EASO SUMMER SCHOOL: MASTERCLASS IN THE PREVENTION AND MANAGEMENT OF OBESITY

European Association for the Study of Obesity

Les Pensières at Fondation Mérieux. Annecy, France: 11 - 15 July 2022

# Complications of obesity: MAFLD

**(Metabolic dysfunction-associated fatty liver disease)**


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EASOCOM

EASO Collaborating Centre for Obesity Management

# VALL D'HEBRON OBESITY UNIT

# Non- alcoholic fatty liver disease
# NAFLD

**NAFLD**

Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.

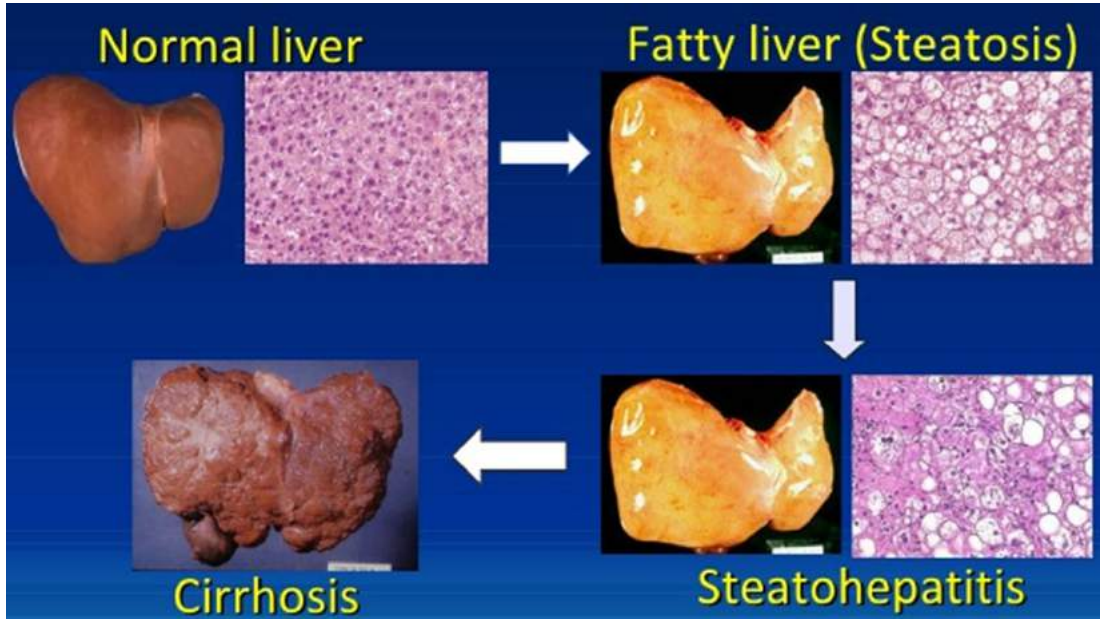
**NAFL**

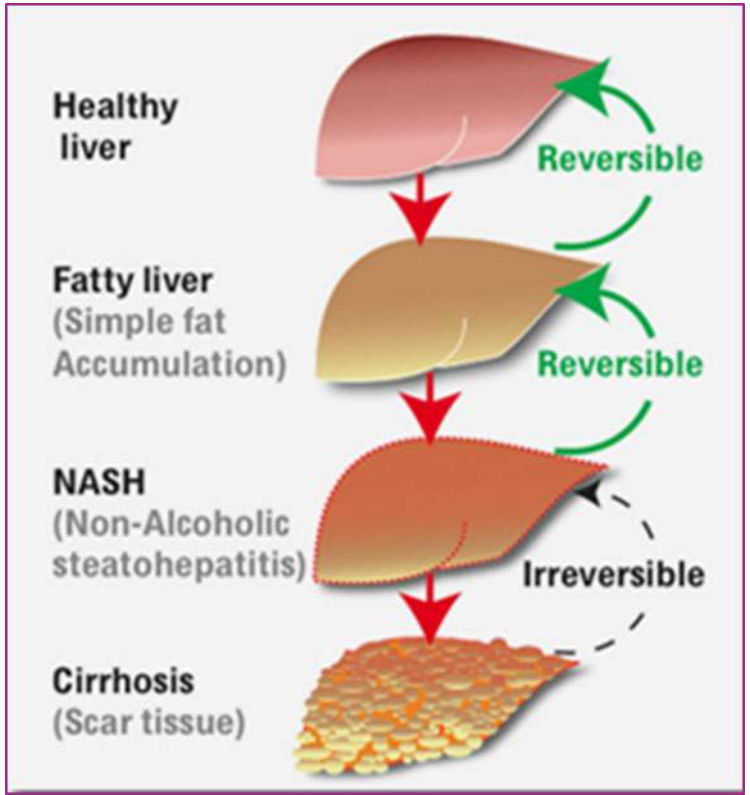
**>5% liver weight is fat, no inflammation**

Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is nominal.

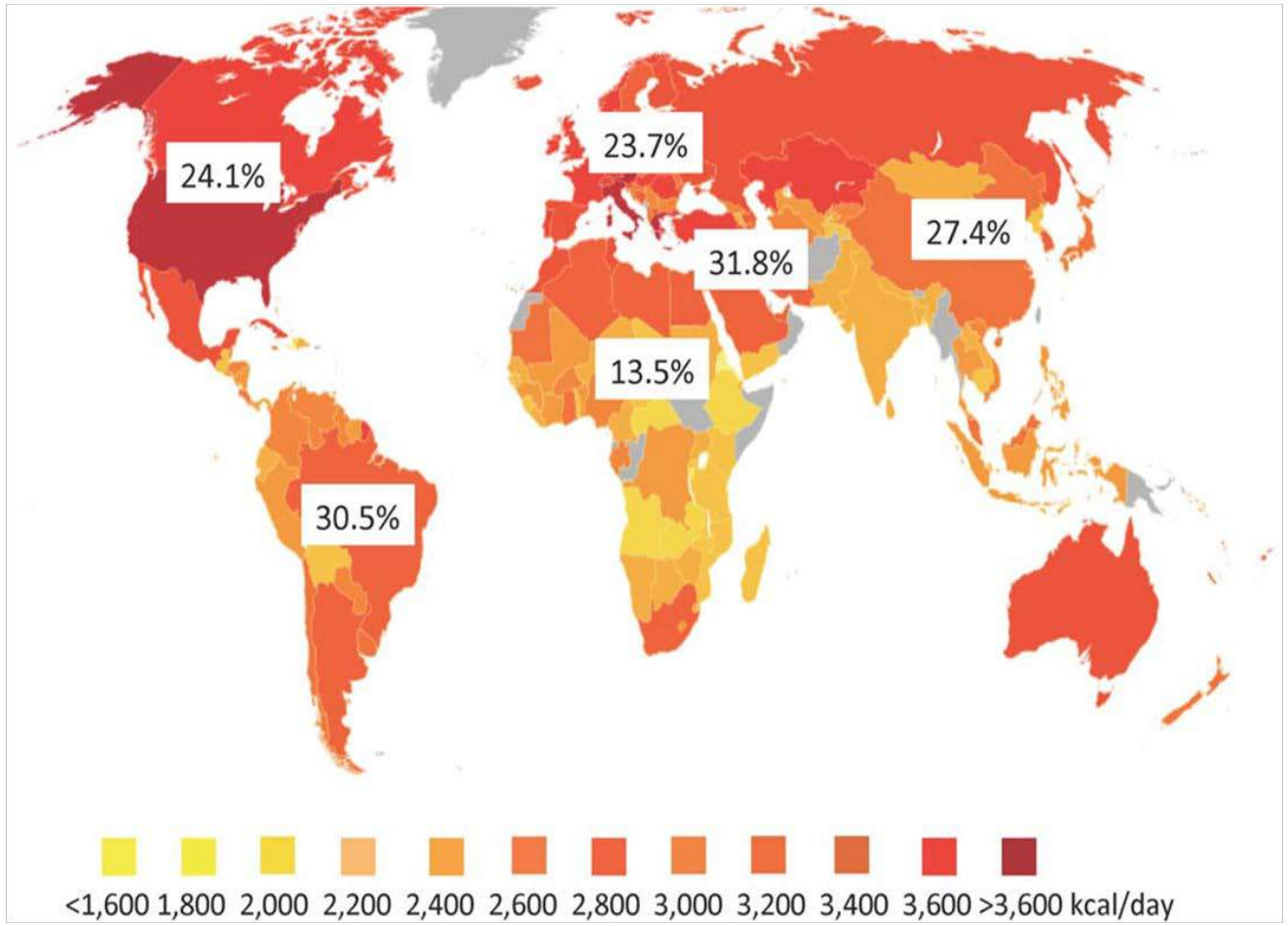
**NASH**

Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and, rarely, liver cancer.



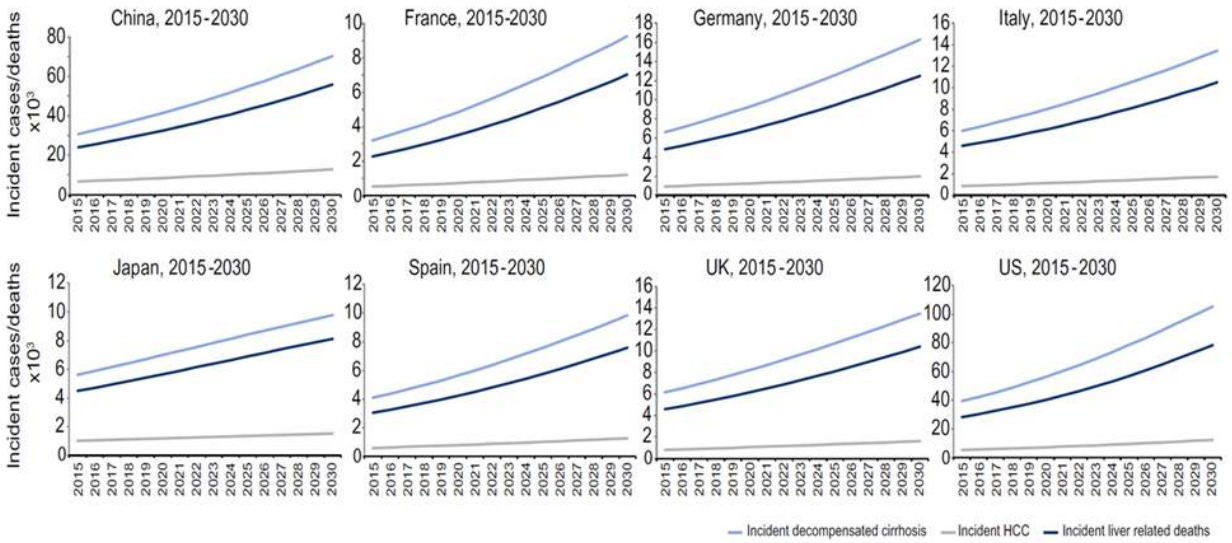
# NAFLD: Most common chronic liver disease globally




