SRI LANKAN SOCIETY OF INTERNAL MEDICINE

Management of NAFLD in 2019

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You can accumulate fat quickly

You can get rid of fat quickly

History NAFLD in humans

It was known by 1960 s that fructose produces worse triglyceridaemia and fatty liver than glucose

HFCS started being marketed as an easy cheap and a cost effective alternative to table sugar(Sucrose) in 1970 s

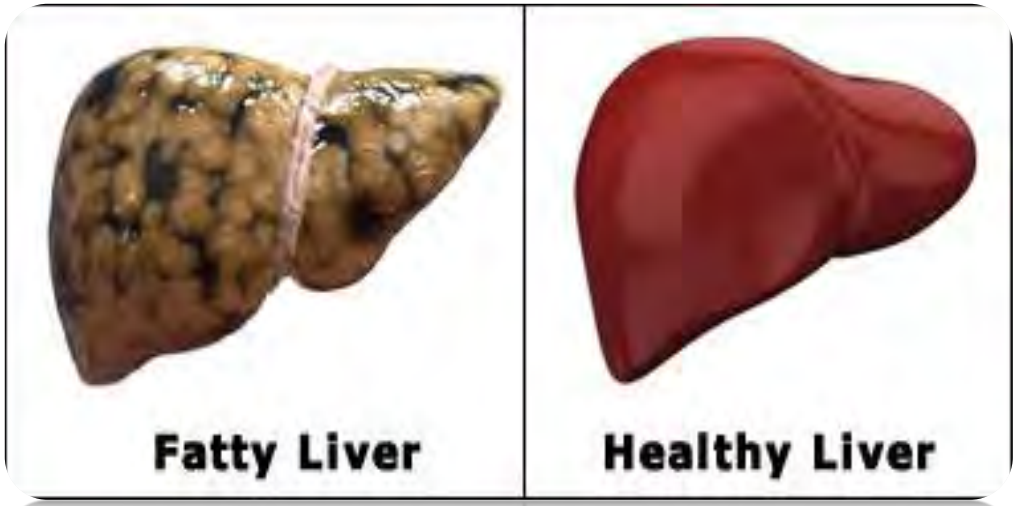
Fast food epidemic (First fast food chain 1955)

Linked DM, Obesity, Colorectal cancer, NAFLD

NAFLD

Complicated metabolic liver illness- Increased liver related mortality

Multisystem disease-increased all cause mortality especially cardiovascular mortality.



What is new in NAFLD

1.Cardiovascular mortality is higher than liver mortality

2.Genetics play a major role (Romeo 2008, Caussy et al 2017))

3. Involvement of the GUT microbiome in the pathogenesis

(Role of fructose/Fast food/Saturated fat through GUT microbiome)

5. Advances in non invasive diagnosis of advanced fibrosis

6. Lifestyle modification still the key intervention.

7. More than 100 drug trials are on a breakthrough is expected soon

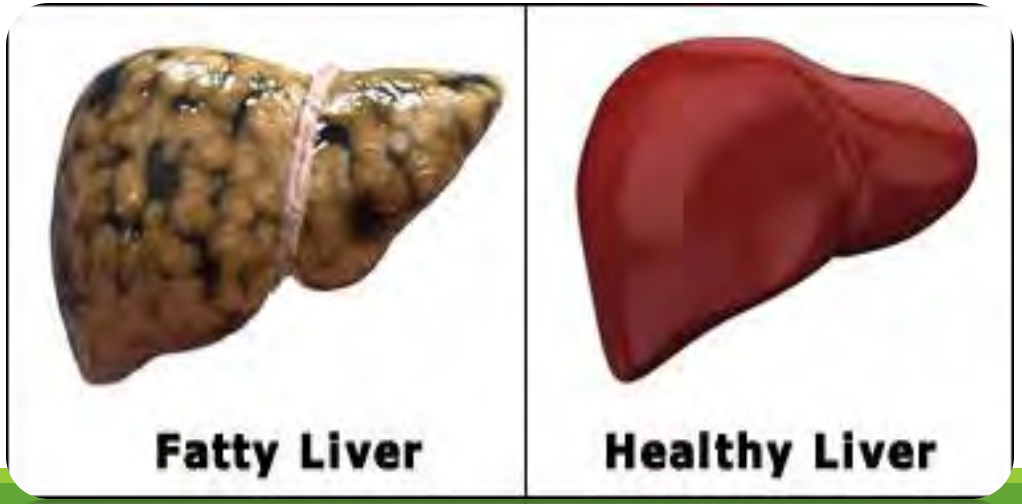
Non progressive NAFLD(80%)

Liver mortality insignificant

Life style modification attend to co morbidities.

