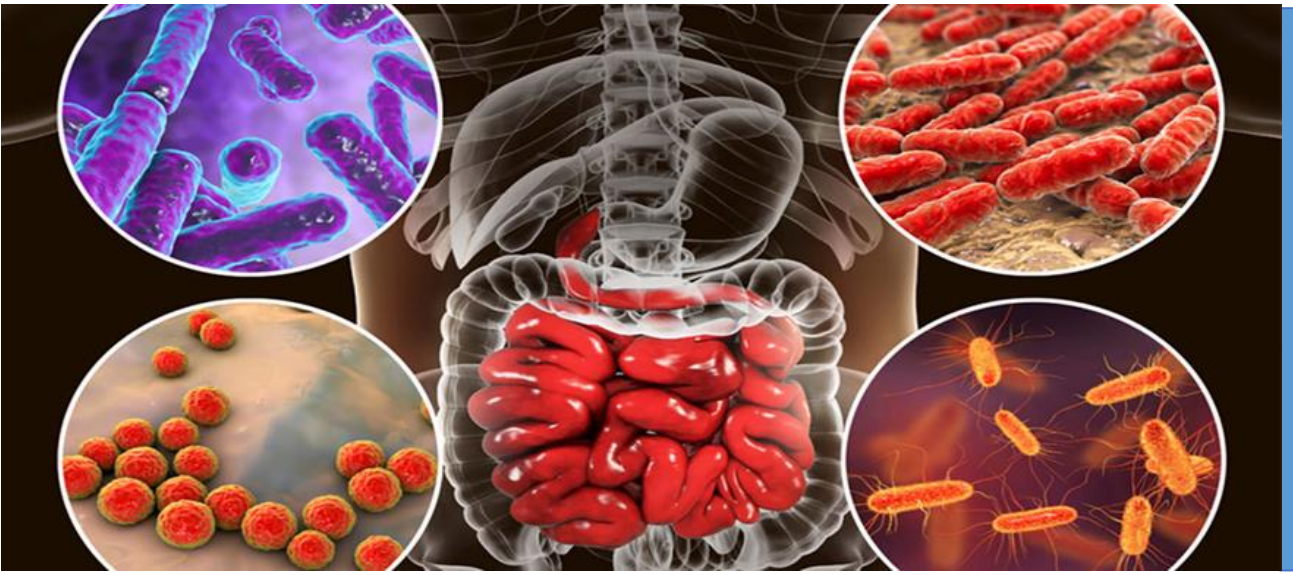
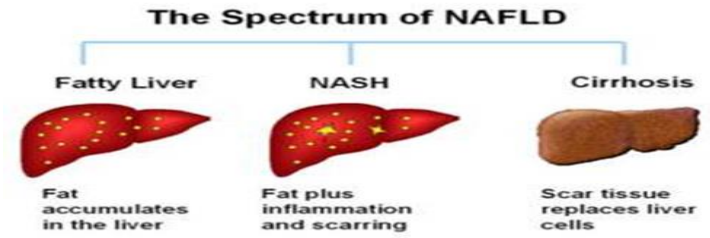


THE INFLUENCE OF THE INTESTINAL MICROBIOTA ON THE PATHOPHYSIOLOGY OF NON-ALCOHOLIC FATTY LIVER DISEASE. STUDY IN PATIENTS WITH SEVERE OBESITY

Authors, co-authors, institution



Unidad de Cirugía Endocrina y Metabólica
Hospital Clínico Universitario
"Virgen de la Vitoria". Málaga