Rinella et al., Hepatology 2016

# Global Burden NAFLD 2030

**Incident decompensated cirrhosis, HCC and liver-related deaths are expected to keep rising 2015–2030**

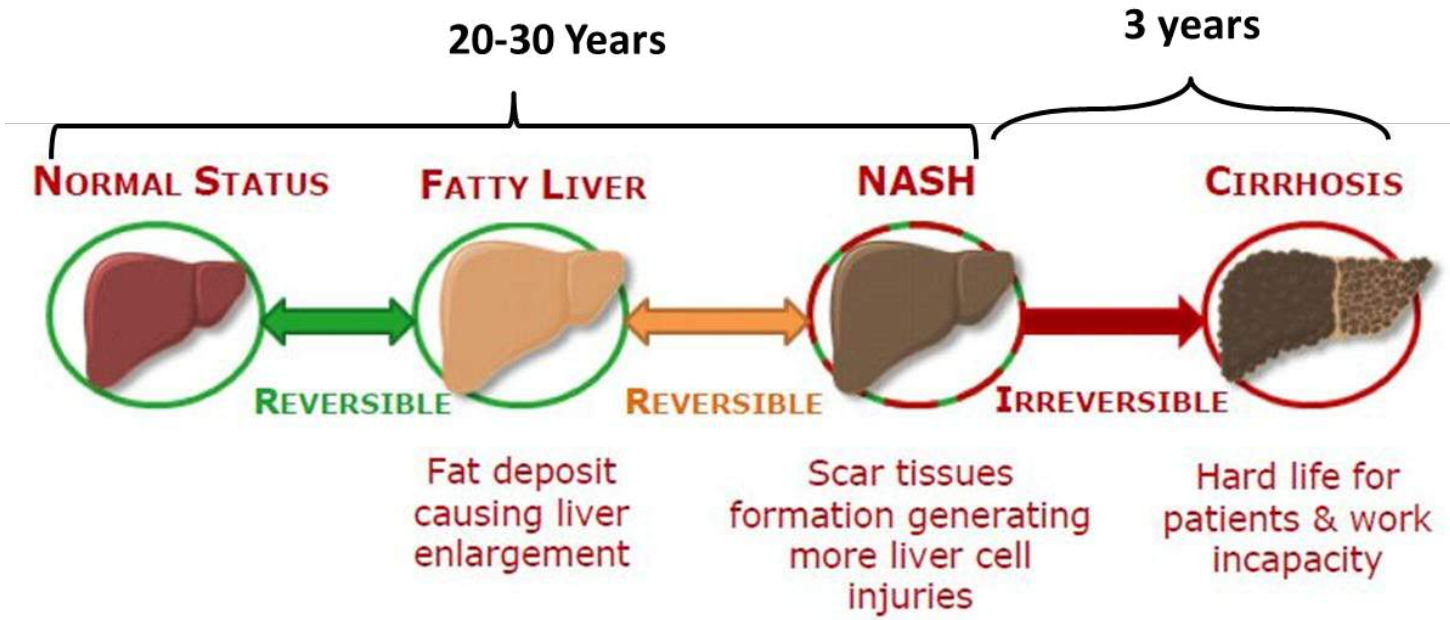



Estes C et al, J Hepatol 2018


**Hepatic viruses are cured**

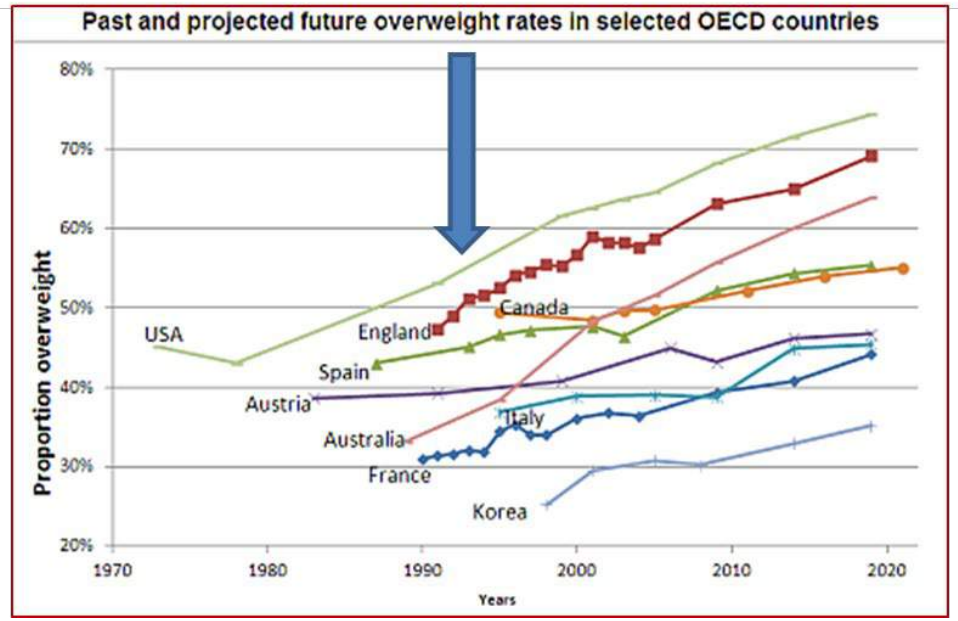
**Hepatologists need “new” disease?**


**LET´S UNDERSTAND** **PHYSIOPATHOLOGY**

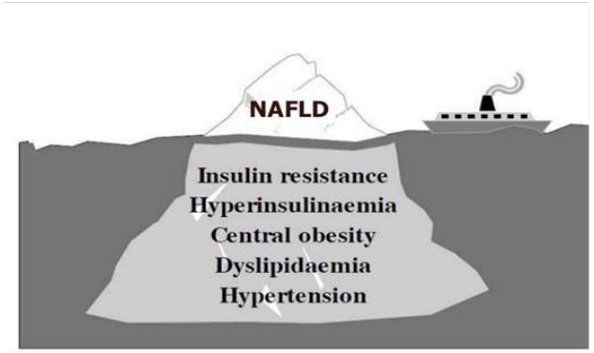


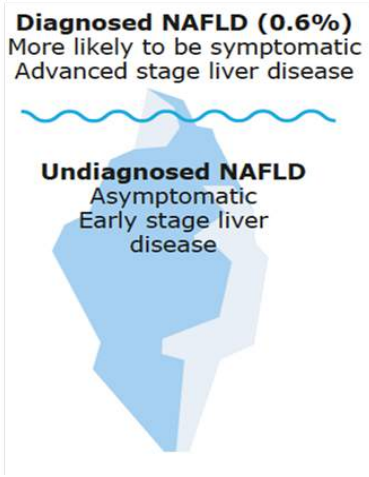

NAFLD in OBESITY: 50-90%

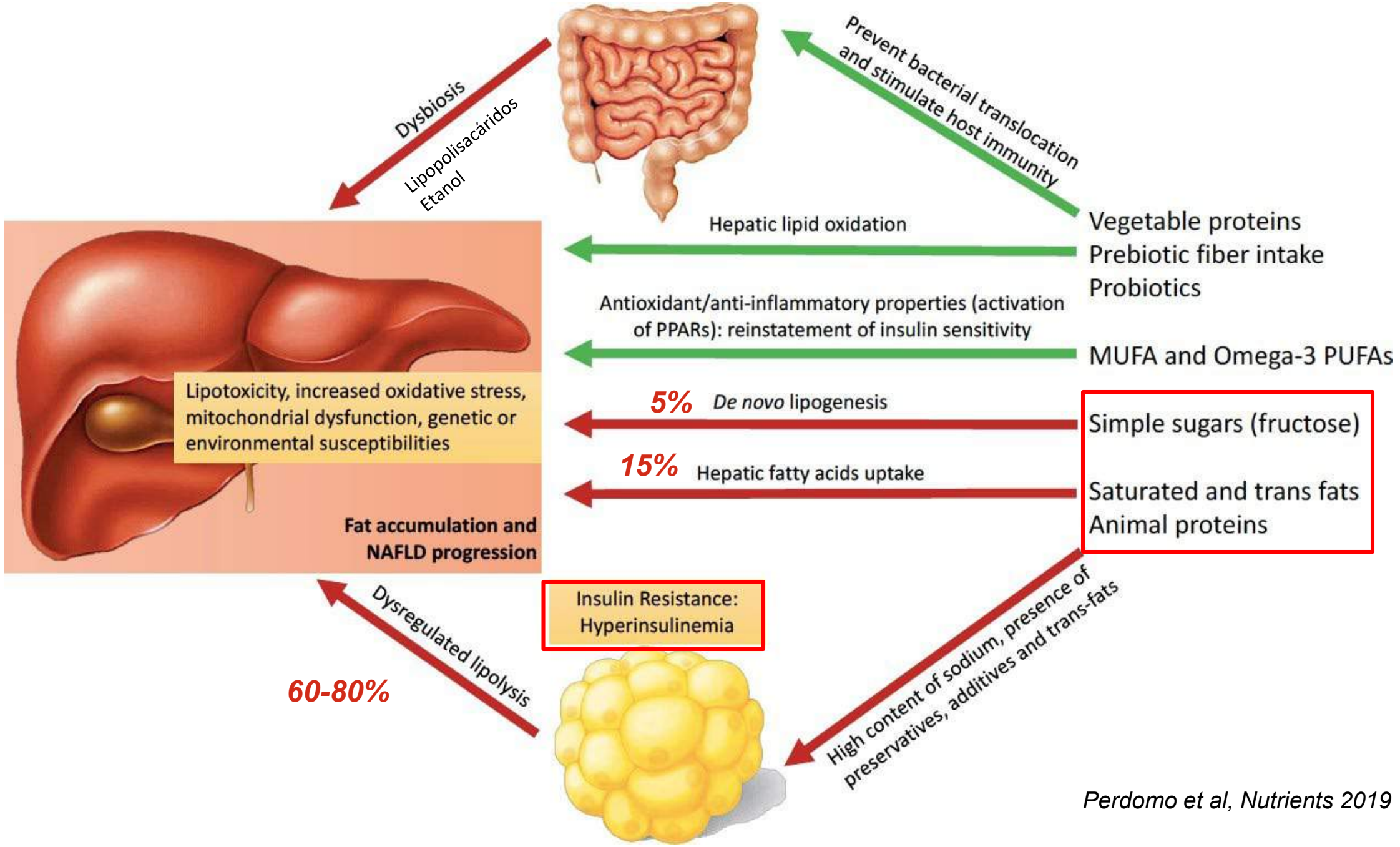
NASH in Obesity: 25-40%




## Paradigm of the iceberg metaphor



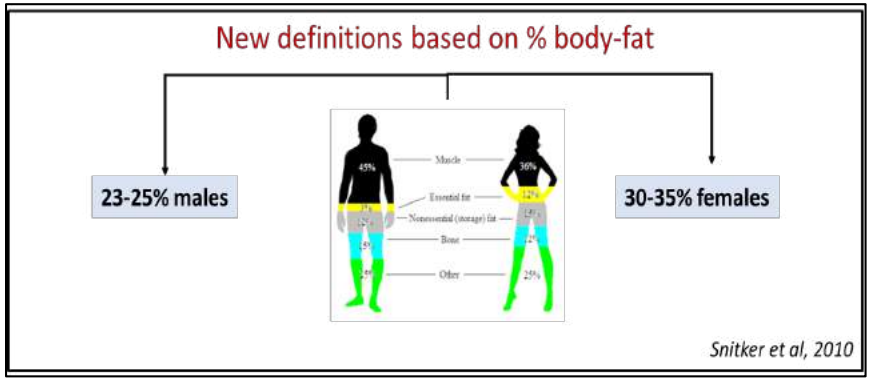



*Perdomo et al, Nutrients 2019*

# Adiposity

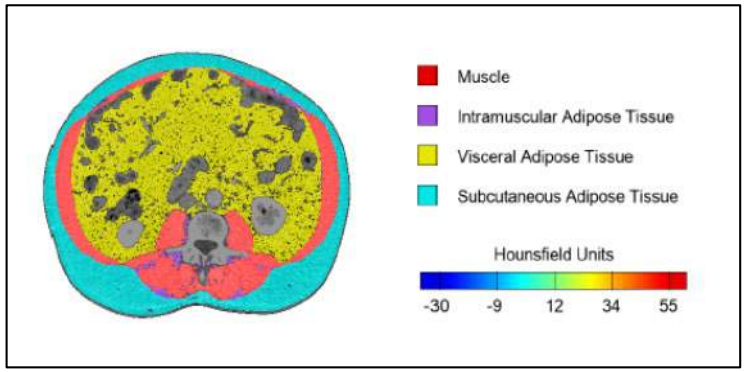
## Total amount of fat

**Body composition %**



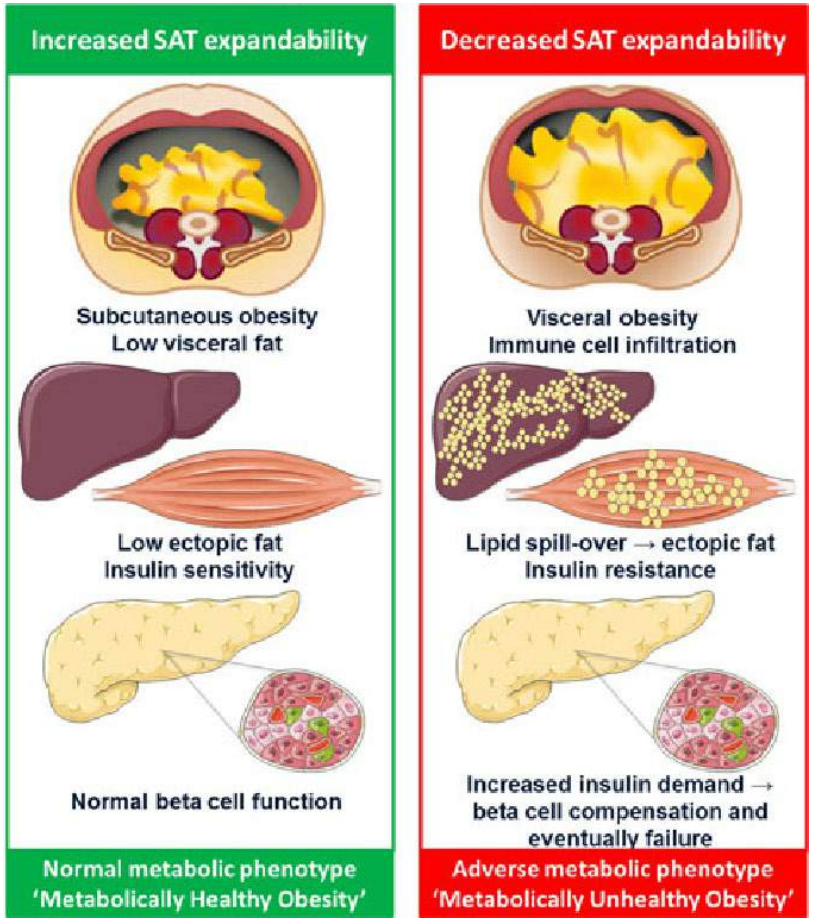

## Distribution

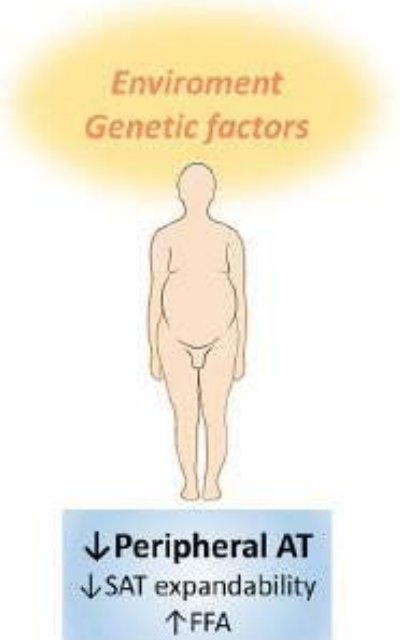
- **Subcutaneous**
- **Ectopic**



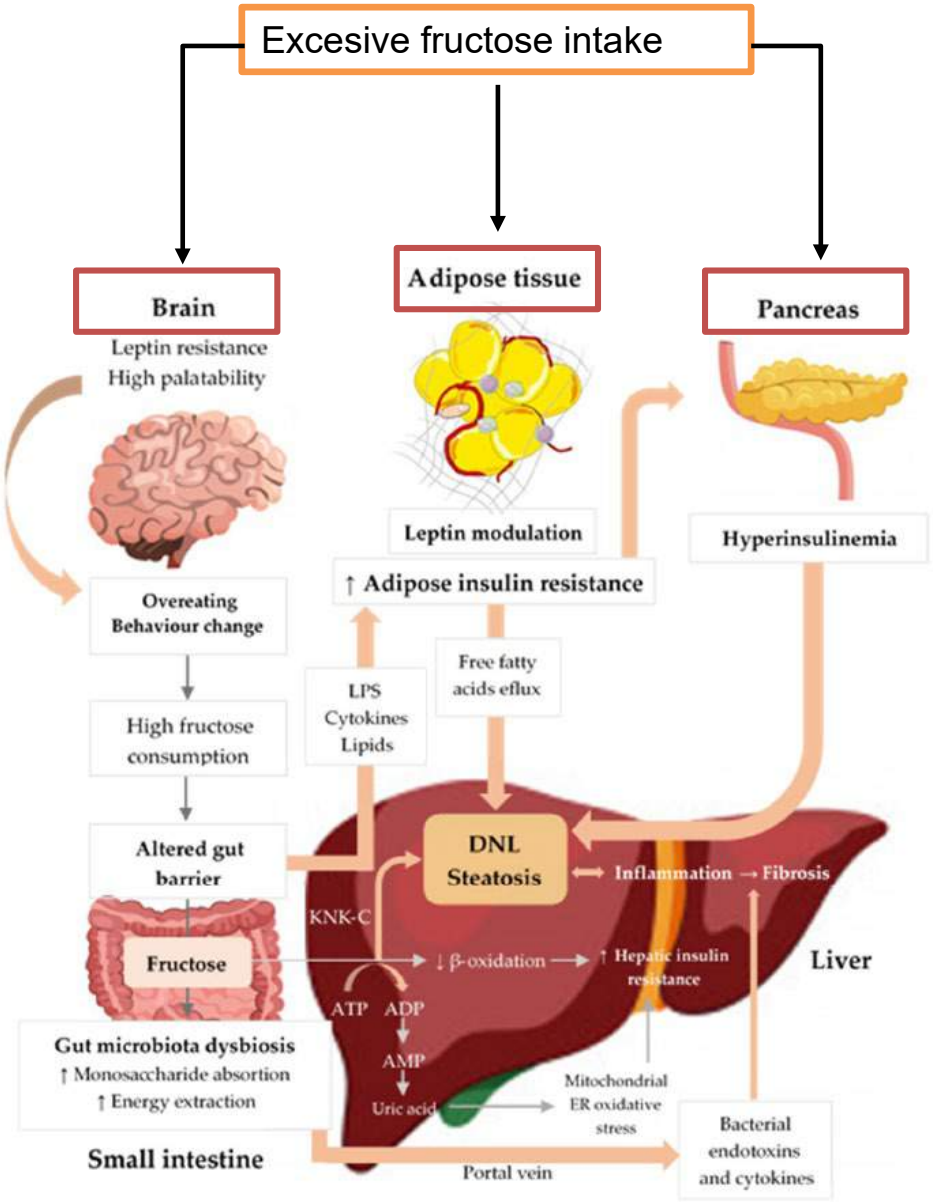

## Function

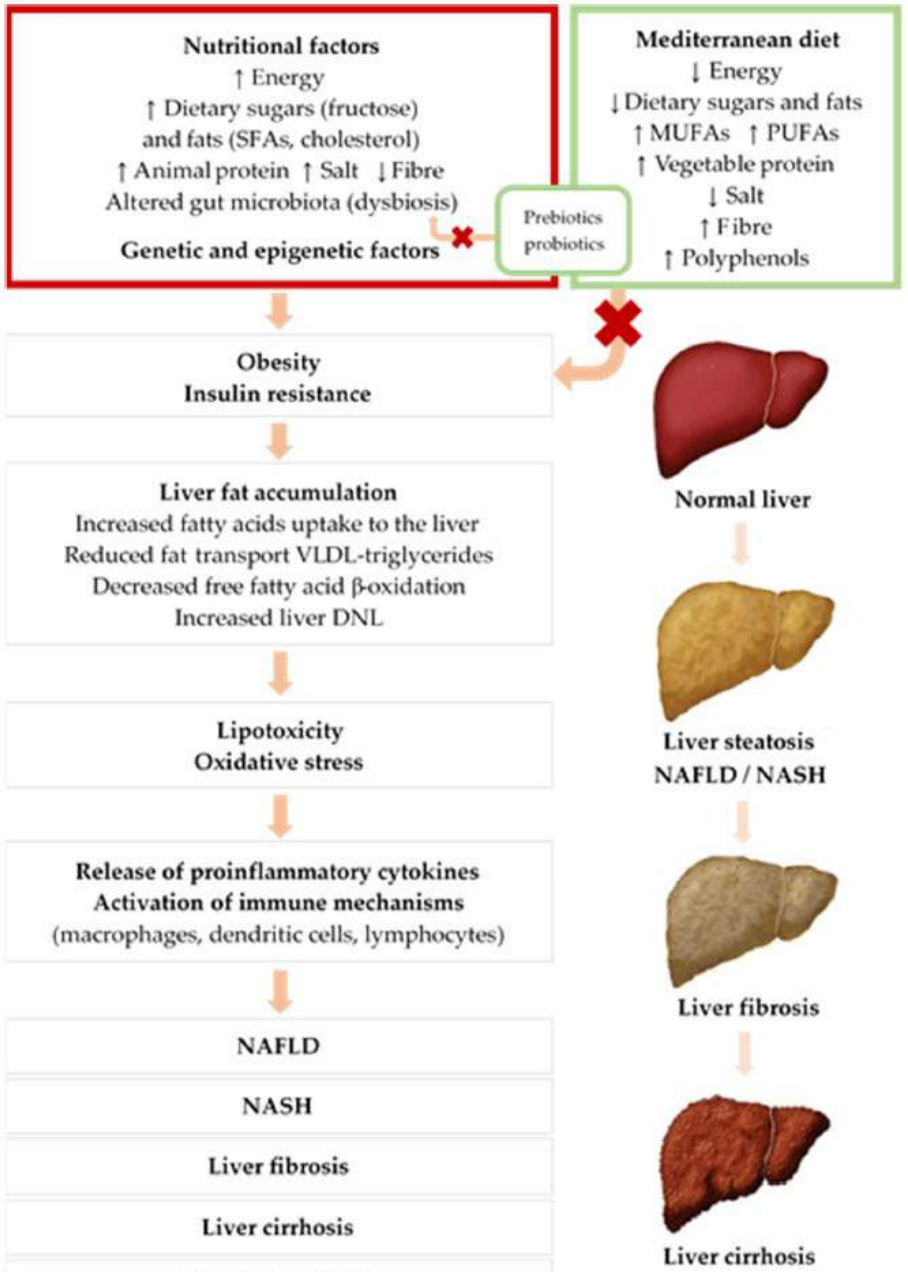
**Expandibility (capacity to store TG)**