Cardiovascular mortality is higher.

Follow up at2-3years with non invasive markers.

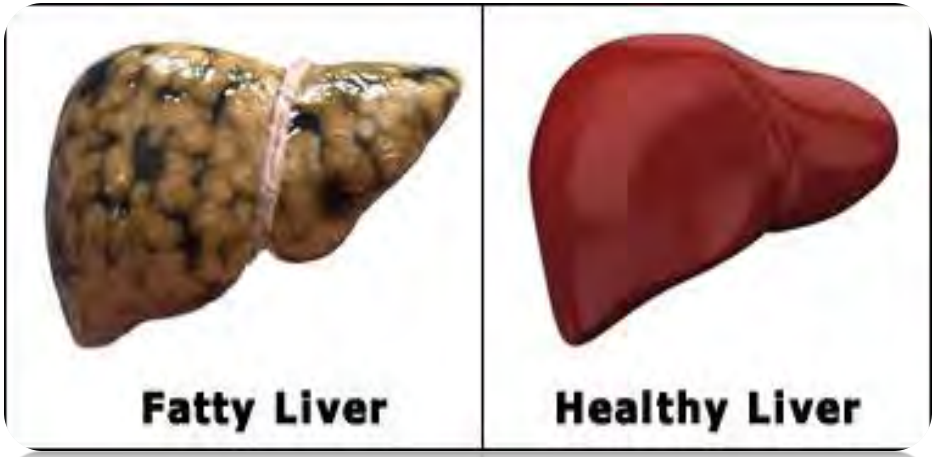


Progressive NAFLD(20%)

About 20% of total NAFLD patients

Leads to hepatocyte injury inflammation and fibrosis cirrhosis and HCC at varying rates of progression

How to identify progressive NAFLD without a biopsy?

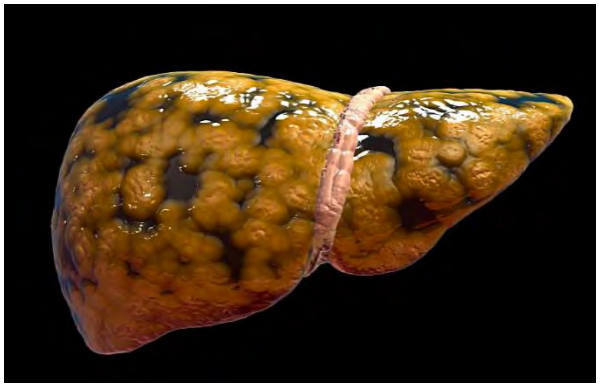


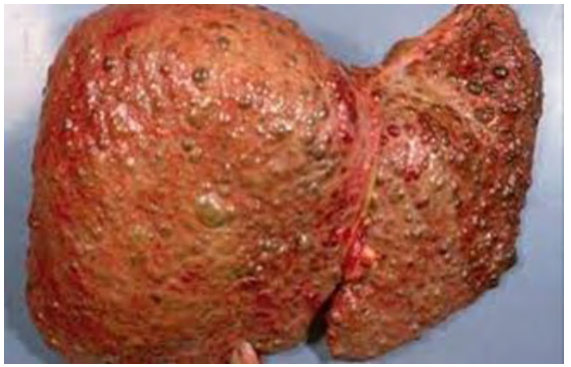
What is the plight of patients with progressive NAFLD?

Pathetic

Majority will present with a complication of cirrhosis(Even in the Developed world)Even if diagnosed early majority will not get proper advice

NAFLD is a silent killer





Two races are on(2019)

1. Develop a drug treatment

Worth 35 billion dollars. More than 100 drugs are tested

2. Develop a non invasive marker of establishing the severity and staging of NASH without a liver biopsy.

- 1. MRI
- 2. Fibroscan
- 3. Scoring systems
- 4. Serological markers

Non Invasive markers & treatment options in 2019

AASLD

EASL

APASL

NICE

Italian guidelines

Non invasive markers should predict

1.Steatosis

2.Inflammation

- No non invasive test predicts inflammation reliably

3. Advanced fibrosis (Only predictor of liver mortality)

- Serological
  - Simple
  - Complex
- Imaging

Noninvasive Diagnosis of Fibrosis

Serologic Markers

- Simple
  - AST/ALT ratio
  - APRI
  - FIB-4 index
  - NAFLD fibrosis score
- Complex
  - NASH *FibroSURE*
  - ELF
  - HA

