide once daily for 48 weeks S/C is associated with greater resolution of SH with less progression of fibrosis
- Liraglutide is associated with greater weight loss and also GI side effect.
- It is premature to consider GLP-1 agonist to specifically treat liver disease in patient with NAFLD

VITAMIN E

- Oxidative stress is a key mechanism of hepatocellular injury
- **Vit-E(800IU/day**) for 96 weeks improves liver histology, decrease aminotransferase in non diabetic adult in biopsy proven NASH
- Vit E is not recommended in
  - NASH ē Diabetes patient
  - NAFLD without liver biopsy
  - NASH cirrhosis
  - Cryptogenic cirrhosis

- **PIVENS trial** :pioglitazone(30mg/day) vs placebo and vitamin E(800IU/day) vs placebo
- **Duration** : 24 month
- Adult with NASH without DM, HCV, cirrhosis
- **Primary end point** was: improvement of NAS score≥2 point
- **PIVENS result**: target was achieved in
  - vitamin E group (43%)
  - pioglitazone (34%)
  - placebo(19%)

- This study concludes that pioglitazone did not meet the primary end point.
- However resolution of NASH, a key secondary end point was achieved in a higher number of patient receiving pioglitazone than placebo.
- So , Vitamin E and pioglitazone were well tolerated and there were no differences in other adverse effect

URSODEOXYCHOLIC ACID(UDCA)

-**UDCA** offers no histological benefit over placebo in patient with NASH

- So UDCA is not recommended for treatment of NAFLD or NASH

OMEGA 3 fatty acid

- **OMEGA 3 fatty acid** improve TG level and improve liver disease but should not be used as a specific treatment of NAFLD or NASH, but may be considered to treat hypertriglyceridemia.

Newer agent

Obeticholic acid and elafibranor is now on phase 3 trail and still not recommended in NAFLD patient

SURGERY

BARIATRIC SURGERY

- Bariatric surgery improves or eliminate comorbid disease and improves long term survival
- There is significant improvement in steatosis, ballooning and resolution of probable or definite NASH at 1 and 5 years following bariatric surgery
- 85% patient had NASH resolution and 33% of patient had improvement in fibrosis 1 year after bariatric surgery

BARIATRIC SURGERY

- Foregut bariatric surgery can be considered in otherwise eligible obese individual with NAFLD
- The type, safety and efficacy of foregut bariatric surgery in otherwise eligible obese individual with cirrhosis attribute to NAFLD are not establised
- Eligible patient with compensated NASH or cryptogenic cirrhosis, foregut bariatric surgery may be considered.

Management of CVD and dyslipidemia

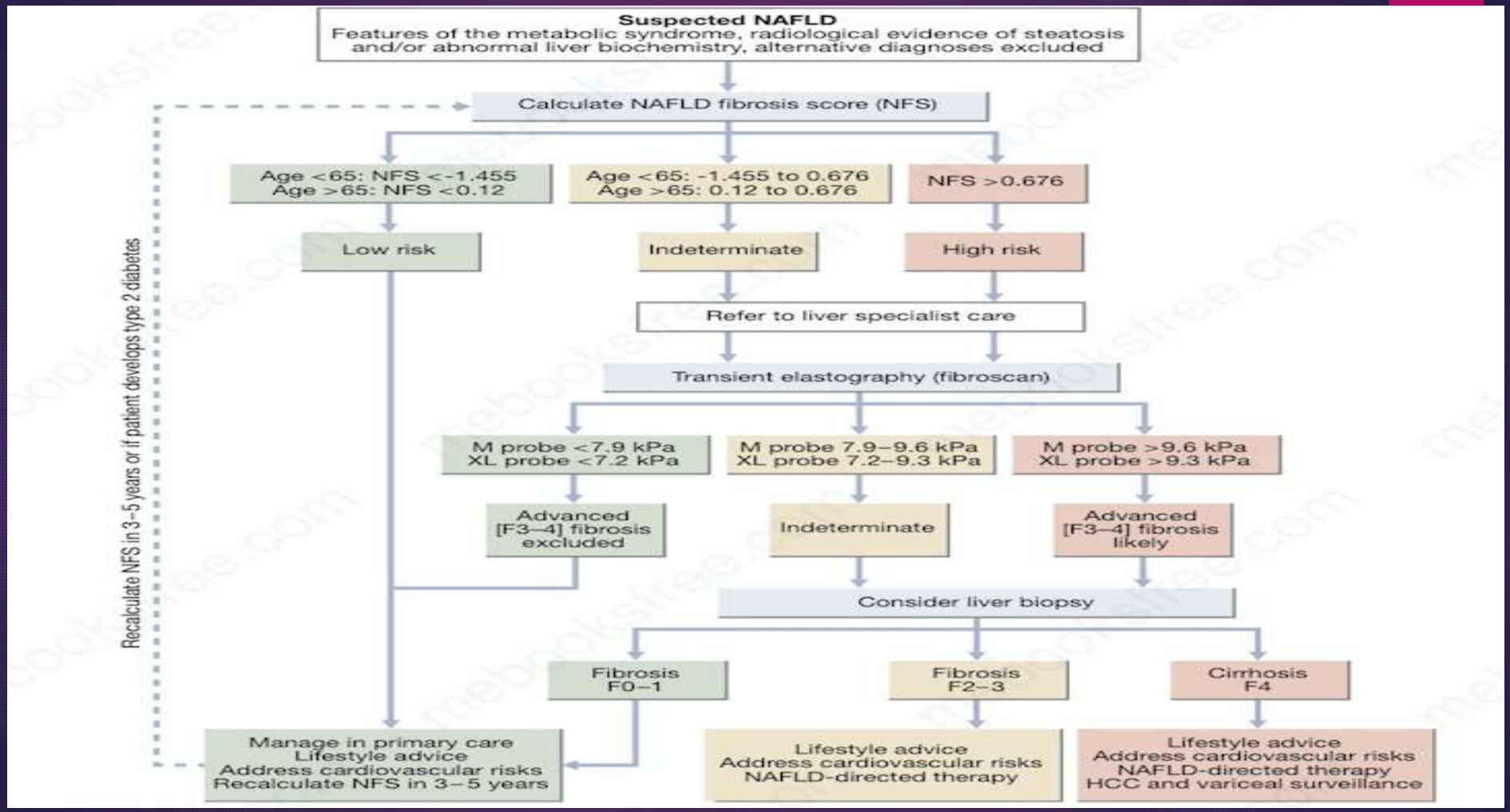
- There are many mechanistic links between NAFLD and various stages of atherosclerotic process
- So risk of CVD event is high in patient with NAFLD
- Patient with NAFLD have high TG, increased LDL, High apolipoprotein B to apolipoprotein A -1 ratio and low HDL
- Statin significantly improves aminotransferase and cardiovascular outcome in patient with elevated aminotransferase with NAFLD