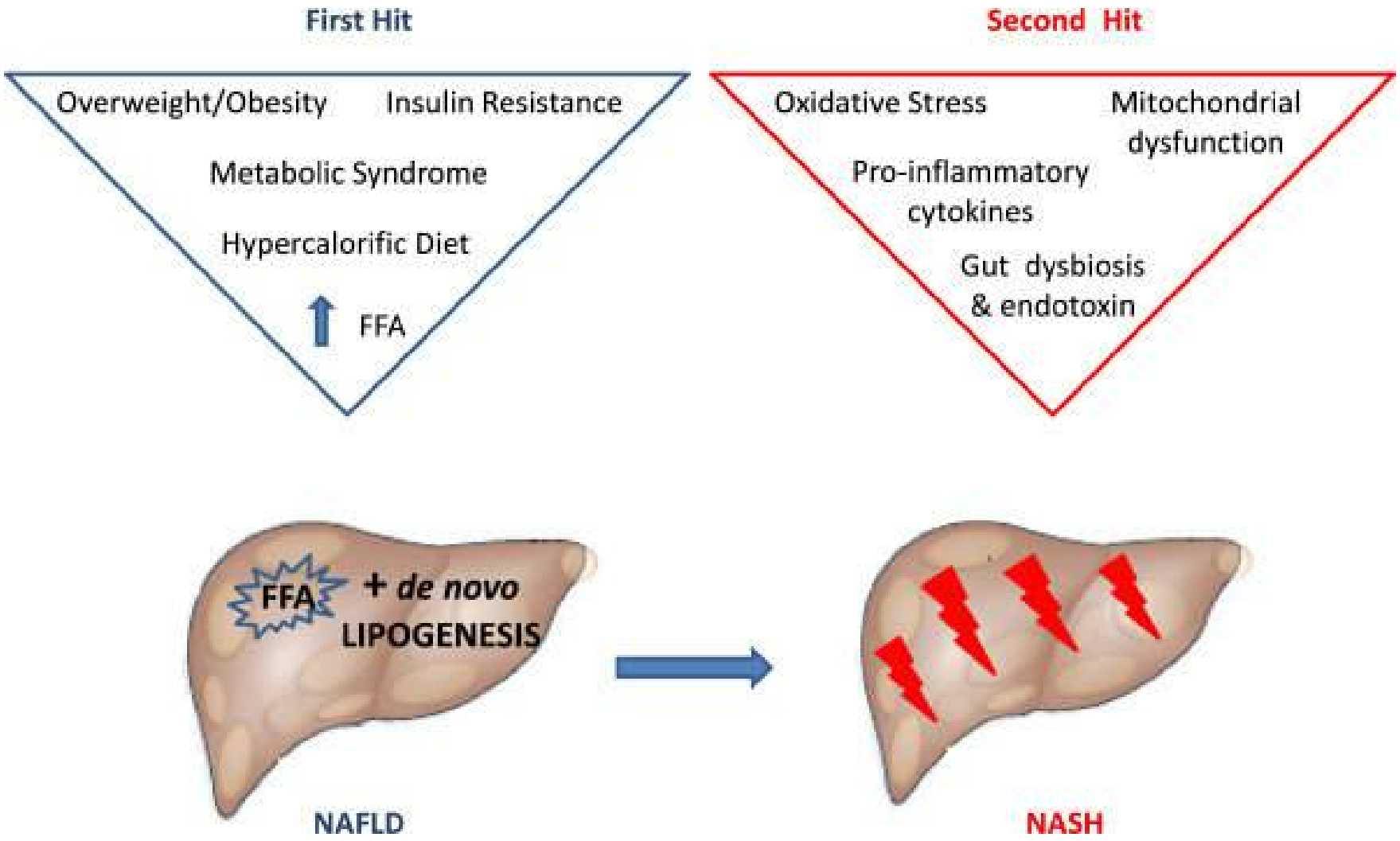

*Godoy-Matos et al, 2020*



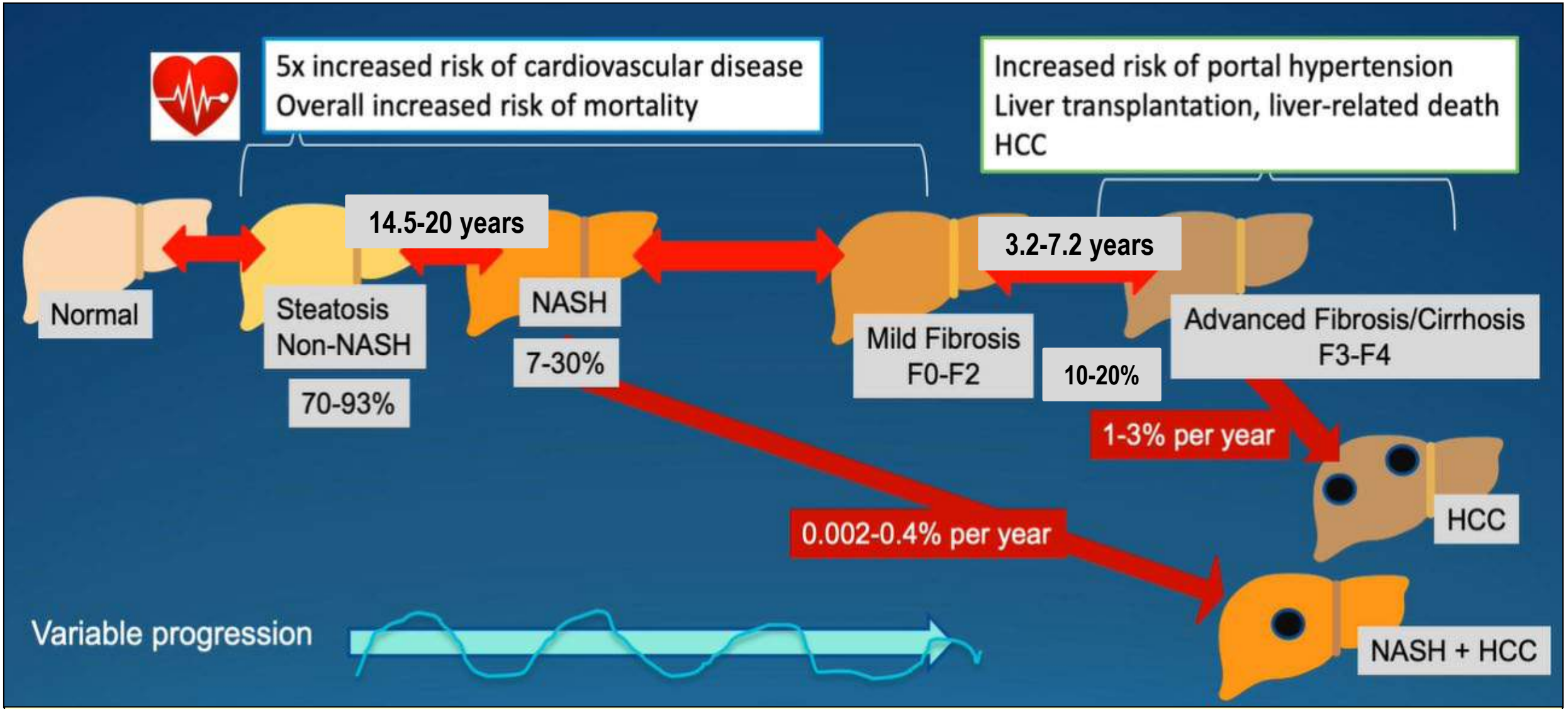




DNL: de novo lipogenesis

# Nartural evolution of the disease: “the two-hit theory”

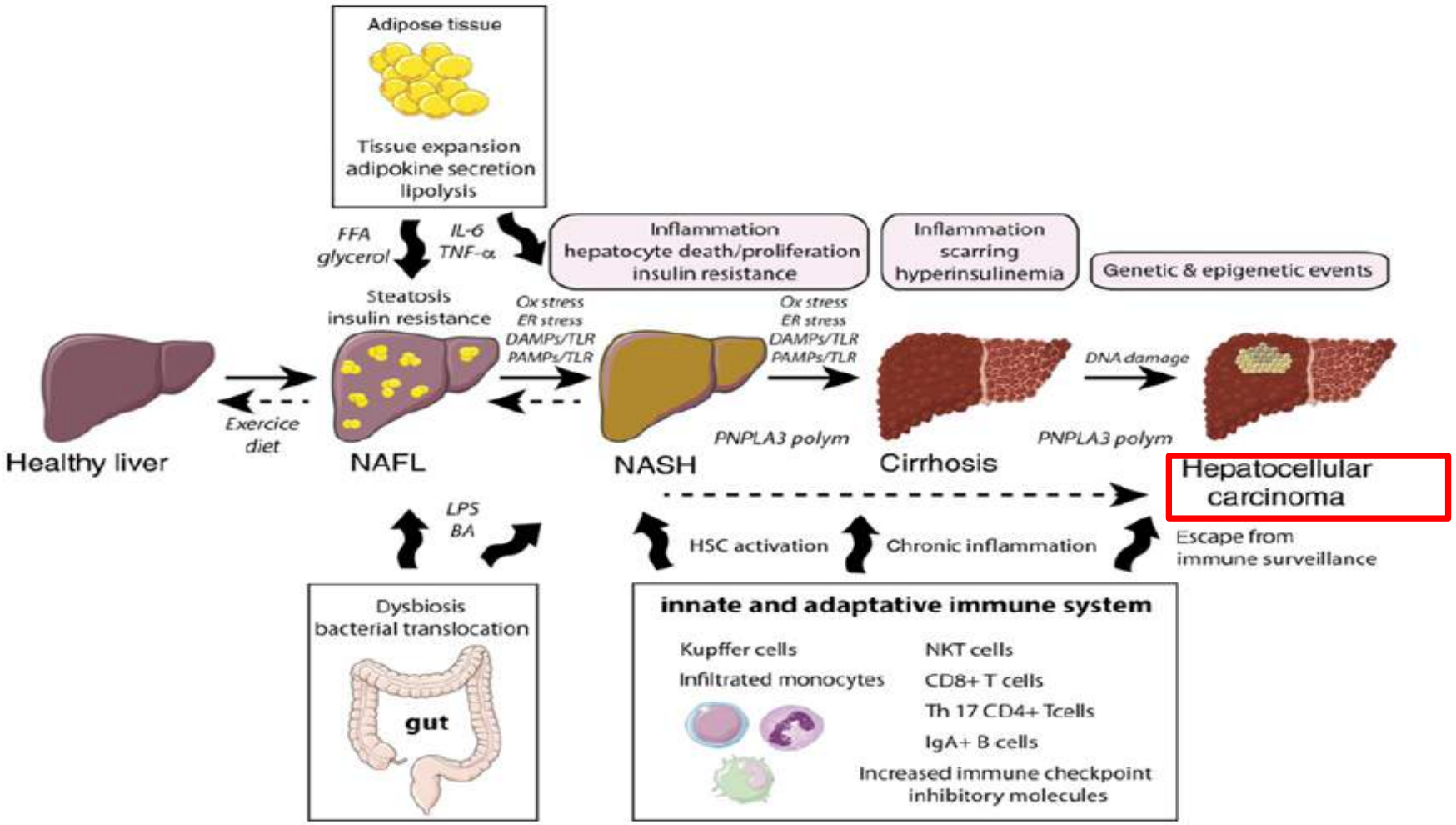


# NATURAL HISTORY




Younossi ZM et al. **Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.** Hepatology. 2018 Jul;68(1):361-371. doi: 10.1002/hep.29724. PMID: 29222911;

# Hepatocarcinoma (HCC ) in patients with NAFLD patients

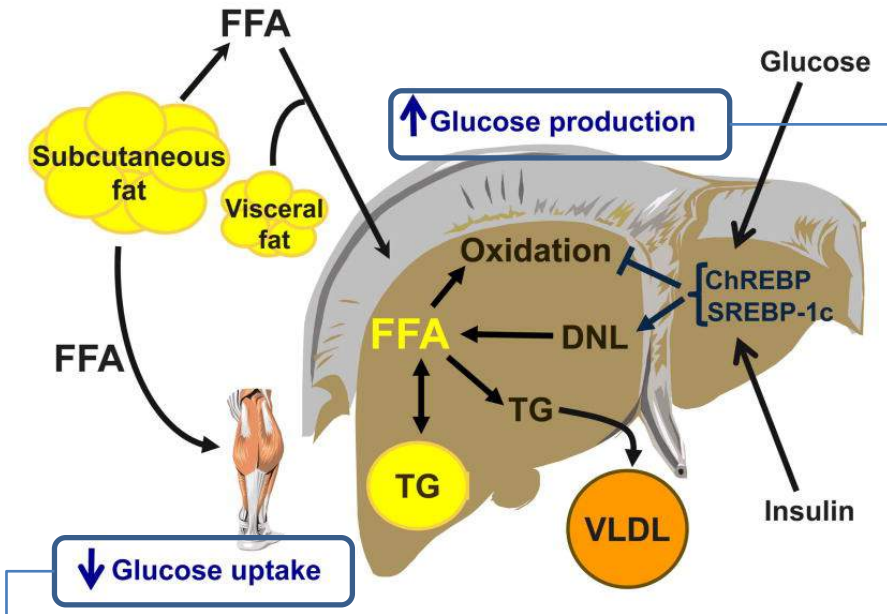



*Younossi & Henry, JHEP Rep 2021*

# OBESITY AND NAFLD

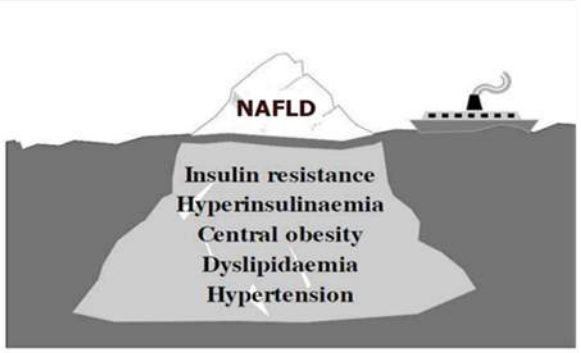
NAFLD in OBESITY:
50-90%

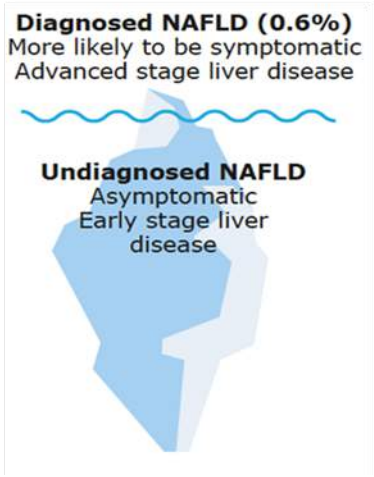
NASH in Obesity:
25-40%




*Fabrinni et al, Hepathology 2010*

## Paradigm of the iceberg metaphor




Godoy-Matos *et al. Diabetol Metab Syndr* (2020) 12:60
https://doi.org/10.1186/s13098-020-00570-y

Diabetology & Metabolic Syndrome

REVIEW Open Access

## NAFLD as a continuum: from obesity to metabolic syndrome and diabetes

Amélio F. Godoy-Matos[1*], Wellington S. Silva Júnior[2] and Cynthia M. Valerio[1]

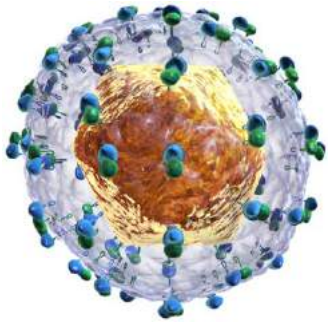
Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

# EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

## NAFLD exclusión diagnosis



- **OH consumption (>30g in males, >20g in females)**
- **No VHB/VHC**
- **No pharmacological treatment (antiepileptics, corticoids)**
- **Hemocromatosis or other liver disease**
- **Endocrinological diseases (polquisitic ovary síndrome)**

# New definition: Metabolic associated fatty liver disease

1986 — Nonalcoholic fatty liver disease (NAFLD) – Schaffner.

Nov - 2019

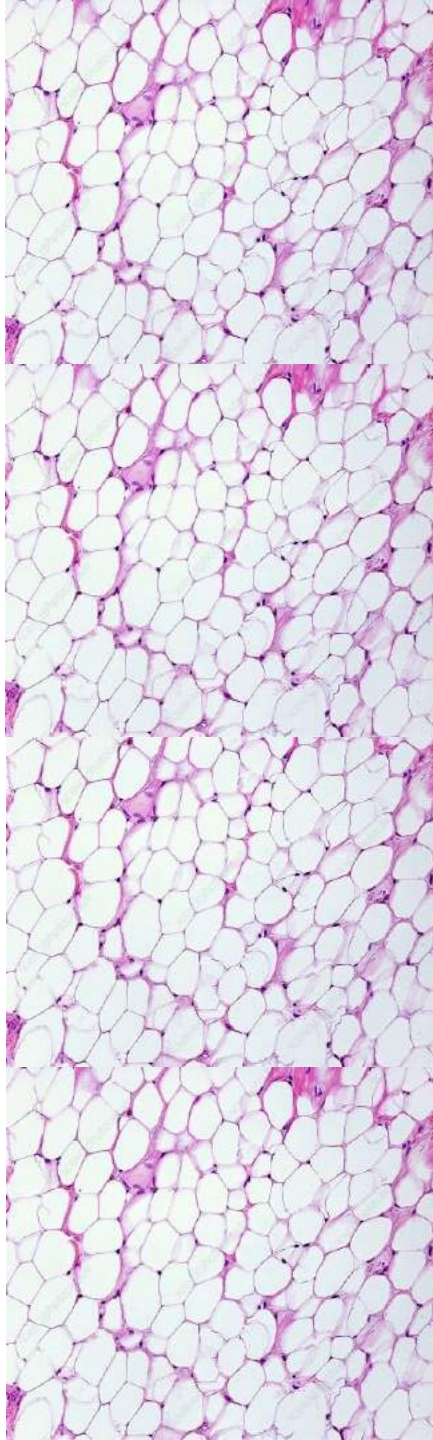
Gastroenterology 2020;158:1999–2014

## MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease



*Mohammed Eslam*[1] *Arun J. Sanyal*[2] *Jacob George*[1], *on behalf of the International Consensus Panel*

[1]*Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia; and* [2]*Virginia Commonwealth University School of Medicine, Richmond, Virginia*



March 2020

Expert Opinion

JOURNAL OF HEPATOLOGY

# A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

Mohammed Eslam[1,*,†], Philip N. Newsome[2,*,†], Shiv K. Sarin[3], Quentin M. Anstee[4], Giovanni Targher[5], Manuel Romero-Gomez[6], Shira Zelber-Sagi[7], Vincent Wai-Sun Wong[8], Jean-François Dufour[9], Jörn M. Schattenberg[10], Takumi Kawaguchi[11], Marco Arrese[12], Luca Valenti[13], Gamal Shiha[14], Claudio Tiribelli[15], Hannele Yki-Järvinen[16], Jian-Gao Fan[17], Henning Grønbæk[18], Yusuf Yilmaz[19], Helena Cortez-Pinto[20], Claudia P. Oliveira[21], Pierre Bedossa[22], Leon A. Adams[23], Ming-Hua Zheng[24], Yasser Fouad[25], Wah-Kheong Chan[26], Nahum Mendez-Sanchez[27], Sang Hoon Ahn[28], Laurent Castera[29], Elisabetta Bugianesi[30], Vlad Ratziu[31,*,‡], Jacob George[1,*,‡]

*"The heterogeneous pathogenesis of metabolic fatty liver diseases and inaccuracies in terminology and definitions necessitate a reappraisal of nomenclature to inform clinical trial design and drug development. A group of experts sought to integrate current understanding of patient heterogeneity captured under the acronym nonalcoholic fatty liver disease (NAFLD) and provide suggestions on terminology that more accurately reflects pathogenesis and can* ***help in patient stratification for management."***

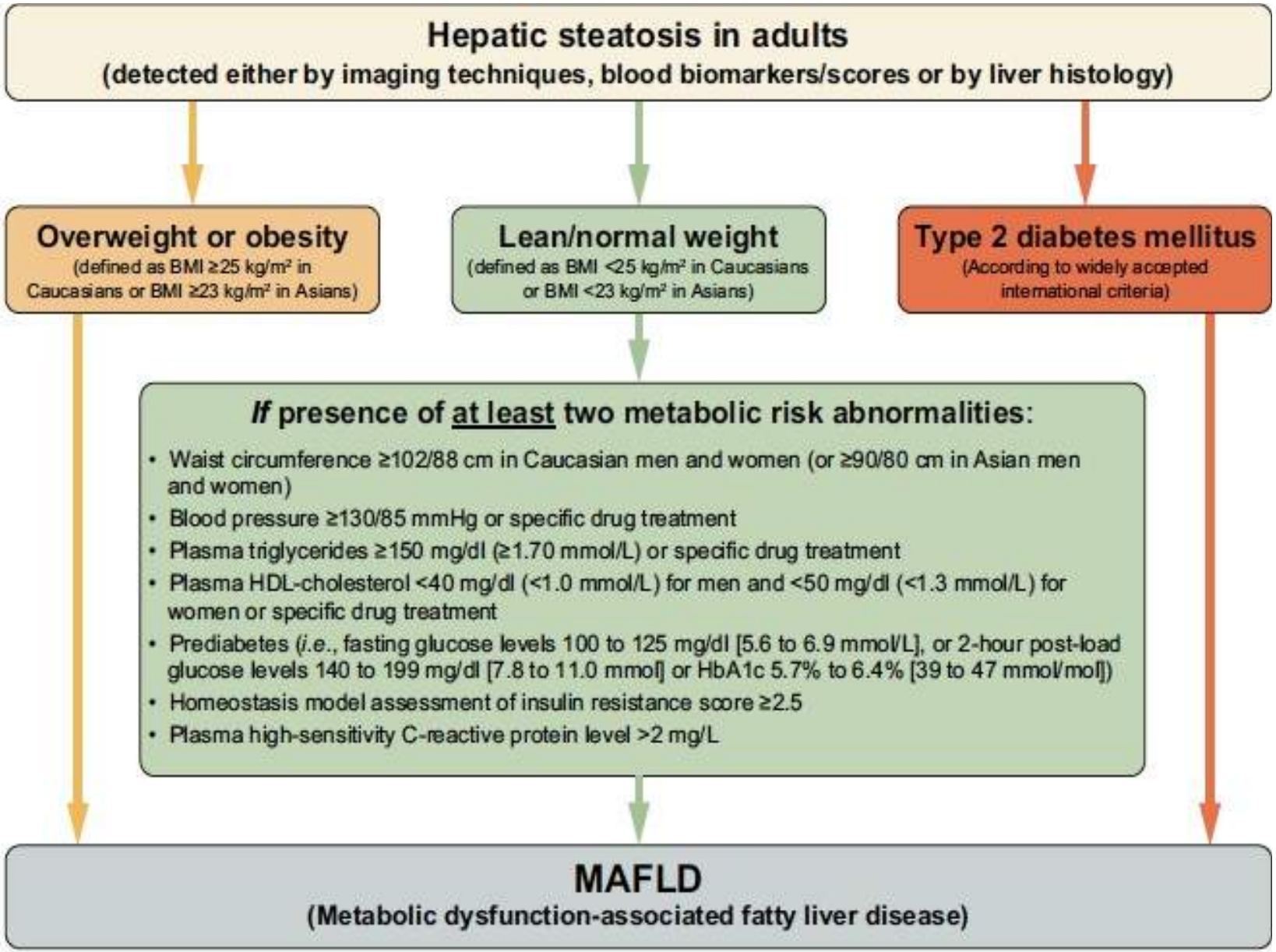
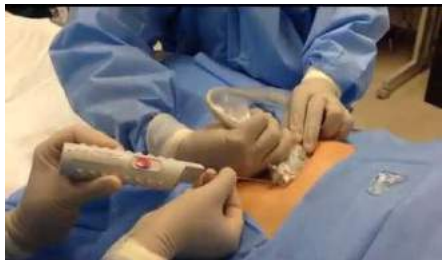