Dr. Ocaña Wilhelmi

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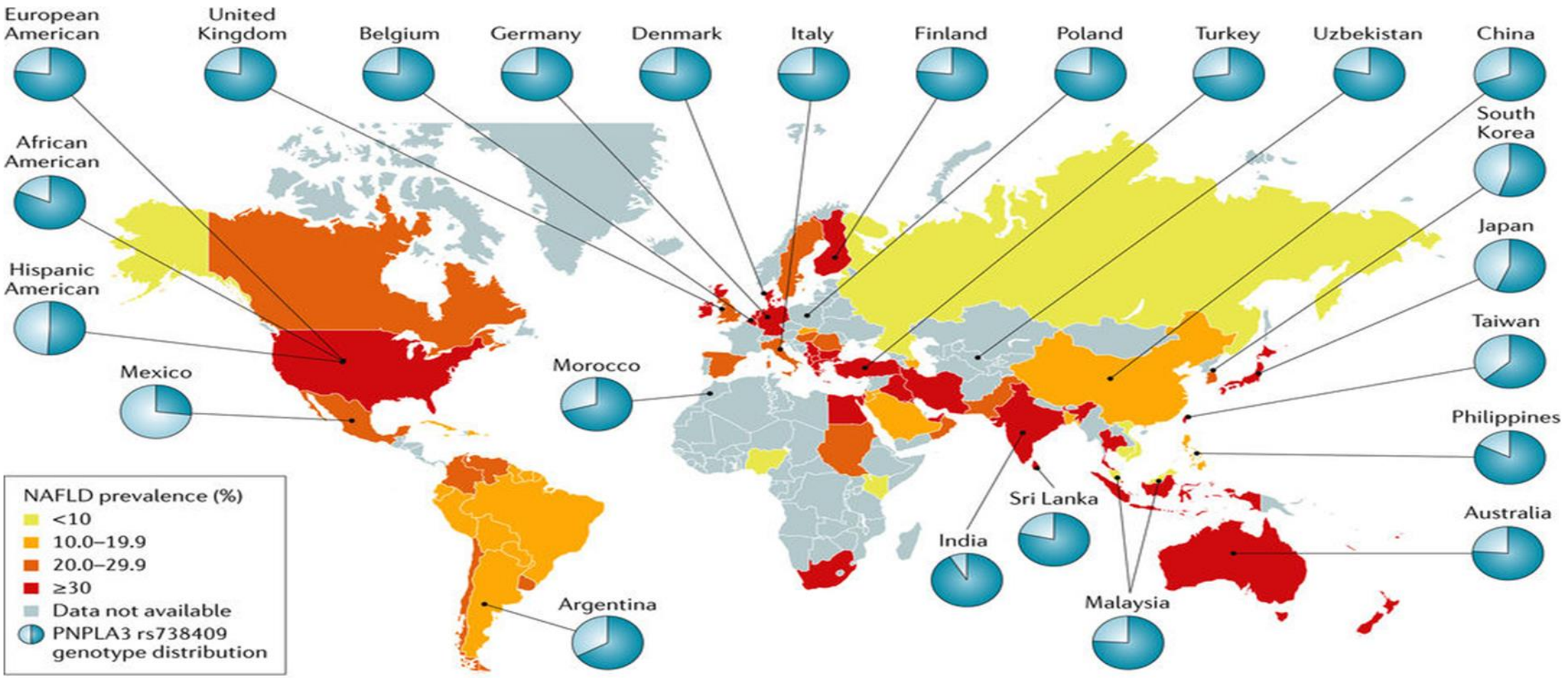
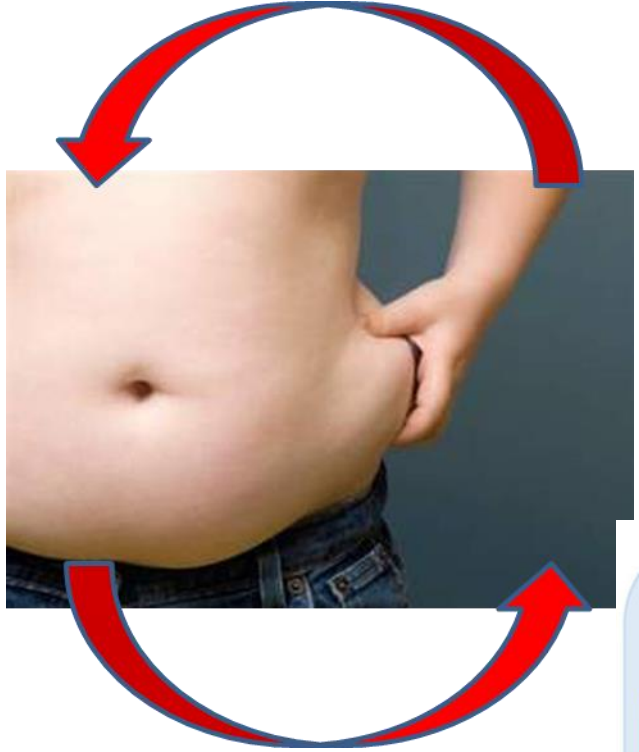
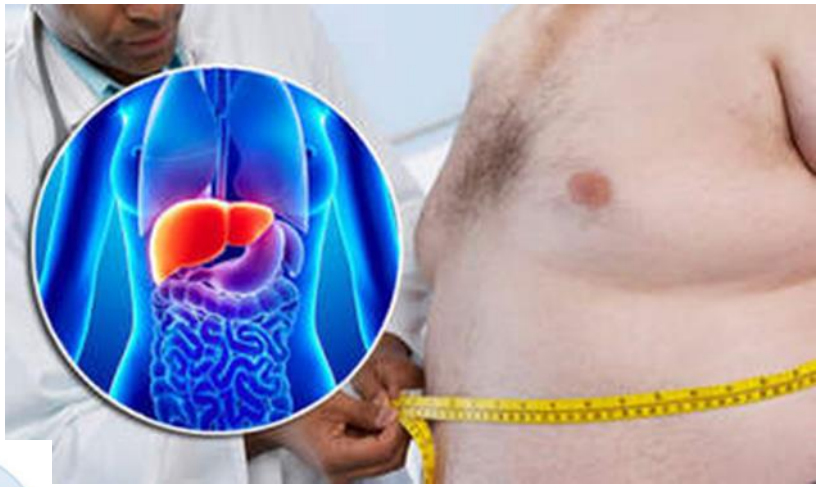
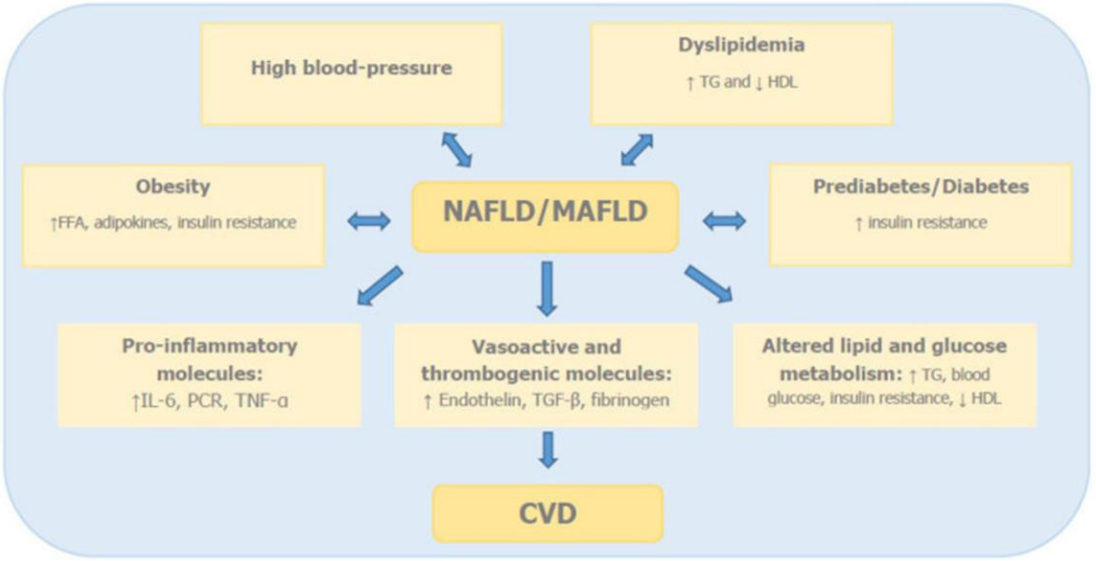
[ ] I have no potential conflict of interest to report



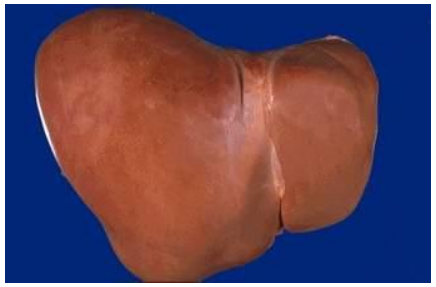
Nature Reviews | Gastroenterology & Hepatology



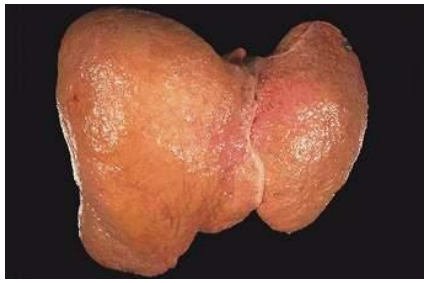




HTA, DM, SAOS, DL.....MAFLD



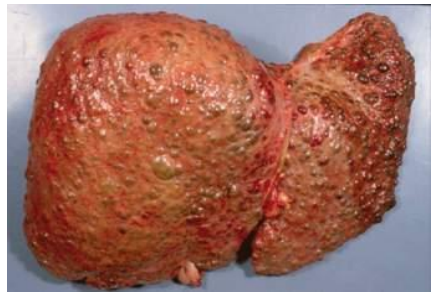
10 – 20 years



Normal Liver → Fat Liver → Hepato-steatosis → Steato-hepatitis

3 -6 years

1 -2 years

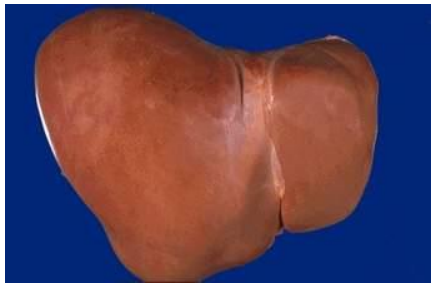


Cirrosis (10-15%) → Cirrosis Bad Evolution → Death

HCC

Liver Transplantation

Natural History of MAFLD and NASH



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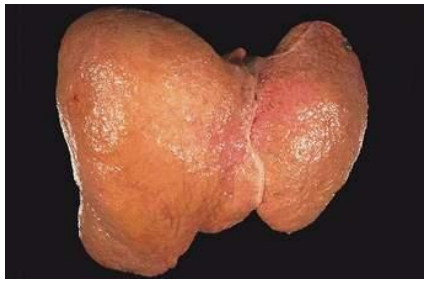