Imaging

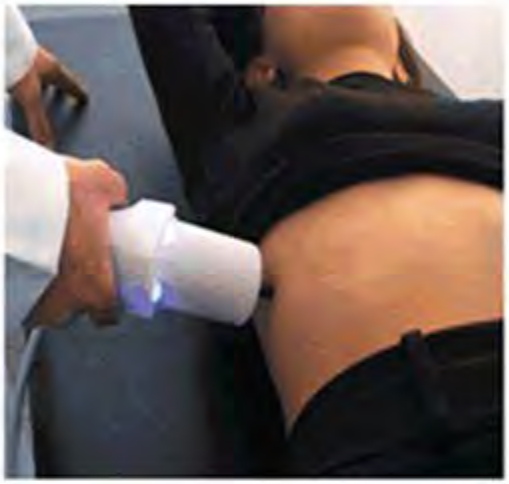
- Elastography
  - VCTE
  - MR elastography
  - ARFI

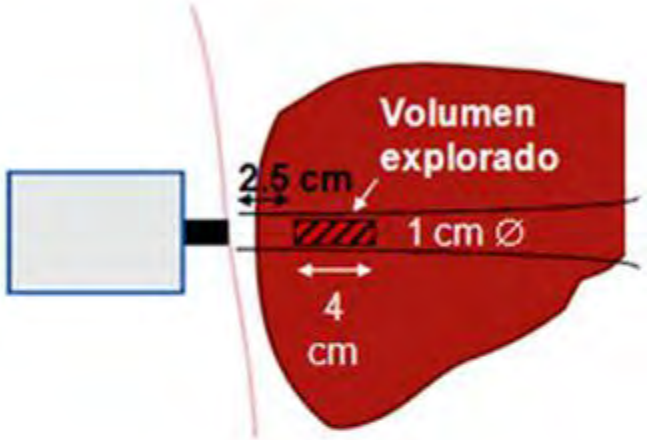
VCTE™

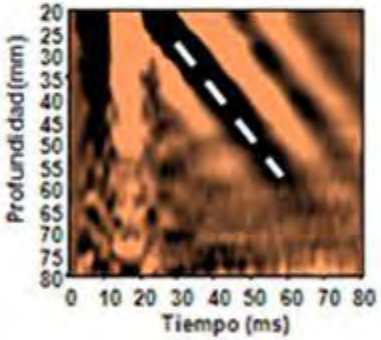
CAP
CONTROLLED ATTENUATION PARAMETER

S+ M+ XL+

Fibroscan

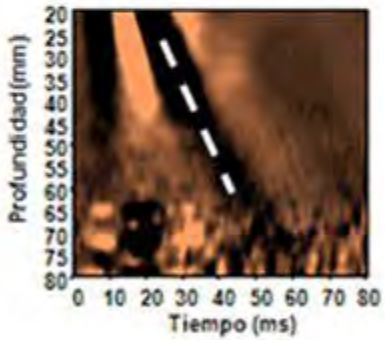






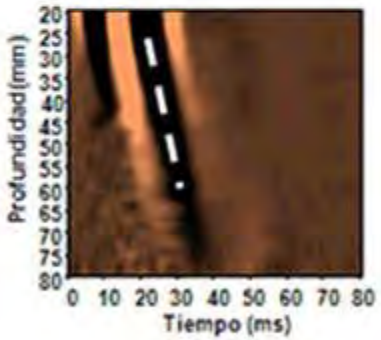