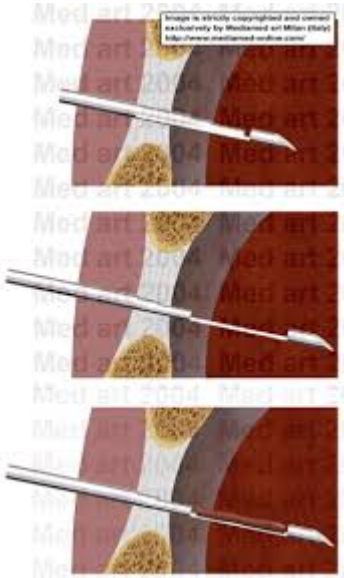

**Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.**

# Diagnostic tests

## Invasive

**Liver biopsy**





## Non-invasive

### SERUM-based

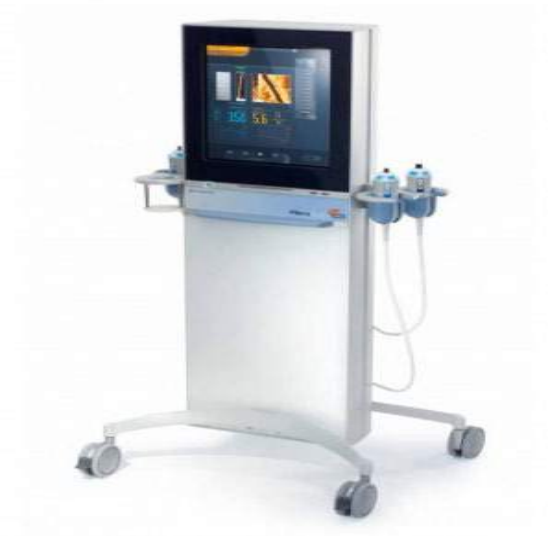
**FLI**
**FIB-4**
NAFLD Fibrosis Score (**NFS**)
HEPAMET score
**ELF**, Fibrotest, etc.

### Imaging

**Transient elastography**
ARFI
SWE
MRI

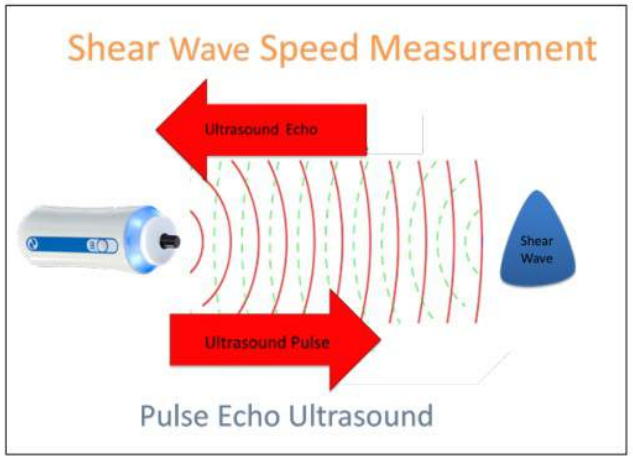
**Liver ultrasound: not reliable**

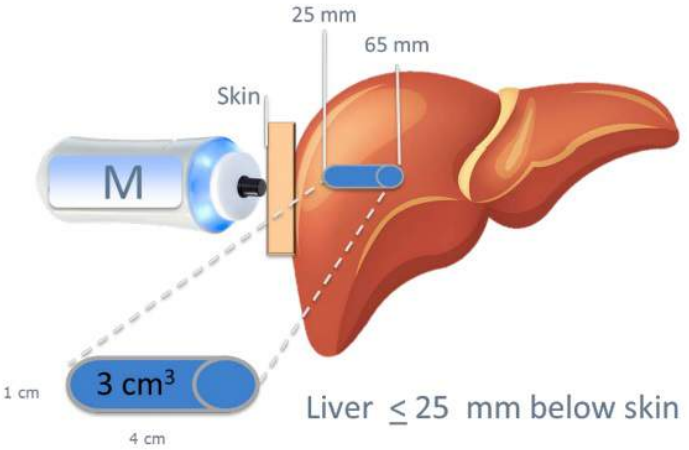
# Transient elastography

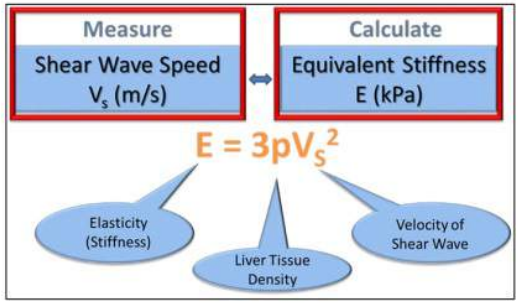


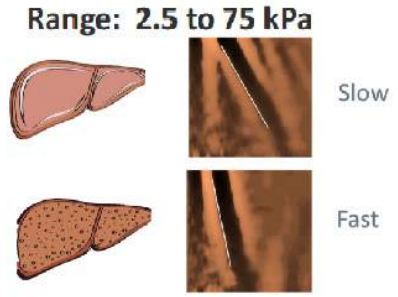
CAP= controlled attenuation parameter- steatosis >278 db/m

| Intervalo | Grado de esteatosis o grasa | Interpretación |
|---|---|---|
| <232 dB | 0 | ~5% de las células hepáticas, con contenido graso |
| 232-256 dB | 1 | 5 - 32% de las células hepáticas, con contenido graso |
| 257-290 dB | 2 | 33 - 65% de las células hepáticas, con contenido graso |
| 290-326 dB | 3 | +66% de las células hepáticas, con contenido graso |



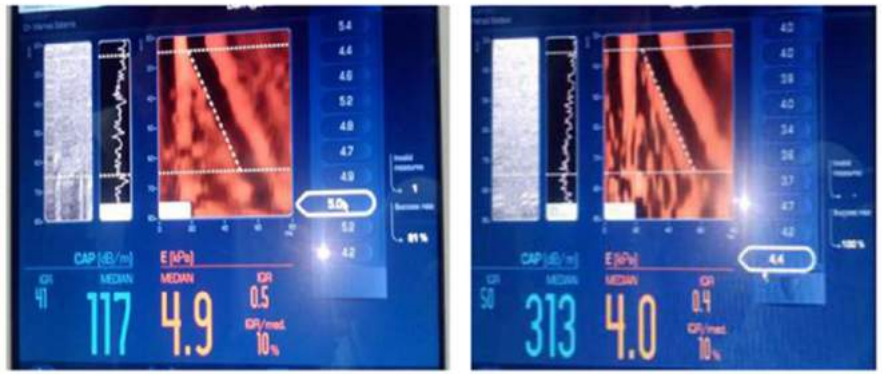



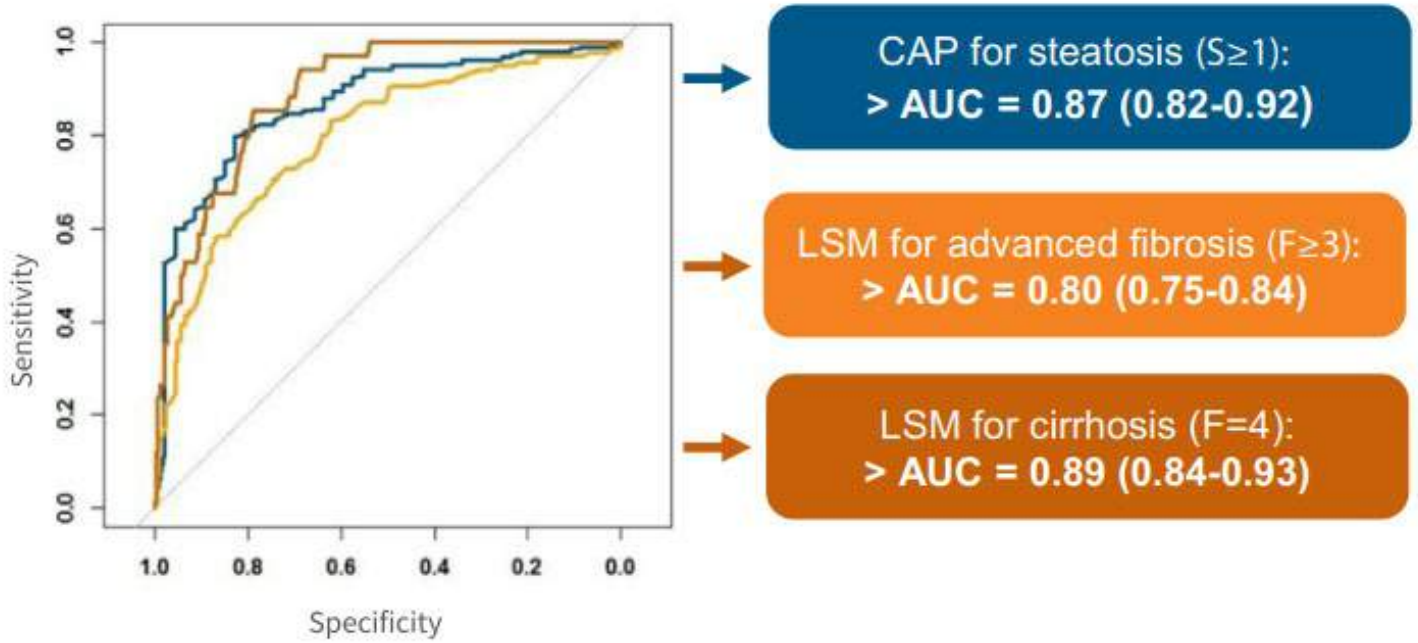




| METAVIR Scoring System | | Fibroscan Cut-off values |
|---|---|---|
| F0 | No fibrosis | -- |
| F1 | Mild fibrosis – portal fibrosis without septa | < 7.1 kPa |
| F2 | Moderate fibrosis – portal fibrosis and few septa | 7.1 to 8.8 kPa |
| F3 | Severe fibrosis – numerous septa without cirrhosis | 9.5 to 9.6 kPa |
| F4 | Cirrhosis | 12.5 to 14.6 kPa |

# LIVER STIFFNESS + CAP

## LS > 8 kPa -> VPN 94-100% ADVANCED FIBROSIS




CAP= controlled attenuation parameter- steatosis >278 db/m

*Eddoward et al. Gastroenterology 2019*

## FIB-4 Score

**(Age x AST) / (Platelets x √ ( ALT))**

>2.67: Suggestive of advanced fibrosis


## HEPAMET Fibrosis Score

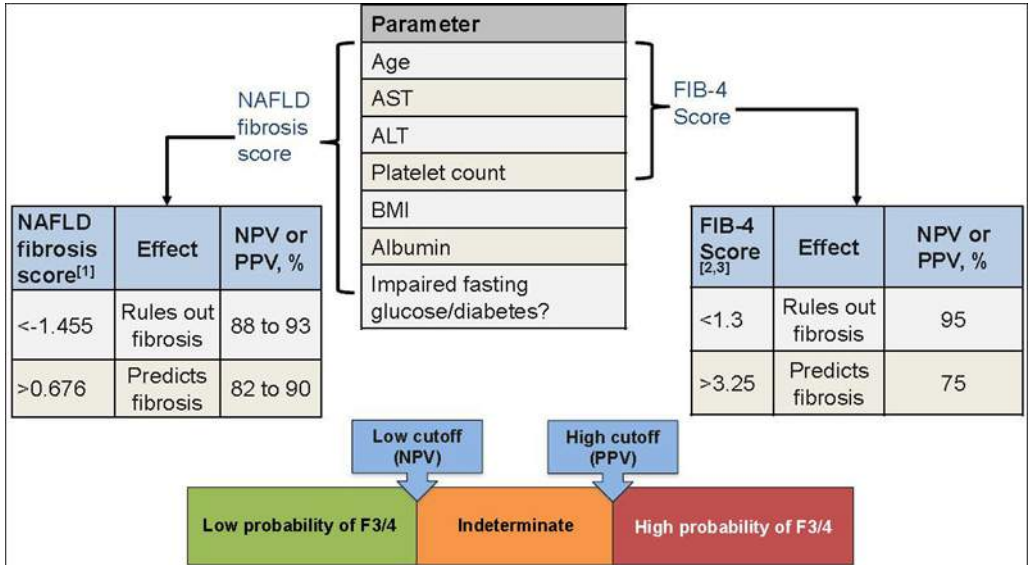
**AST, glucose, insulin, albumin, age**

>0.47: Suggestive of advanced fibrosis

## NAFLD Fibrosis Score

**-1.675 + (0.037 x age [years]) + (0.094 x BMI [kg/m$^2$]) + (1.13 x IFG/diabetes [yes = 1, no = 0]) + (0.99 x AST/ALT ratio) – (0.013xplatelet count [×10$^9$/L]) – (0.66xalbumin [g/dl])**