- Patient with NAFLD or NASH are not at higher risk for serious liver injury from statin.
- Statin can be used to treat dyslipidemia in patient with NAFLD or NASH and also in NASH cirrhosis
- Statin should be avoided in patient with decompensated cirrhosis.

NASH, obesity and liver transplantation

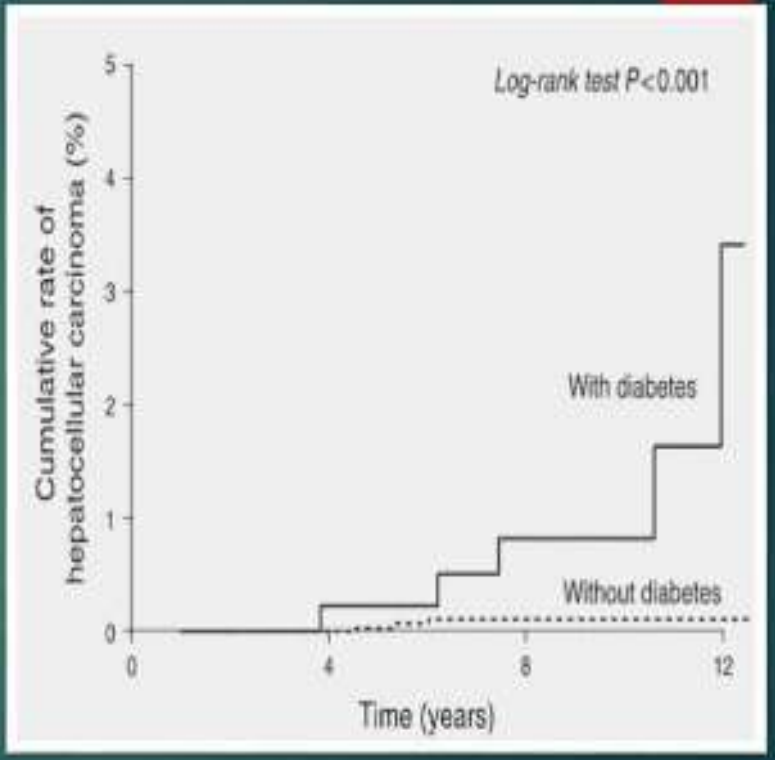
- NASH is the most common indication for liver transplantation in USA
- Patient with class III obesity(BMI>40 kg/m^2) at the time of transplant have higher frequency of post transplant complication
- Pretransplant weight reduction and subsequent successful LT has been reported with class III obesity
- Posttransplant outcome are generally good following LT
- The 5 year graft survival suggests that recurrence of NASH is uncommon.

Management Algorithm of NAFLD



NAFLD - Prognosis

- Increased overall mortality compared to matched control populations.
- Commonest cause of death in patients with NAFLD, NAFL and NASH is cardiovascular disease.
- Increased liver-related mortality rate – increasingly common indication for liver transplantation (15-20%).



Kawamura Y et al (2011). Large scale long term follow up study of Japanese patients with NAFLD for the onset of HCC. American Journal of Gastroenterology

TAKE HOME MESSAGE

- NAFLD represent a major global public health problem.
- It is also an emerging epidemics in Bangladesh
- Spectrum extends from Fatty liver, NASH, Cirrhosis and hepatocellular carcinoma
- Lifestyle modification with diet and exercise for reduction of weight is the established mode of treatment

- Vitamin E is the only recommended drug for NASH without diabetes
- UDCA and Metformin not recommended for NASH
- Obeticholic acid and Elafibranor is upcoming drug
- Treatment of associated conditions with Metformin, statin and telmisartan may be helpful


Thank You!