Normal Liver

18 years

Fat Liver

Hepato-steatosis

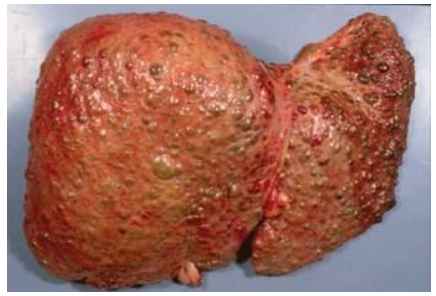
Steato-hepatitis

3 -6 years

1 -2 years

Cirrosis (10-15%)

Cirrosis Descompensada

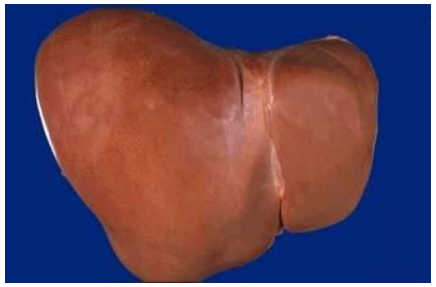


HCC

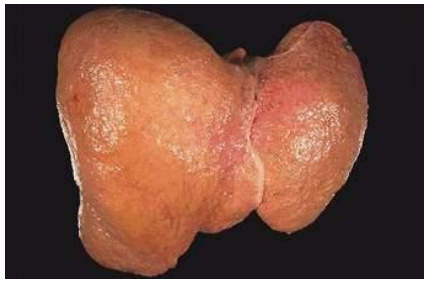
Liver Transplantation

Death

Natural History of MAFLD and NASH



10 – 20 years



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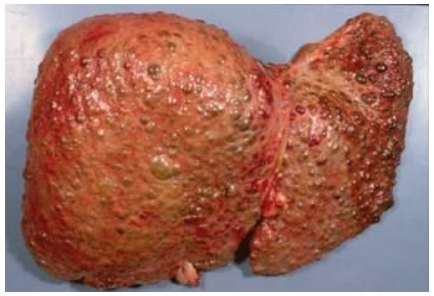


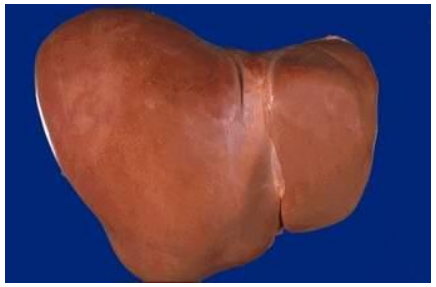
44/46 years

Death

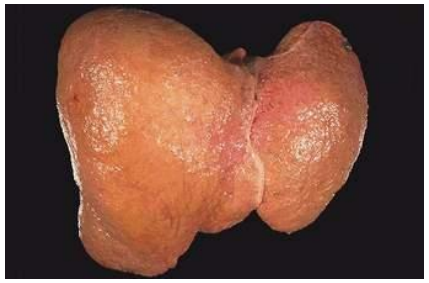
HCC

Liver Transplantation

Natural History of MAFLD and NASH



10 – 20 years



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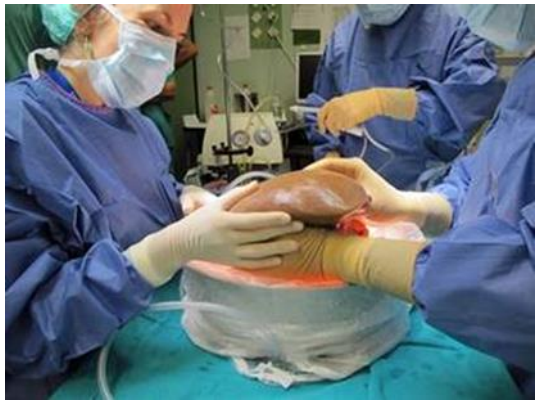
Hepato-steatosis

Steato-hepatitis

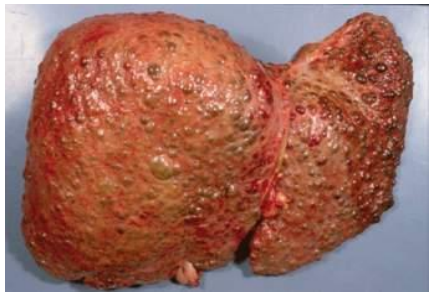


3 -6 years

1 -2 years

Cirrosis (10-15%)

Cirrosis Descompensada

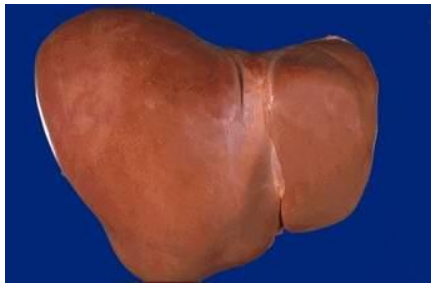


44/46 years

Death

HCC

Liver Transplantation



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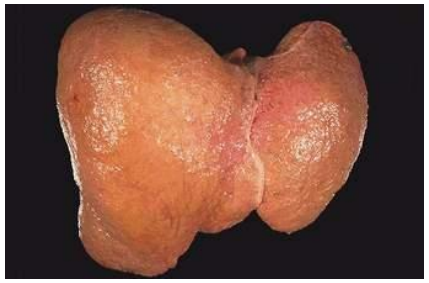

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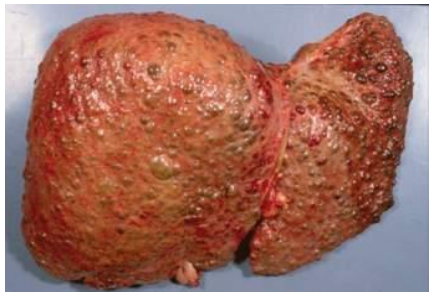