> 0.675: F3-F4 Suggestive of advanced fibrosis



# MAFLD compared to NAFLD: heterogeneity

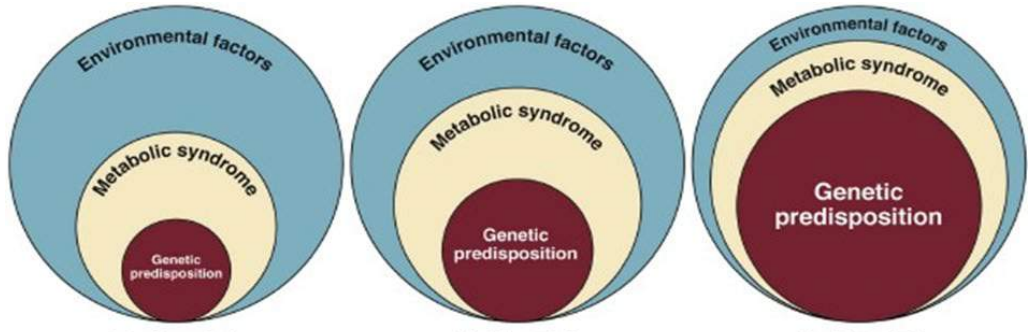
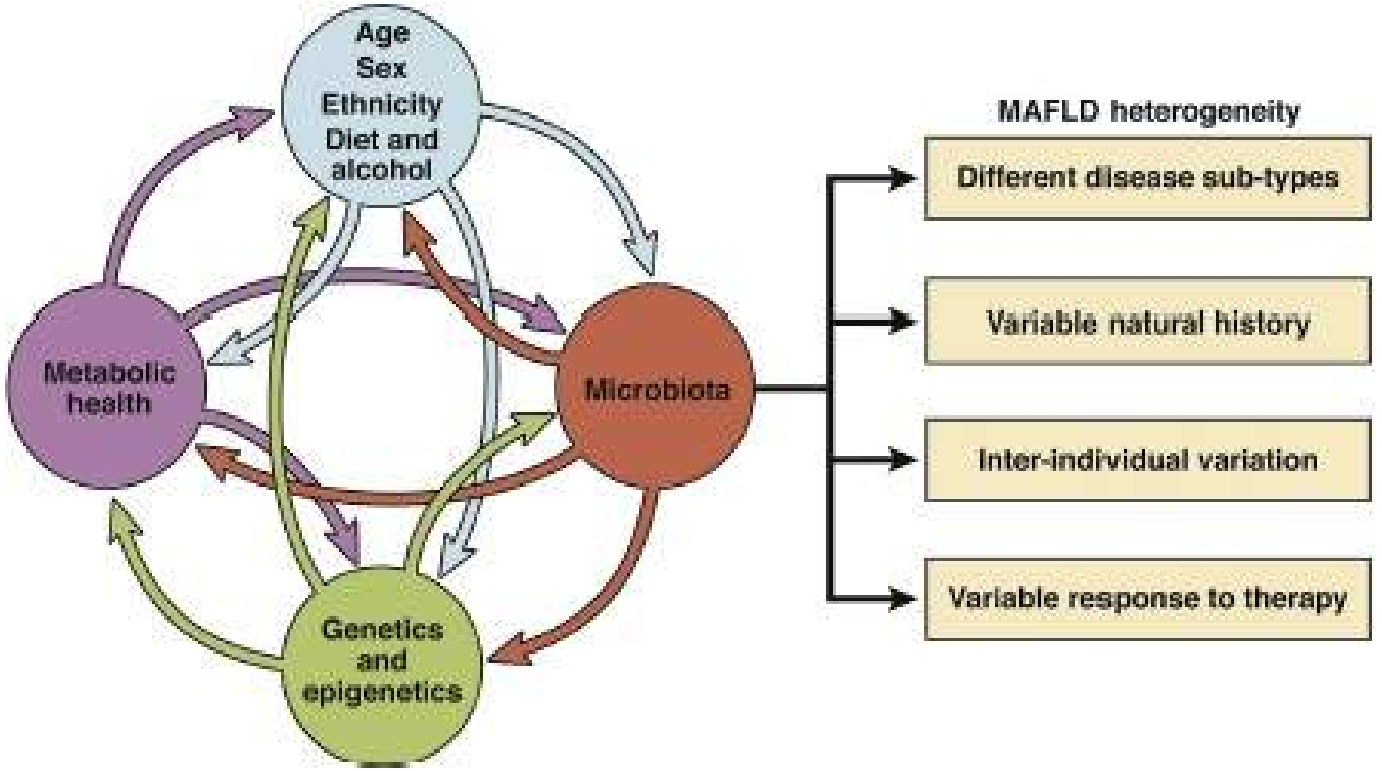



**Figure 2.** Interindividual variation in the predominant drivers of MAFLD. MAFLD is a complex phenotype shaped by the dynamic interaction of genetic predisposition with environmental factors and components of the metabolic syndrome. The effect size of genetic variants and the predominant drivers can exhibit marked interindividual variation. As an example, disease in patient 1 is driven predominantly by environmental influences with less contribution from genetic predisposition; in patient 2, metabolic syndrome is the predominant driver, whereas disease in patient 3 is driven by genetic factors with a limited contribution from other factors. Identification of the predominant drivers in every patient can help in personalization of medicine.




**PNPLA3 rs738409**
**TM6SF2 rs58542926**

# MAFLD

## Is not an exclusión criteria

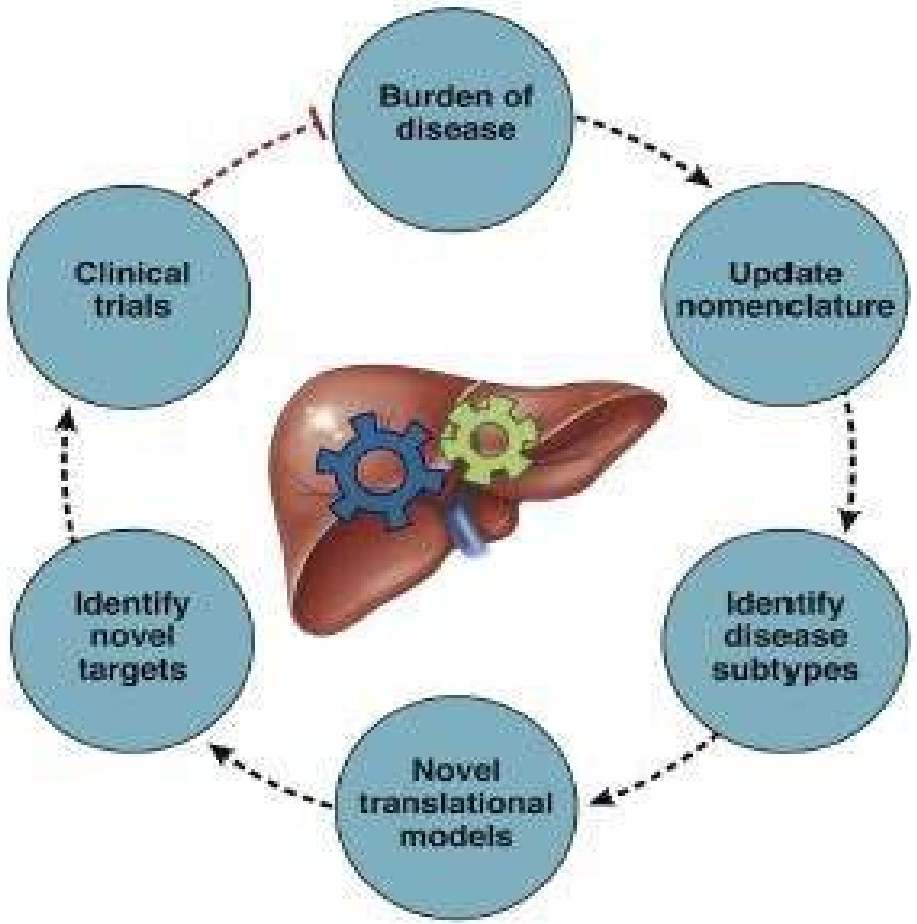



**Table 1.** Statements of the Consensus Panel

**Nomenclature and definition of metabolic associated fatty liver disease (MAFLD)**

- We suggest that the nomenclature of NAFLD should be updated to MAFLD.
- The diagnosis of MAFLD should be based on the presence of metabolic dysfunction not the absence of other conditions.
- MAFLD can coexist with other liver diseases.
- A reference to alcohol should not be included in the MAFLD acronym.
- Patients with both MAFLD and a contribution from alcohol to their liver disease represent a large and important group that requires further investigation and characterization.

**MAFLD heterogeneity**

- MAFLD is a heterogeneous entity.
- Appropriate patient stratification must be considered when noninvasive fibrosis scores are developed and in clinical trial design.
- Studies are required to map the landscape of MAFLD and to precisely define subtypes of the disease.

**Clinical trials for MAFLD**

- Detailed patient stratification and tailoring clinical trial inclusion criteria based on drivers of disease will likely yield more informative and meaningful results.
- Innovative designs for clinical trials and personalized combination therapy approaches will likely be required to overcome the challenges of disease heterogeneity and for optimal clinical efficacy.

**Agosto 2020**

n: 765 pacientes

Received: 6 August 2020 | Revised: 15 September 2020 | Accepted: 18 September 2020

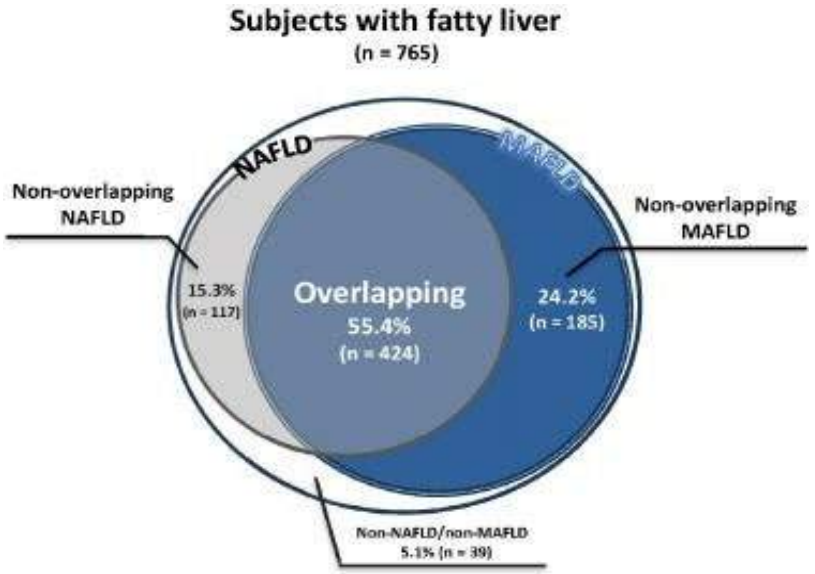
DOI: 10.1111/liv.14675

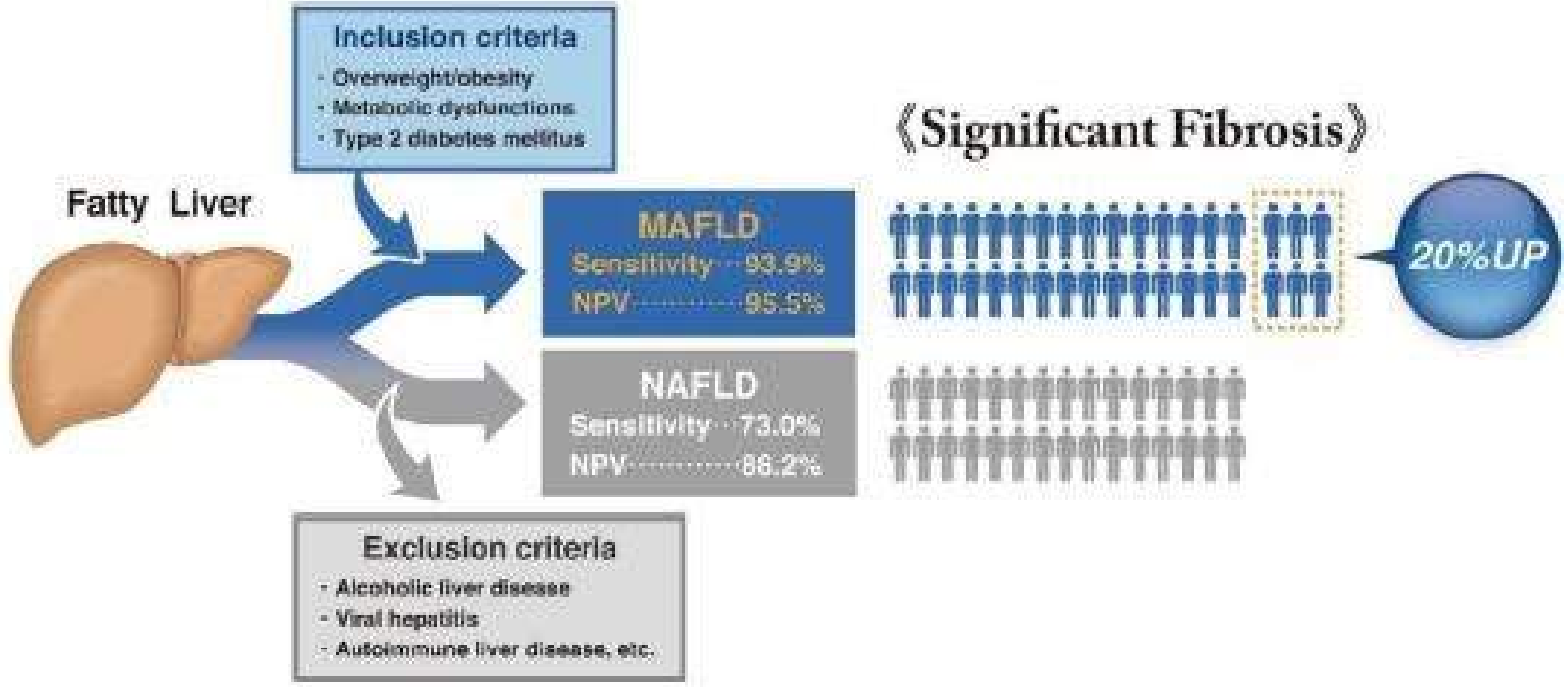
ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

# MAFLD identifies patients with significant hepatic fibrosis better than NAFLD

Sakura Yamamura[1] | Mohammed Eslam[2] | Takumi Kawaguchi[1] | Tsubasa Tsutsumi[1] | Dan Nakano[1] | Shinobu Yoshinaga[3] | Hirokazu Takahashi[4] | Keizo Anzai[4] | Jacob George[2] | Takuji Torimura[1]




- **MAFLD better defines subjects with risk of fibrosis**
- **Low-grade OH consumption: higher risk of fibrosis in vulnerable population.**

# MAFLD management

Clinical Practice Guidelines

Journal of Hepatology **2016** vol. 64 | 1388–1402

# EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

*Recommendations*

- Unhealthy lifestyles play a role in the development and progression of NAFLD. The assessment of dietary and physical activity habits is part of comprehensive NAFLD screening (**A1**)

*Recommendations*

- Follow up is mandatory in obesity, which is the major phenotype and risk condition for NAFLD, driven by IR, and also increases the risk of advanced disease (**A1**)
- Most lean persons with NAFLD display IR and altered body fat distribution even though they have less severe metabolic disturbance than overweight NAFLD. Follow-up is nonetheless required because of possible disease progression (**B2**)