V_S = 1.1 m/s

~ 3 kPa



V_S = 1.7 m/s

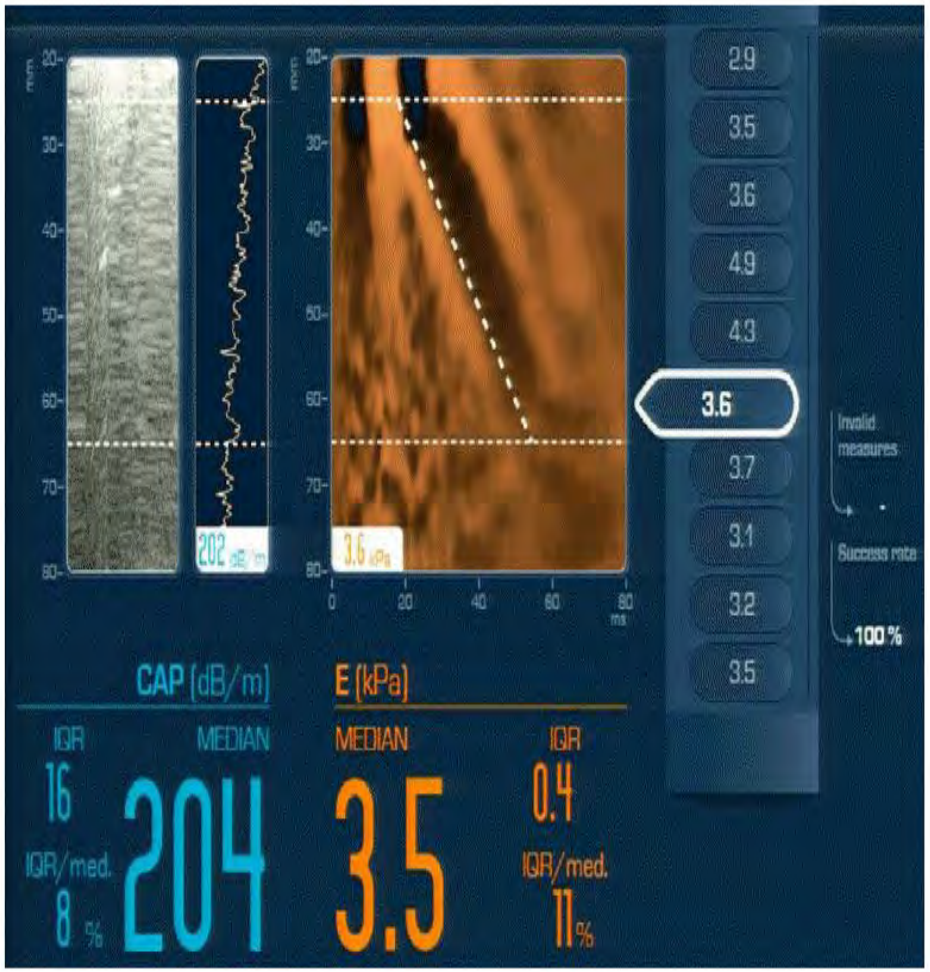
~ 9 kPa



V_S = 3.6 m/s

~ 40 kPa

F0 F1 F2 F3 F4


2.9
3.5
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Invalid measures
Success rate
100 %
CAP (dB/m)
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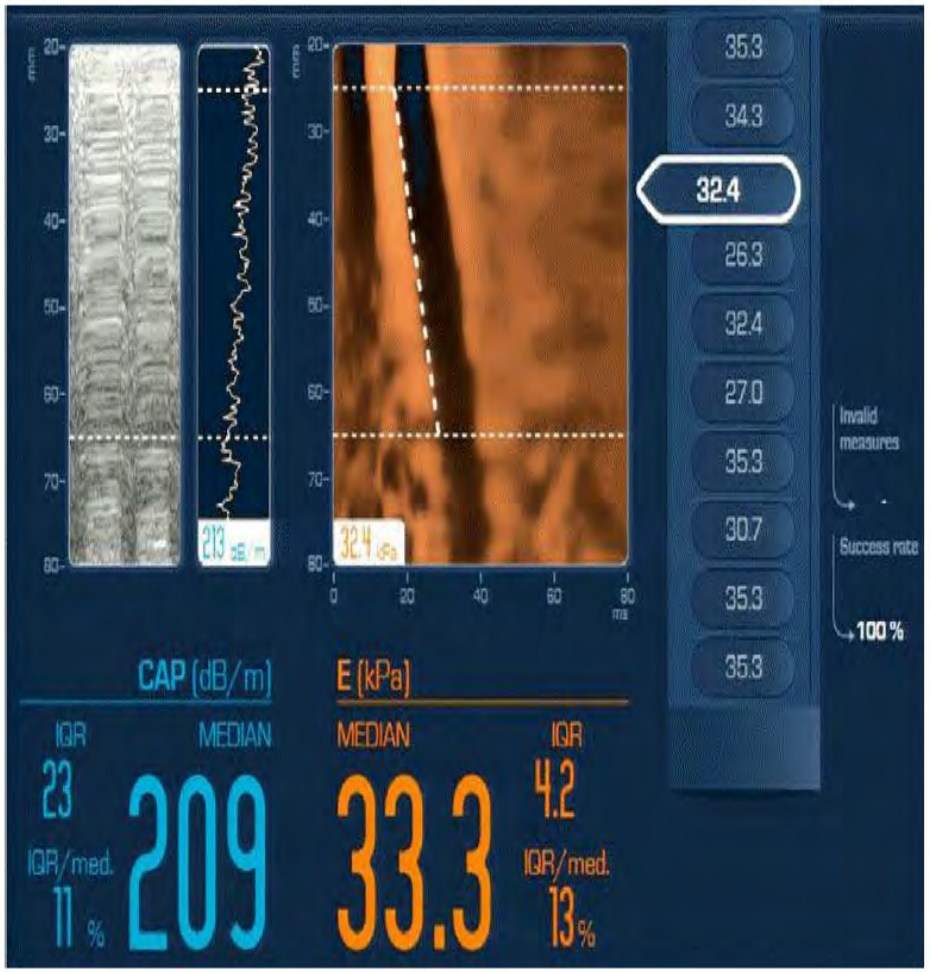
0.4
IQR/med.
11%