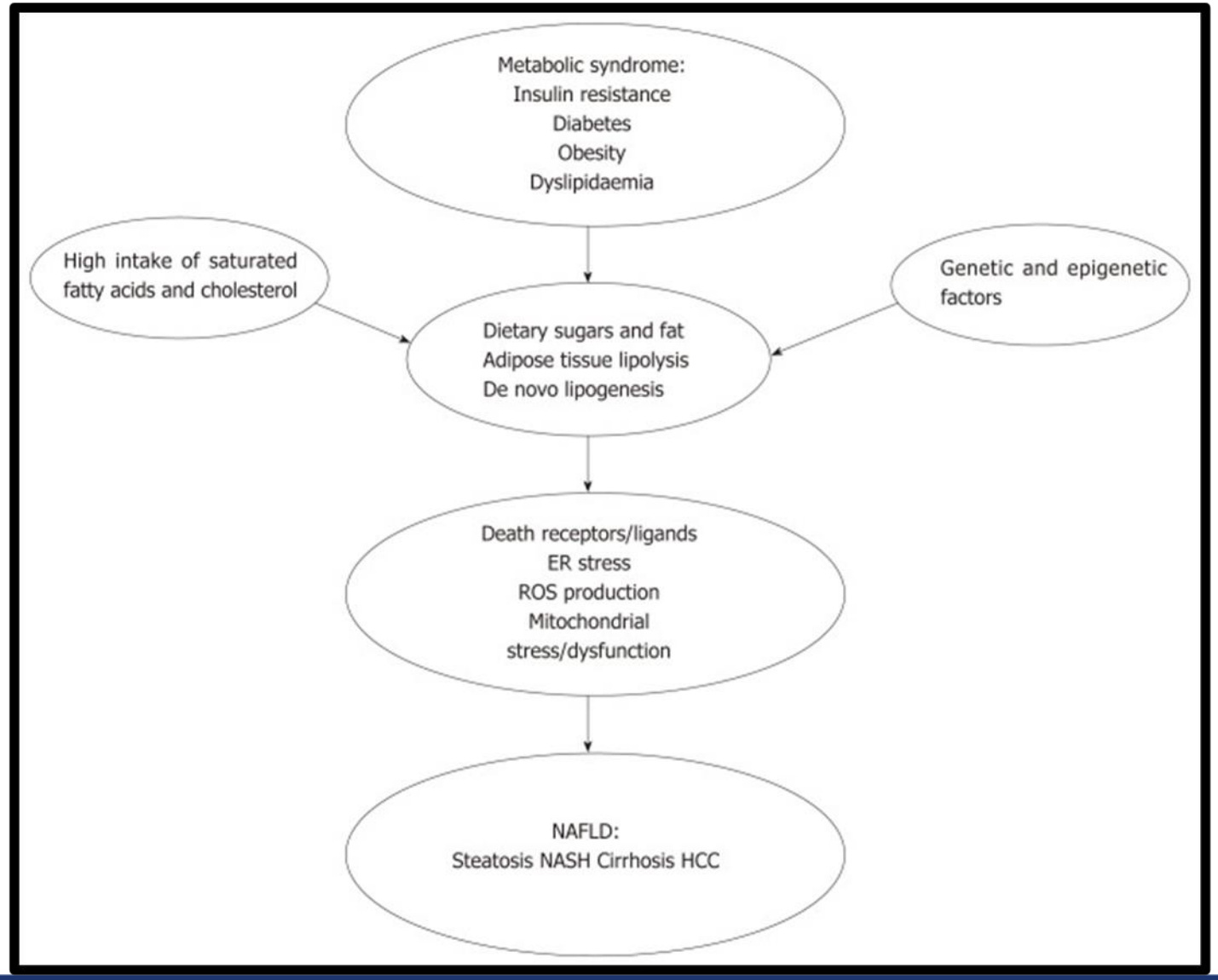
44/46 years

Death

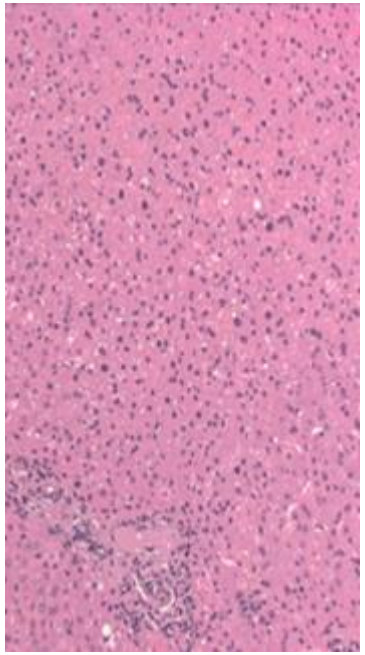
HCC

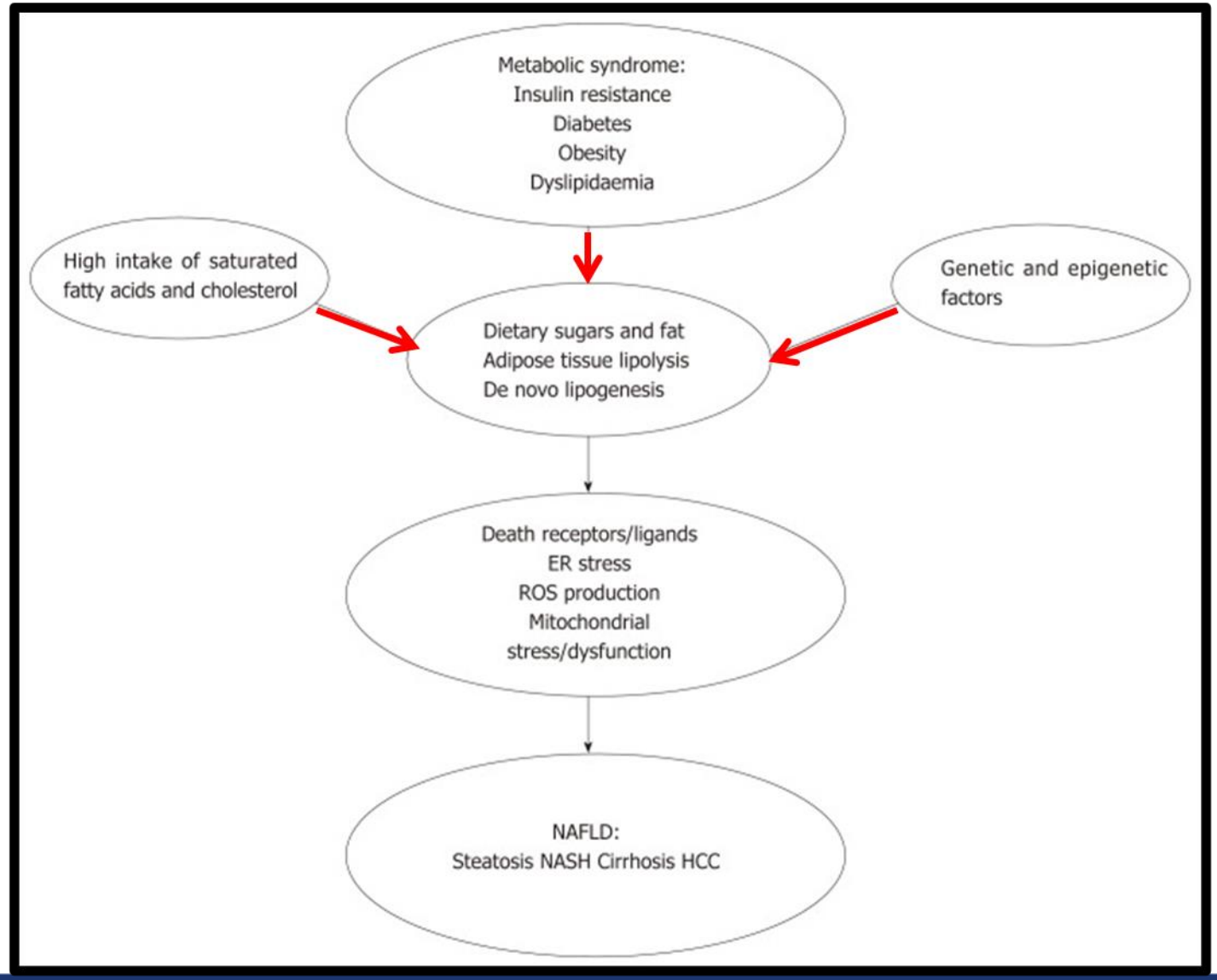
Liver Transplantation

Pathophysiology of MAFLD