**Table 5. Elements of a comprehensive lifestyle approach to NAFLD treatment.**

| Area | Suggested intervention | Supportive literature |
|---|---|---|
| Energy restriction | • 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week | Calorie restriction drives weight loss and the reduction of liver fat, independent of the macronutrient composition of the diet [107] |
| | • 7-10% total weight loss target | A 12-month intensive lifestyle intervention with an average 8% weight loss leads to significant reduction of hepatic steatosis [108] |
| | • Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment | Hepatic fat increases along with total body fat regain, but most of the beneficial metabolic effects are maintained and progression to T2DM is delayed [109]. |
| Macronutrient composition | • Low-to-moderate fat and moderate-to-high carbohydrate intake<br>• Low-carbohydrate ketogenic diets or high-protein | Adherence to the Mediterranean diet has been reported to reduce liver fat on $^{1}$H-MRS, when compared with a low fat/ high carbohydrate diet in a cross-over comparison [110, 111] |
| Fructose intake | • Avoid fructose-containing beverages and foods | In the general population, an association has been reported between high fructose intake and NAFLD [9] |
| Alcohol intake | • Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women) | In epidemiological surveys, moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis at histology [112-114]. Total abstinence is mandatory in NASH-cirrhosis to reduce the HCC risk [115] |
| Coffee drinking | • No liver-related limitations | Protective in NAFLD, as in liver disease of other aetiologies, reducing histological severity and liver-related outcomes [116] |
| Exercise/physical activity | • 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling)<br>• Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors<br>• High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise | Physical activity follows a dose-effect relationship and vigorous (running) rather than moderate exercise (brisk walking) carries the full benefit, including for NASH and fibrosis [110, 117, 118]<br>Any engagement in physical activity or increase over previous levels is however better than continuing inactivity |

*nutrients*

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MDPI

*Review*

# Overview of Non-Alcoholic Fatty Liver Disease (NAFLD) and the Role of Sugary Food Consumption and Other Dietary Components in Its Development

Pau Vancells Lujan [1], Esther Viñas Esmel [1,2] and Emilio Sacanella Meseguer [1,2,*]

**Table 1.** Epidemiological and pathological differences between NAFLD and NASH, and their respective minimum weight loss goals in dietary treatment [13,14].

| | NAFLD | NASH |
|---|---|---|
| Overall prevalence (estimated in general population) | 25% | 3–5% (7–30% of NAFLD patients) |
| Pathology | (a) Steatosis alone<br>(b) Steatosis with lobular or portal inflammation, without ballooning<br>(c) Steatosis with ballooning but without inflammation | Steatosis, ballooning, and lobular inflammation |
| Fibrosis progression | 1 stage of progression over 14 years | 1 stage of progression over 7 years |
| Liver cirrhosis 10–20-year time | 2–3% | 15–20% |
| HCC incidence rate | 0.44 per 1000 person years | 5.29 per 1000 person years |
| Liver-specific mortality incidence rate | 0.77 per 1000 person years | 11.77 per 1000 person years |
| Overall mortality incidence rate | 15.44 per 1000 person years | 25.56 per 1000 person years |
| Pharmacological treatment | Non approved | Non approved |
| Weight loss goal in dietary treatment | 3–5% of weight loss | 7–10% of weight loss |

Abbreviations: NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma.

*nutrients*

MDPI

*Review*

# Impact of Nutritional Changes on Nonalcoholic Fatty Liver Disease

**Carolina M. Perdomo [1], Gema Frühbeck [1,2] and Javier Escalada [1,2,*]**

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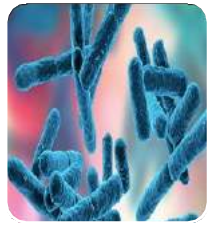
| RECOMMENDED | |
|---|---|
| Whole grains | Probiotics [a] |
| MUFAs | Resveratrol [a] |
| Omega-3 PUFAs | Coffee [a] |
| Vegetable protein | Taurine [a] |
| Prebiotic fiber Frutas | Choline [a] Huevo |
| **TO BE AVOIDED** | |
| Simple sugars (fructose) | Omega-6 |
| Saturated and trans fats | PUFA |
| Animal protein (red and processed meat) | |



**PROBIÓTICS**

**Coffe**

**RESVERATROL?**

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**OMEGA-6/OMEGA-3 1-2 :1).**

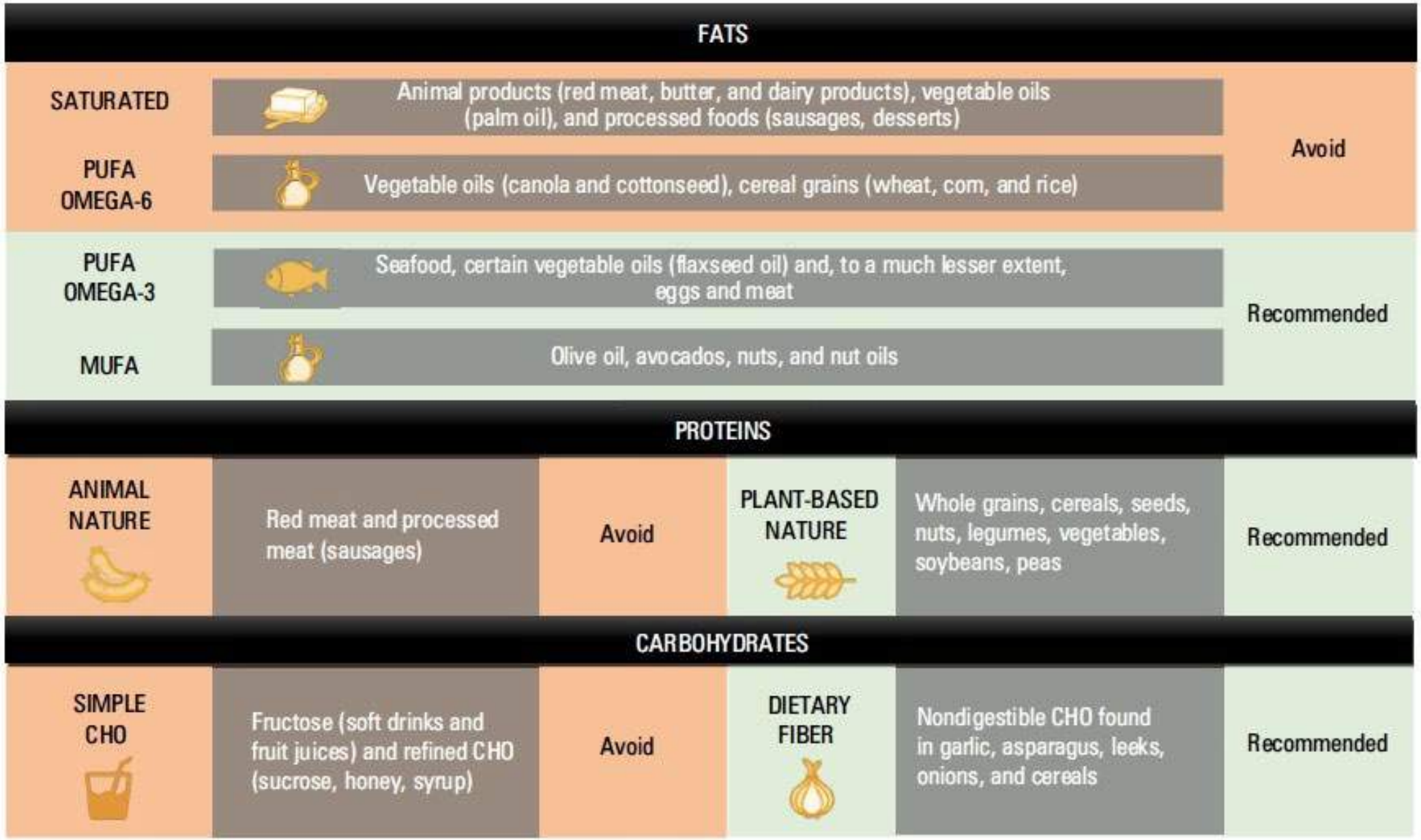



**FIGURE 3** Dietary treatment according to macronutrient composition in the treatment of nonalcoholic fatty liver disease and type 2 diabetes
Abbreviations: CHO, carbohydrates; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid

**TABLE 1** The histological effects of antidiabetic treatment in patients with type 2 diabetes and nonalcoholic fatty liver disease

| Antidiabetic agent | Steatosis | Inflammation | Fibrosis |
|---|---|---|---|
| Pioglitazone 45 mg | ↓ | ↓ | ↓ |
| Pioglitazone 30 mg | ↓ | ↓ | ⇆ |
| Liraglutide | ↓ | ↓ | ⇆ |
| Exenatide | ↓[a] | NA | NA |
| Empagliflozin | ↓[a] | NA | NA |
| Canagliflozin | ↓[a] | NA | ⇆[a] |
| Dapagliflozin | ↓[a] | NA | ⇆[a] |
| Ipragliflozin | ↓[a] | NA | ↓ |
| Luseogliflozin | ↓[a] | NA | ⇆[a] |
| Metformin | ⇆ | ⇆ | NA |
| Sitagliptin | ⇆ | ⇆ | ⇆ |
| Vildagliptin | ↓[a] | NA | NA |
| Saxagliptin | ↓[a] | NA | NA |

a No histological evidence
Abbreviations: NA, no data available; ↓, decrease; ⇆, neutral effect

**Semaglutide :**
**↓esteatosis y NASH**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

**Pioglitazone**

**Associate with iSGLT2**

**TABLE 2** The histological effects of antihypertensive treatment in patients with arterial hypertension and nonalcoholic fatty liver disease

| Antihypertensive agent | Steatosis | Inflammation | Fibrosis |
|---|---|---|---|
| Atorvastatin | ↓[a] | ↓[a] | ⇆ |
| Rosuvastatin | ↓[a] | ↓[a] | ⇆ |
| Pitavastatin | ⇆ | ⇆ | ⇆ |
| Ezetimibe | ⇆ | ⇆ | ⇆ |
| Fibrates | ⇆ | ⇆ | ⇆ |
| Omega-3 fatty acid supplements | ⇆ | ⇆ | ⇆ |
| PCSK9 inhibitors | NA | NA | NA |

a No histological evidence

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; others, see TABLE 1

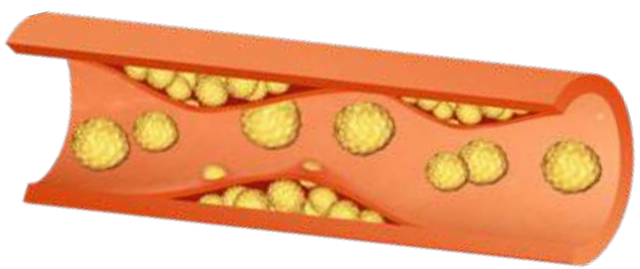


**TABLE 3** The histological effects of lipid-lowering treatment in patients with dyslipidemia and nonalcoholic fatty liver disease

| Lipid-lowering agent | Steatosis | Inflammation | Fibrosis |
|---|---|---|---|
| Telmisartan | ↓ | ↓ | ↓[b] |
| Losartan | ⇆ | ⇆ | ⇆ |
| Olmesartan | ⇆ | ↓[a] | ⇆ |
| Valsartan | ↓ | ⇆ | ⇆ |
| Candesartan | NA | NA | NA |
| Ramipril | NA | NA | NA |
| Perindopril | NA | NA | NA |
| Captopril | NA | NA | NA |

a No histological evidence

b Insufficient data to make recommendations

Abbreviations: see TABLE 1

## Clinical case 1: female, age 66 years

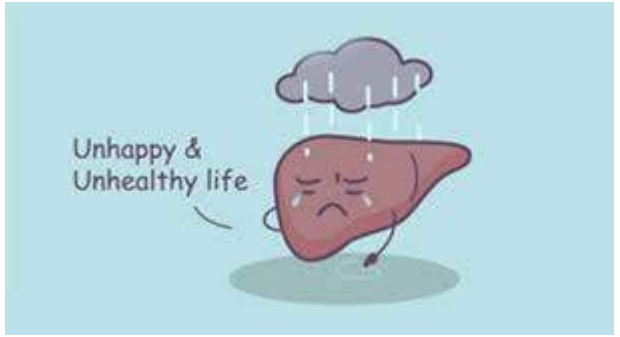
- **Medical history**:

- Total thyroidectomy in 1992 (multinodular goiter)- sustitutive treatment with levothyroxine.

- **NASH diagnosed in 2017 during admission to hospital for another reason.**

- **Anthropometric data (2017):**

- Weight 85kg, height 155cm, BMI 35.37kg/m2

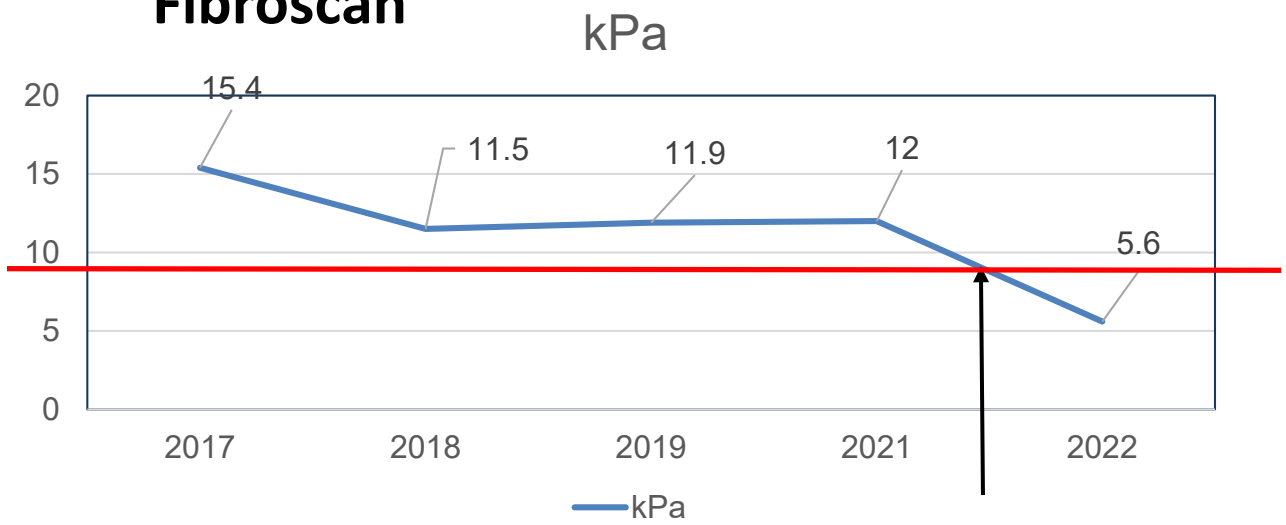


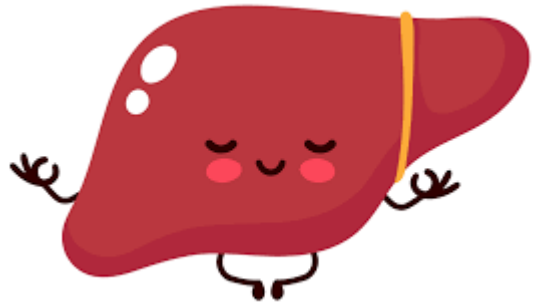

- **Liver parameters (**2017):

- Liver elastography 15,4kPa, CAP 359
- US: heterogeneous liver with geographical steatosis.
- Weight loss was indicated.