A


35.3
34.3
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26.3
32.4
27.0
35.3
30.7
35.3
35.3
Invalid measures
Success rate
100 %
CAP (dB/m)
IQR
23
MEDIAN
209
IQR/med.
11 %
E (kPa)
MEDIAN
33.3
IQR
4.2
IQR/med.
13%

B

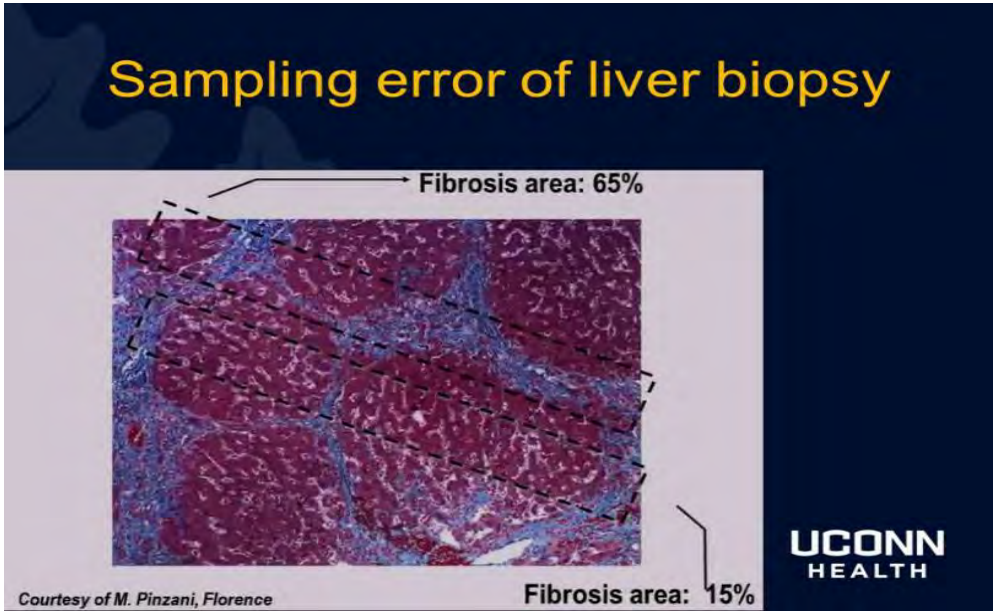
Why not a liver biopsy?

Invasive , Needs admission, Painful, Morbidity and a mortality

Sampling issues (25mmx1.6mm 30g biopsy is 1 in 50,000 of the liver)

Reserved for uncertain diagnosis and advanced liver disease

AASLD/EASL/APASL



Therapeutics of NAFLD 2019

Treatment of NAFLD

- Non pharmacological
  - Diet
  - Exercise
  - Weight loss
- Pharmacological- For biopsy proven NASH
  - Vit E
  - Pioglitazone

Treatment of other risk factors CV risk- Refer appropriately

Weight Loss Pyramid

Figure courtesy of S. Harrison

1. Vilar-Gomez. Gastroenterology 2015; 2. Promrat. *Hepatology*. 2010; 3. Harrison. *Hepatology*. 2009; 4. Wong. *J Hepatol*. 2013,
5. Harrison. *Hepatology*. 2015.
*Depending on degree of weight loss