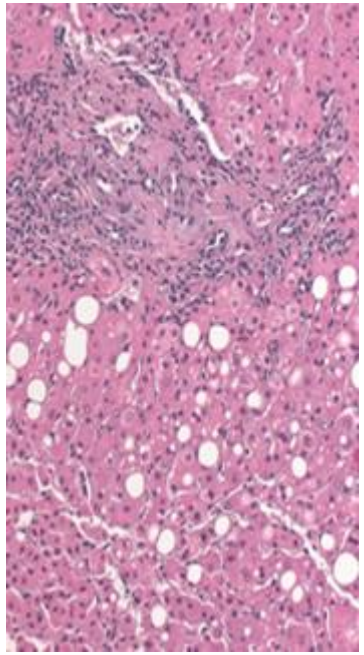


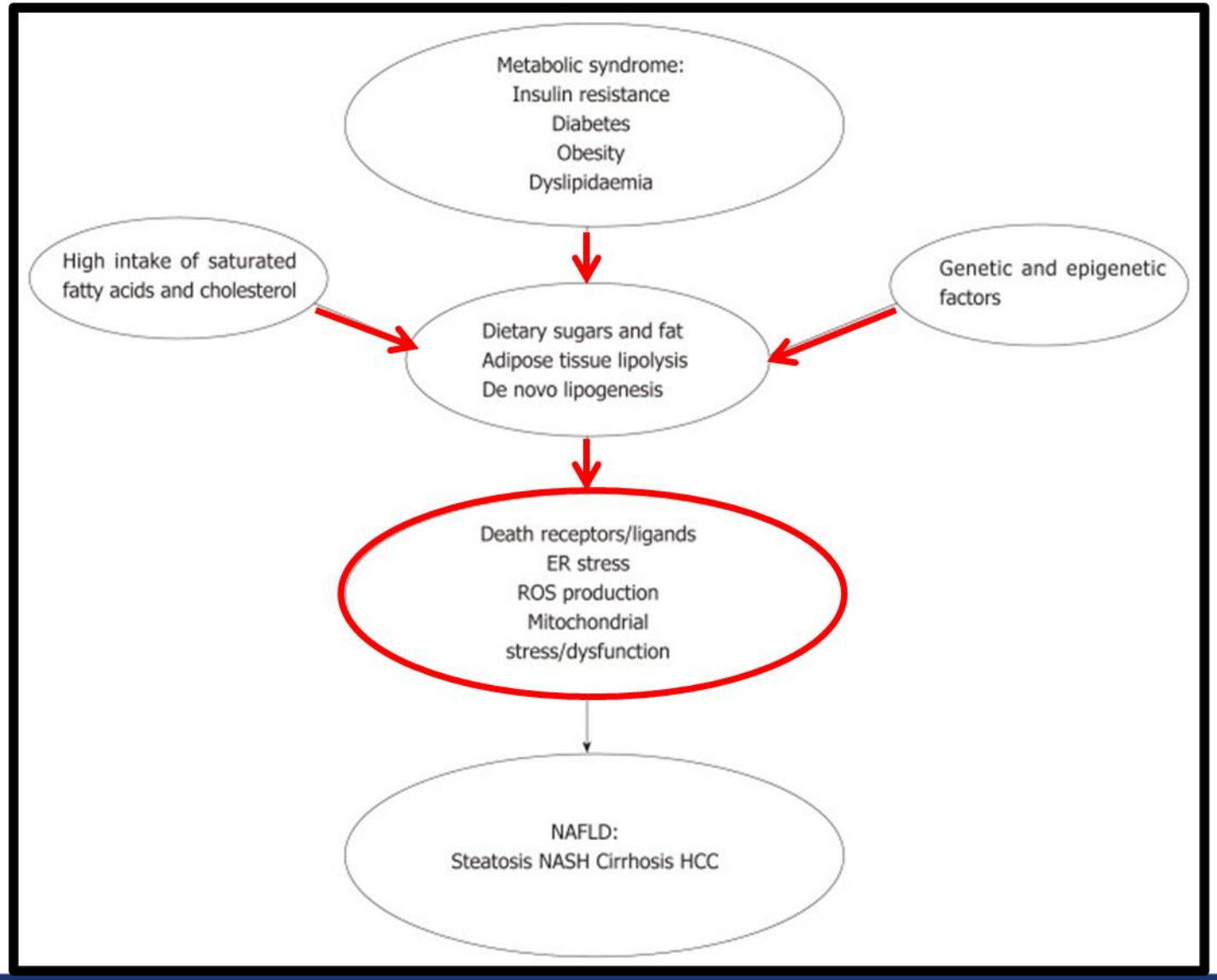
Pathophysiology of MAFLD



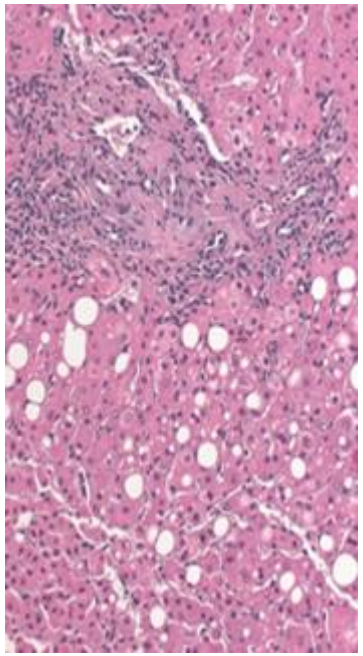


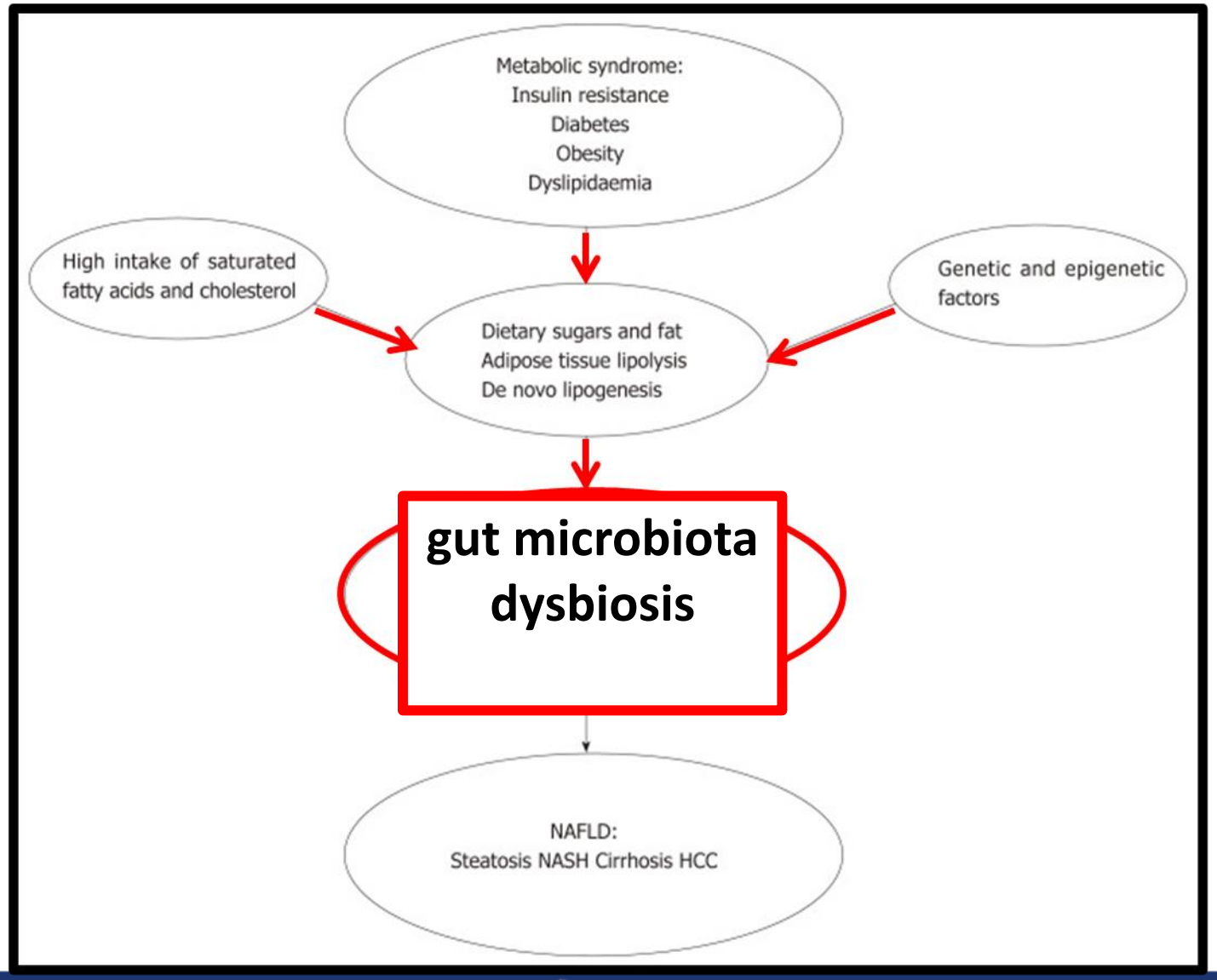