**She tryed to lose weight without any specific diet or guidance.**

## Fibroscan



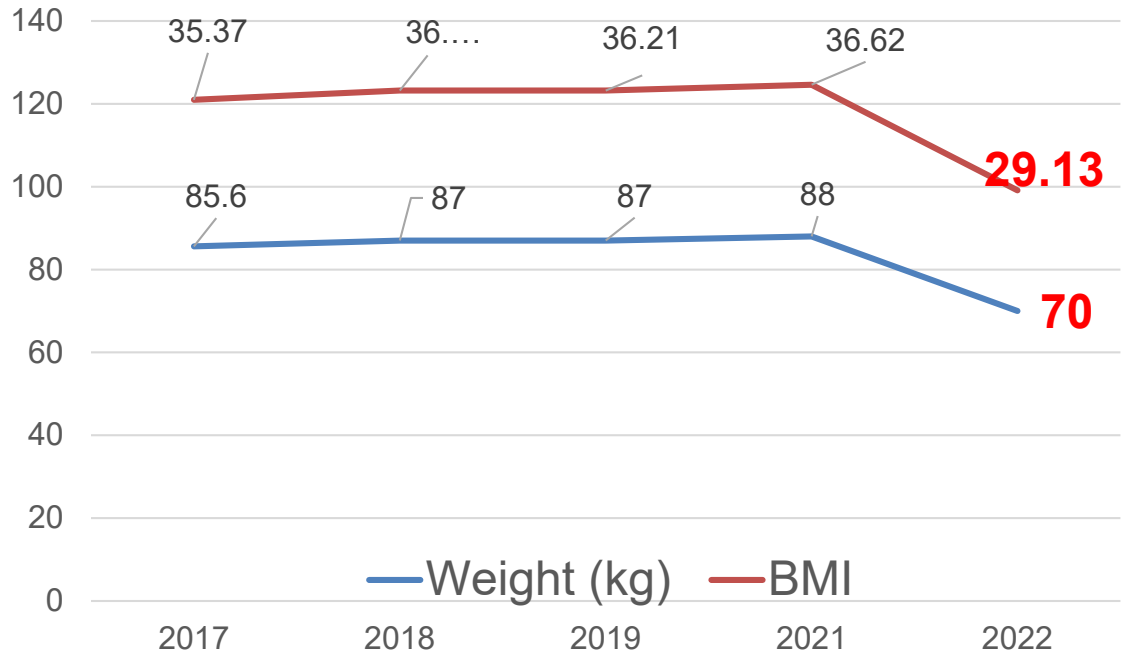



**%Total weight loss in 1 year: 20,45%**

**What happened?**

**<u>April 2021: 1st visit to the Obesity Unit</u>**

Low-carb diet (20% CH) is indicated



## Clinical case 2: male, age 50 years

- **Medical history:**

- Type 2 diabetes (2018) metformin and sitagliptin (DPPIV inhibitor)

**- NASH diagnosed in 2019: liver biopsy**

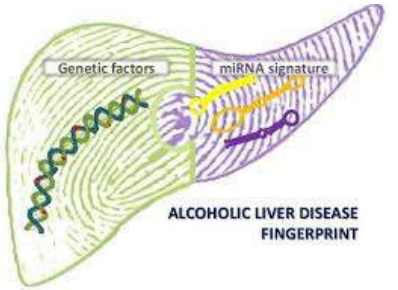
- **Anthropometric data (2019):**

-Weight 130kg, height 172cm, BMI 43.94kg/m2

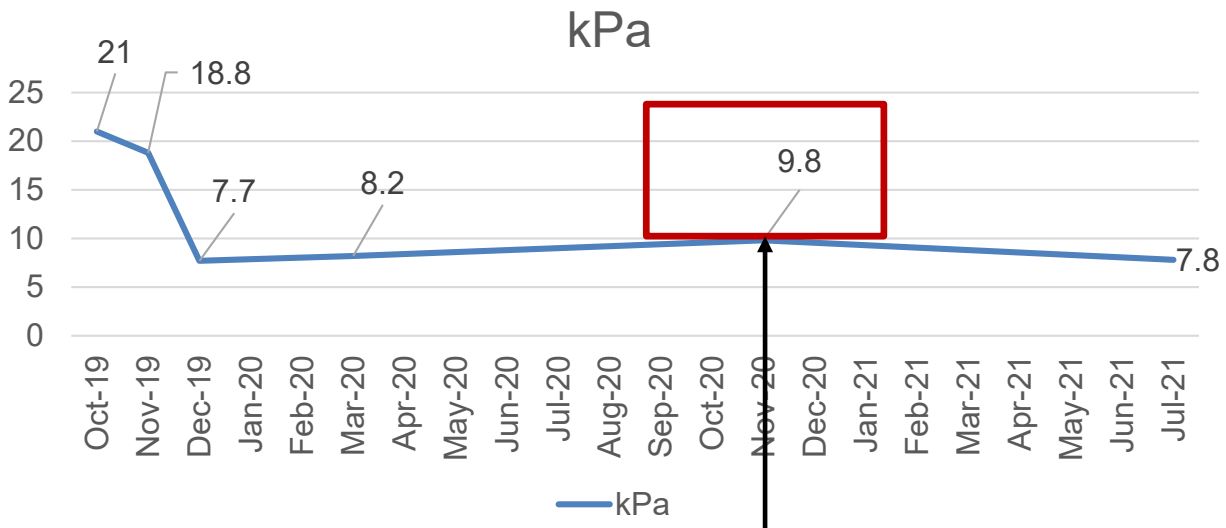
- **Liver parameters (2019):**

- Liver elastography: 21kPa, CAP 377

- US: severe steatosis



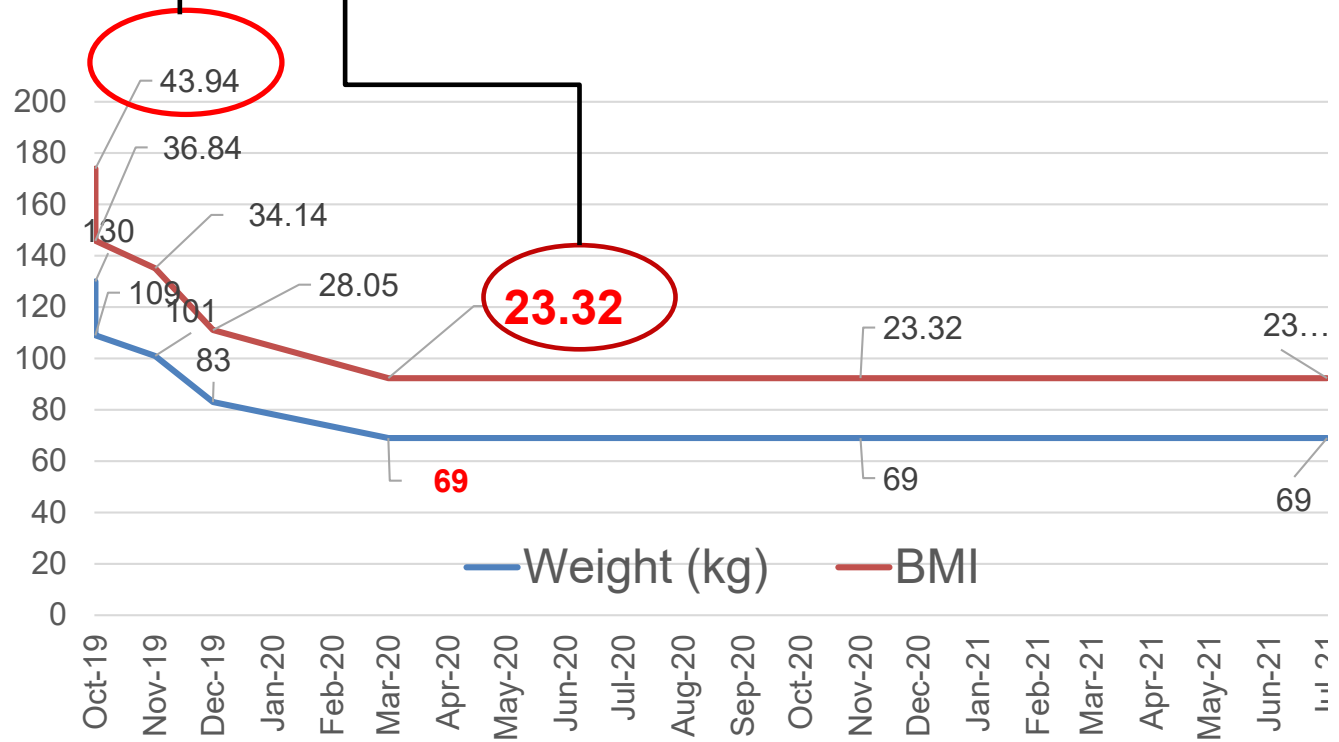

*Family history: Father and grandfather : NASH-related cirrosis*





## Uncontrolled diet

46.92% TWL in 6 month!!!!



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# Aggressive non-alcoholic steatohepatitis following rapid weight loss and/or malnutrition

Jia-Huei Tsai[1,2], Linda D Ferrell[3], Vivian Tan[4], Matthew M Yeh[5], Monika Sarkar[6], and Ryan M Gill[3]

Females that underwent bariatric surgery
(jejuno-ileal by-pass, highly malabsorptive, now contraindicated).

Rapid and significant weight loss.

Presented with acute liver injury.

Genetic predispostion might have an influence.

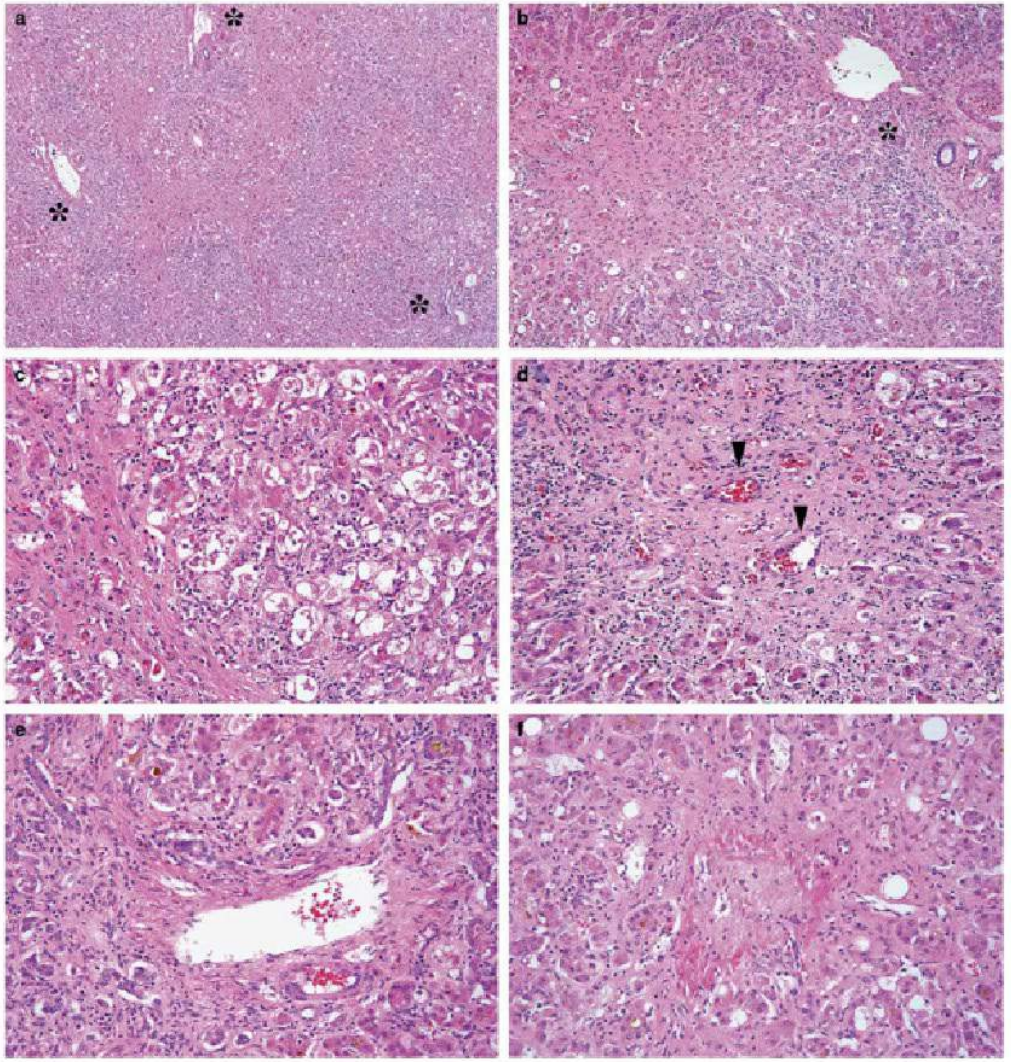


Figure 1.
Pathologic features of aggressive non-alcoholic steatohepatitis in patient 2. (a) and (b) Examples of severe centrizonal scarring with pericellular fibrosis. Asterisks indicate portal tracts. (c) Prominent ballooned hepatocytes with Mallory–Denk bodies. (d) Centrizonal arteries (arrowheads) in fibrous central zones. (e) Ductular reaction and cholestasis. (f) Perivenular sclerosis with central vein occlusion. (a–f: H&E stain; original magnification: (a): × 40; (b): × 100; (c–f): × 200). H&E, hematoxylin and eosin.

# MANAGEMENT OF MAFLD: MULTIDISCIPLINARY


**Lose weight not too quick in a safe way**