Methods cont-

750 Kcal less than daily requirement (Miffin St Joer Equation)

Daily food diary/200min walking per week

Meeting them to promote and adherence to diet every 8 weeks

Diabetics were included

All most all were whites

All were over weight or obese

No Vit E or pioglitazone allowed

Only a minority achieved significant weight loss

Vilar Gomez et al Gastoenterology 2015

Beneficial in non obese Wong et al 2019

Alcohol consumption in NAFLD

Recent evidence suggests no alcohol consumption is healthy

Mehta et al Jour of Hepatol Jan 2019

Coffee & NAFLD

Beneficial

Physician as a weight loss expert/Food expert

Intense counselling and support needed by these patients like that offered by DM/Obesity clinics

Childhood Fructoholism and Fructoholic Liver Disease

Fructose is a major component of table sugar and of many added sugar syrups

Excessive fructose consumption can lead to addictive behavior: "Fructoholism"

Fructose metabolization leads to hepatic steatosis and cirrhosis: "Fructoholic Liver Disease"

Global strategies to reduce ingestion of added sugar are needed:

- Education campaigns to promote a healthy diet
- Increasing taxes on foods with added sugars

- Subsidies to promote accessibility to fruit & vegetables
- Strict food industry regulation

Ribeiro, et al. Hepatol Commun. 2019

HEPATOLOGY COMMUNICATIONS
Open Access

What are high fructose food

Sugar

Dried fruits

- Dates
- Raisings

Honey/Kithul Treakle

High fructose corn syrup

- Soft drinks-Colas
- Cordials
- All commercially made deserts

Case discussion

A 55 year old man followed up by an endocrinologist for Type 2 DM complained of weight loss for 6 months. The endocrinologist attributed it to Metformin. The patient had a family history of cirrhosis. The patients siblings including 2 medical consultants wanted a second opinion and he was diagnosed to have an inoperable HCC and succumbed to his illness 2 months later.

Discussion- How to avoid?

Screening diabetics for NAFLD

- APASL- Screen
- EASL- Screen (Metabolic syndrome)
- AASLD- Vigilance
- NICE- Screen
- Sri Lanka?

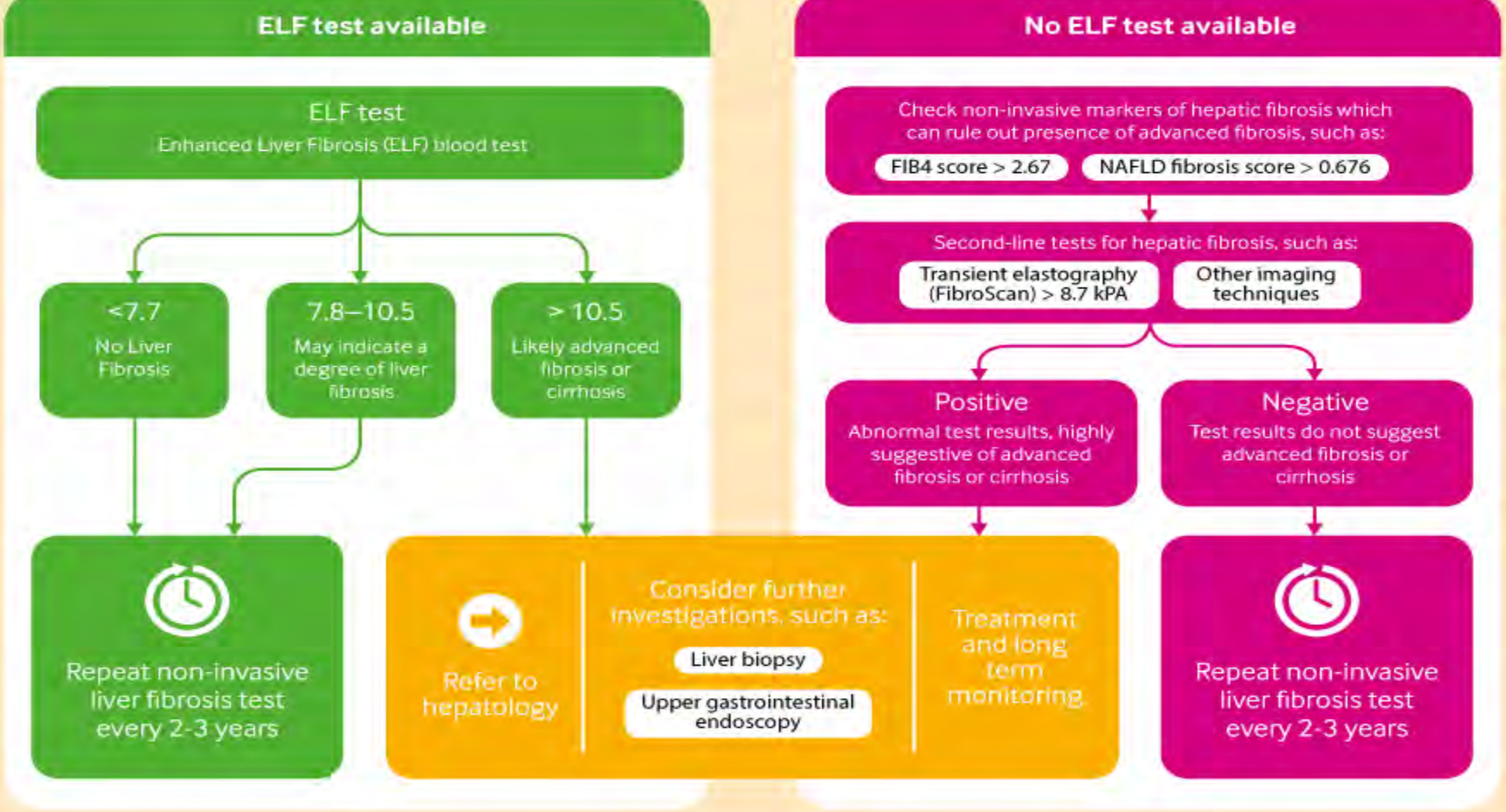
Patients with NAFLD follow them up with non invasive markers 2-3 yearly