Pathophysiology of MAFLD



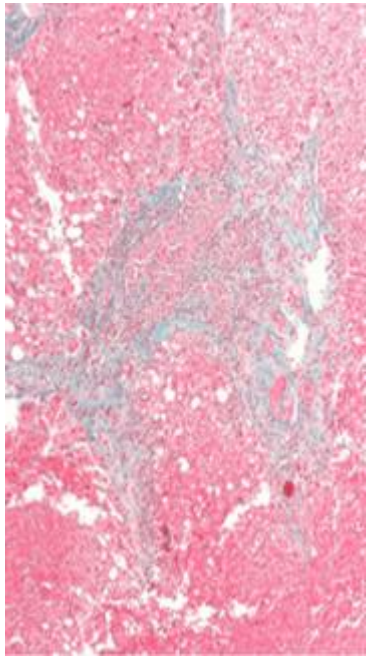


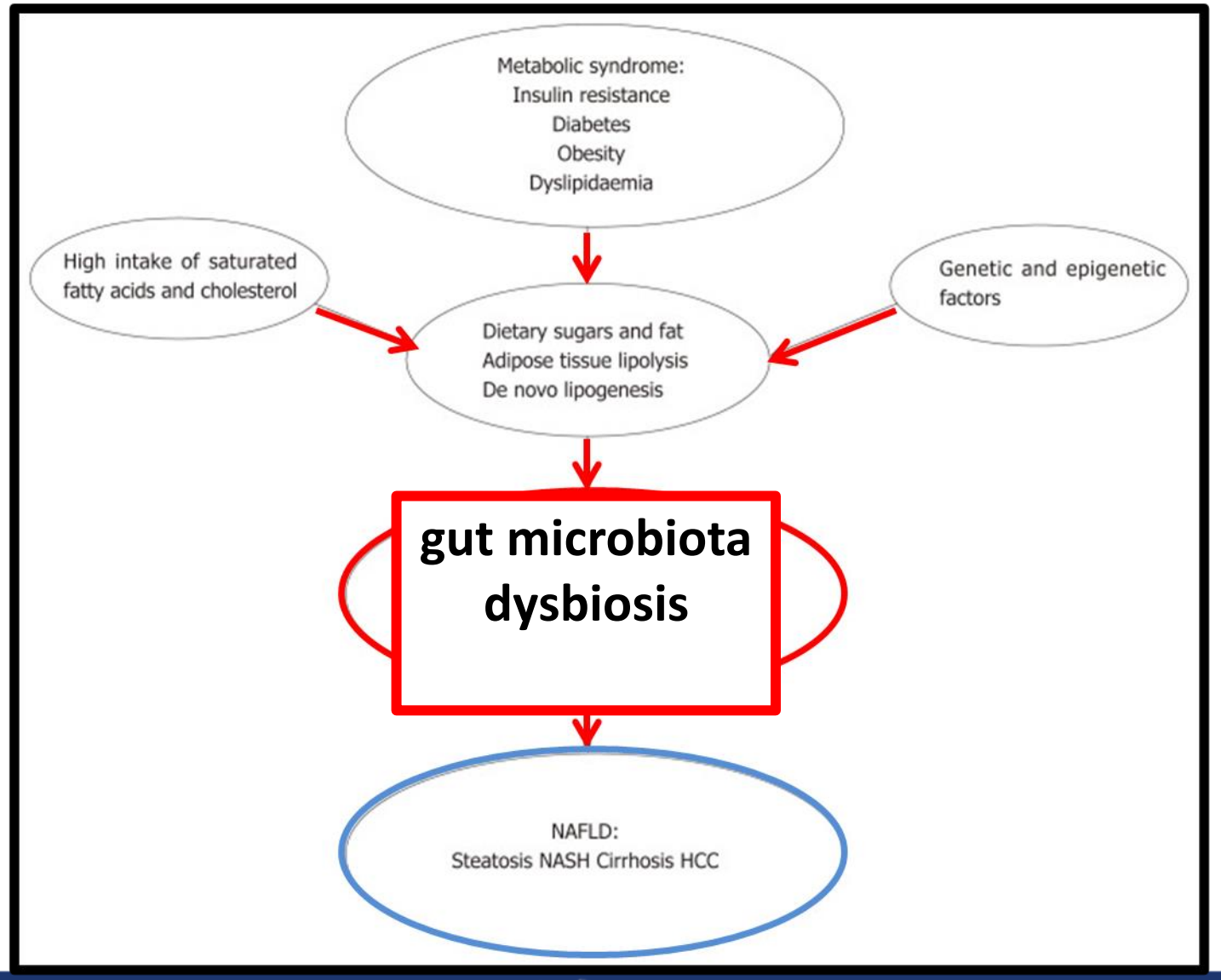
Pathophysiology of MAFLD





Pathophysiology of MAFLD