Fibroscan

Advanced fibrosis and cirrhosis – Surveillance for HCC

Detection of small a HCC- Curative treatment

Be sensitive to subtle signals



Lifestyle advice

Patients with NAFLD can benefit from making heathier lifestyle choices. Offer education and advice irrespective of whether referral is needed or not.

Weight loss and physical activity

Especially if the patient is overweight or obese

Control cardiometabolic risk factors

NAFLD may present with or without these commonly co-existing conditions. These are associated with increased severity of NAFLD and increased risk of liver fibrosis

- Type 2 diabetes
- Obesity (BMI ≥ 30)

Cardiovascular risk assessment

Offer annual monitoring for patients being treated for diabetes, hypertension or with statins to decrease CVD risk

Patients with biopsy-proven NASH

Consider pioglitazone or vitamin E

ELF test

Hyaluronic acid (HA)

Procollagen III amino terminal peptide (PIIINP)

Tissue inhibitor of metalloproteinase 1 (TIMP-1)

ELF score guidance

ELF Test Score	Interpretation	Action plan
>9.8	Likely severe fibrosis	Biopsy may not be required for liver fibrosis assessment.
7.7-9.8	Uncertain; may be moderate fibrosis	Biopsy may be recommended.
<7.7	Likely no or mild fibrosis	Biopsy may not be required for liver fibrosis assessment.

FIB 4 score

Age

ALT

AST (make sure no extrahepatic cause for elevation)

Platelet count

<1.45 negative predictive value of 90% for advanced fibrosis

>3.25 97% specificity for advanced fibrosis

Sterling et al Hepatology 2006

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

Example 1

Age 30

ALT (SGPT) 80

AST (SGOT) 40

Platelets 240.000

FIB 4 .56(<1.45)

Example 2

Age 55

ALT 60

AST55

Platelets 180.000

FIB 4 2.17(>1.45,<3.5)

Need a fibroscan

Example 3

Age 60

ALT 55

AST 65

Platelets 150,000

FIB 4 score 3.51(>3.25)

Probably cirrhosis

Example 4

Age 60

ALT 40

AST 80

Platelets 110000

FIB 4 score 6.9

Established cirrhosis

Treatment-statins

- **Statins**
  - Definitely safe
  - Dramatic decrease in HCC in pts with DM II on statins
    - OR 0.63 (0.5 – 0.8)*
  - Less severe NASH in dyslipidemics on statins
  - Even improved LFTs in some cases

*El Serag et al Gastro 2009; 136: 1601-8
**Basaranoglu M J Hepatol 1999; 31(2)384

Are guidelines/Guidance documents helpful for us?

Guidelines don't agree on a lot of important points

- Screening of high risk patients & treatment options

South Asians /Asians are under represented

- South Asian NASH may be different (De Silva et al 2016)

Not helpful in a majority of our patients

- Without a biopsy
- Diabetes
- Early cirrhosis. Needs the treatment most

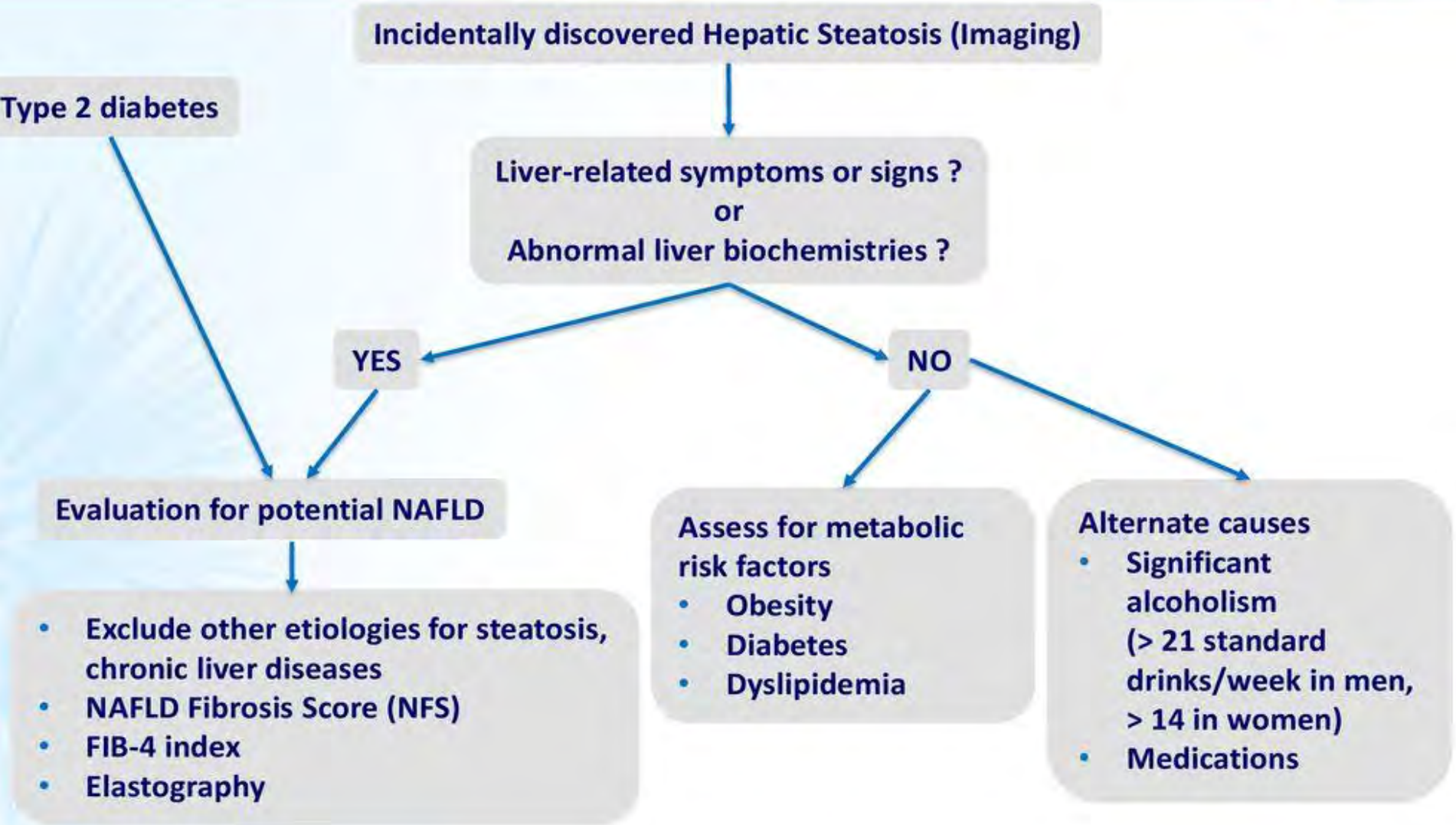
Management of hyperlipidaemia not discussed adequately

- Should be for more liberal use of statins

"Off label treatment" is it a crime?

- No . 20 % of all prescriptions are off lable
- Use of Vit E in diabetics –Most NASH specialists in the US use it

Screening for NAFLD



Adapted from Chalasani N. Practice Guidance from the AASLD; Hepatology 2018;67:328-357

Summary

- NAFLD mostly food related - GUT microbiome & genetics play major roles
- Non invasive prediction is gaining momentum
- Life style modification is the key- 10% weight reduction reverses fibrosis but few can achieve it.
- Pharmacological breakthrough is close by but will be costly. FDA approval expected in 2021
- Statins have a role to play appears underused
- International guidance statements and guidelines appear inadequate in at least our set up.

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"