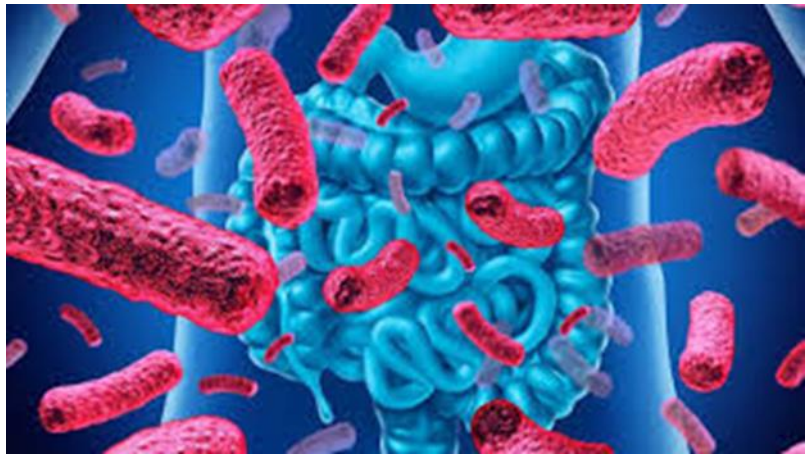




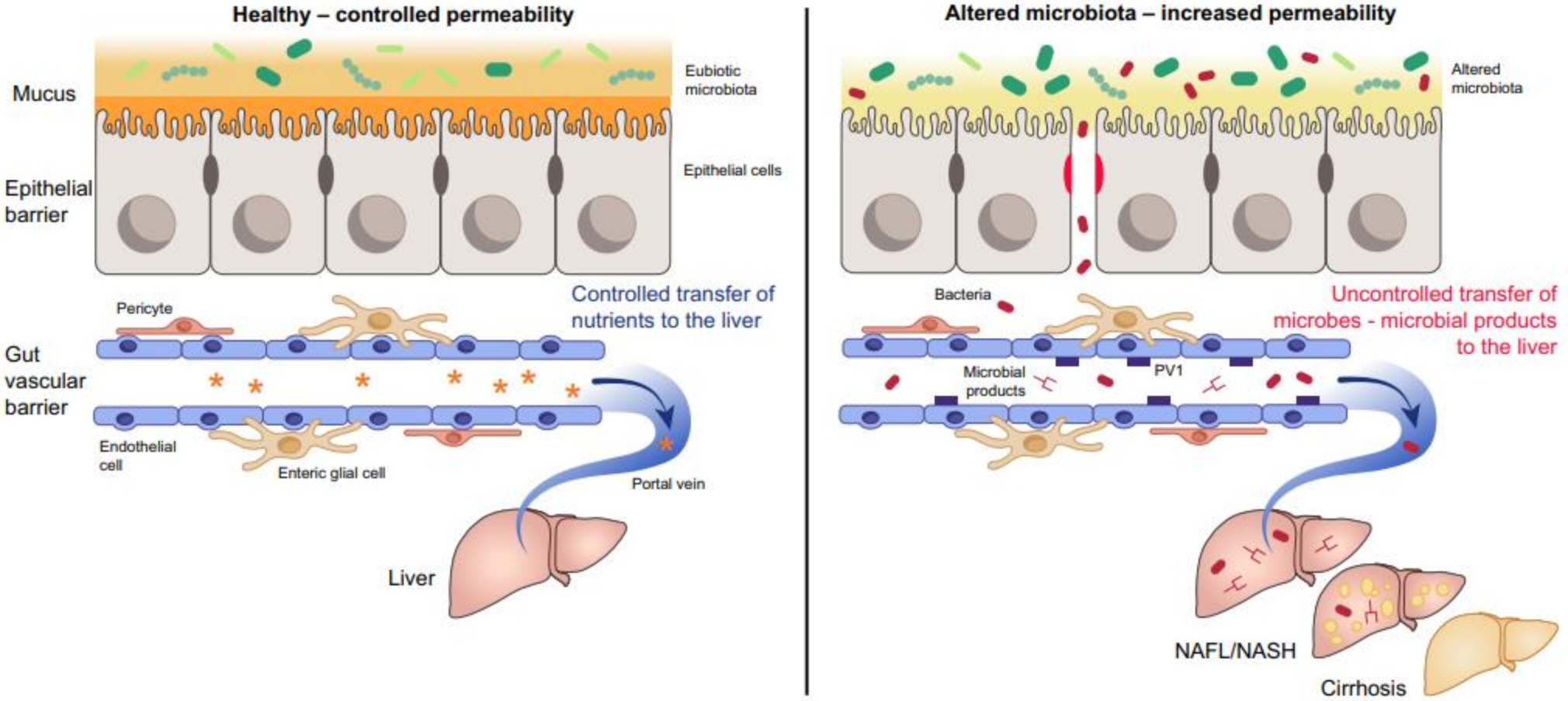
The gut microbiota is considered to be a virtual metabolic organ involved in the pathogenesis of numerous metabolic diseases:

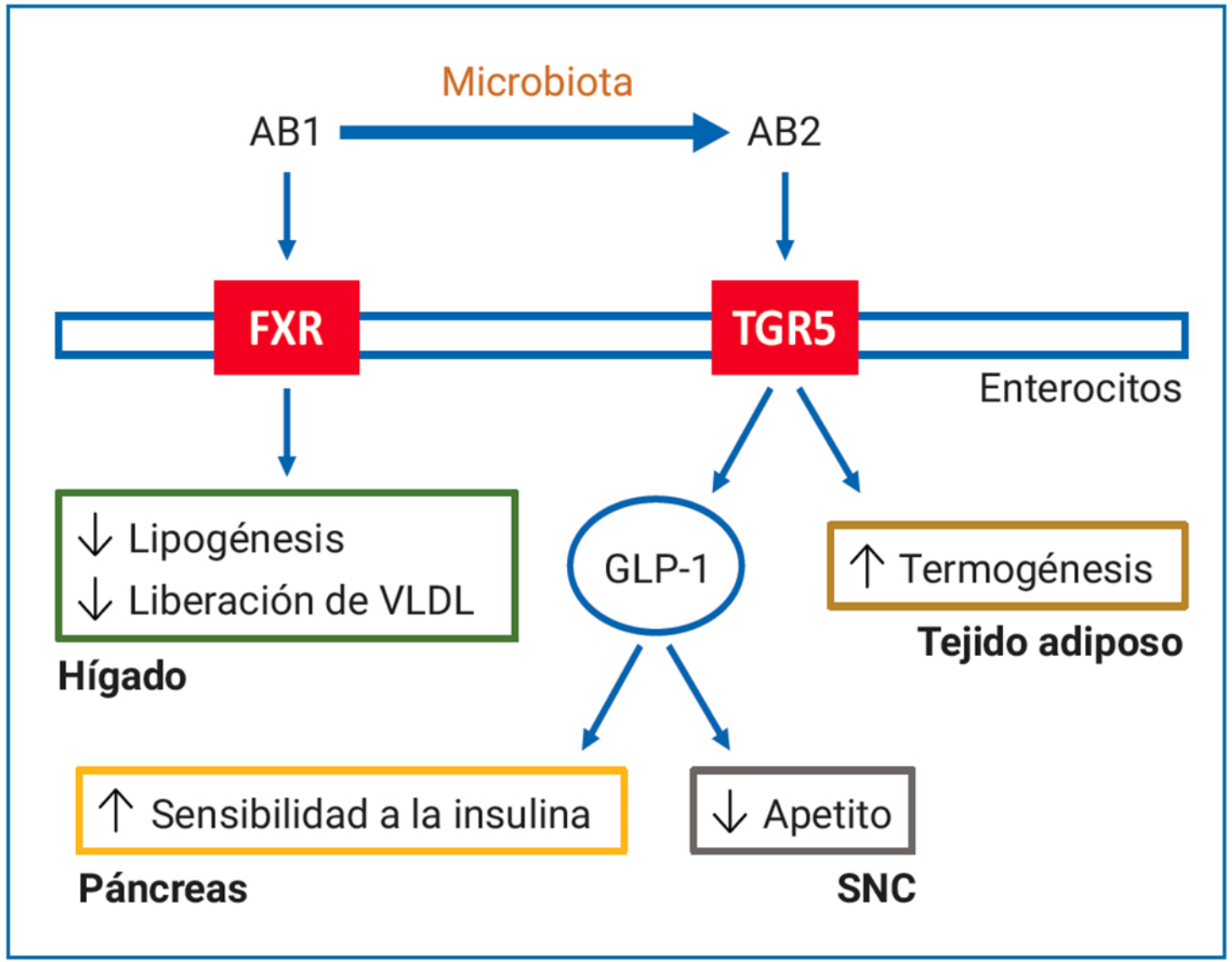
---obesity,
---dyslipidemia,
---type 2 diabetes mellitus,
---atherosclerosis,
---MAFLD.

Alterations in gut microbiota composition and/or its functionality might contribute to disturbed energy and substrate metabolism, including efects on metabolism and liver injury:



---changes in the microbial composition involved in the conversion of bile acids,
---the production of short chain fatty acids (SCFA),
---the promotion of chronic exposure to pathogen-associated molecular patterns such as lipopolysaccharides (LPS), peptidoglycans, or trimethylamine (TMA),
---oxidative stress caused by increased endogenous ethanol or those involved in immune regulation and IgA production


Healthy – controlled permeability
Mucus
Eubiotic microbiota
Epithelial barrier
Epithelial cells
Controlled transfer of nutrients to the liver
Pericyte
Gut vascular barrier
Endothelial cell
Enteric glial cell
Portal vein
Liver
Altered microbiota – increased permeability
Altered microbiota
Bacteria
Uncontrolled transfer of microbes - microbial products to the liver
Microbial products
PV1
NAFL/NASH
Cirrhosis


Microbiota
AB1
AB2
FXR
TGR5
Enterocitos
↓ Lipogénesis
↓ Liberación de VLDL
Hígado
GLP-1
↑ Termogénesis
Tejido adiposo
↑ Sensibilidad a la insulina
Páncreas
↓ Apetito
SNC

Lipids in Health and Disease

Lipids Health Dis. 2021; 20: 22.
Published online 2021 Feb 26. doi: 10.1186/s12944-021-01440-w

PMCID: PMC7908766
PMID: 33637088

Compositional alterations of gut microbiota in nonalcoholic fatty liver disease patients: a systematic review and Meta-analysis

Fuxi Li,# Junzhao Ye,# Congxiang Shao, and Bihui Zhong

gut microbiota signatures of MAFLD
---increased abundance of Escherichia, Prevotella, Streptococcus
---decreased abundance of Coprococcus, Faecalibacterium and Ruminococcus

Aim of this study

The aim of this study is to describe the composition and predicted functionality of gut microbiota in patients with morbid obesity undergoing bariatric surgery with diferent degrees of MAFLD assessed by liver biopsy.

Second, we analyzed gut microbiota composition according to diferent histological alterations.

Methods

.- This single-centre, transversal cohort study was approved by and in accordance with the recommendations of the Biomedical Research Ethics Coordinator Committee of Andalucía (CCEIBA).

.- All patients provided written consent confrming their willingness to participate in the study.

.- Between 2018 and 2021, 110 patients with morbid obesity who were consecutively included in the surgical waiting list for bariatric surgery at Virgen de la Victoria University Hospital were invited to participate in this study.

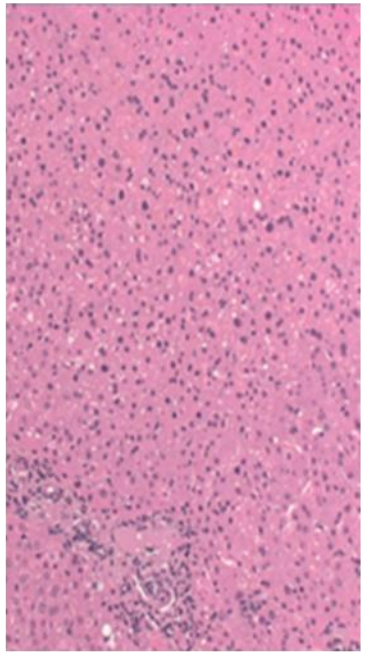
.- The inclusion criteria were the acceptance of informed consent for liver biopsies to be performed during bariatric surgery and the provision of a stool sample for microbiota analysis prior to surgery.

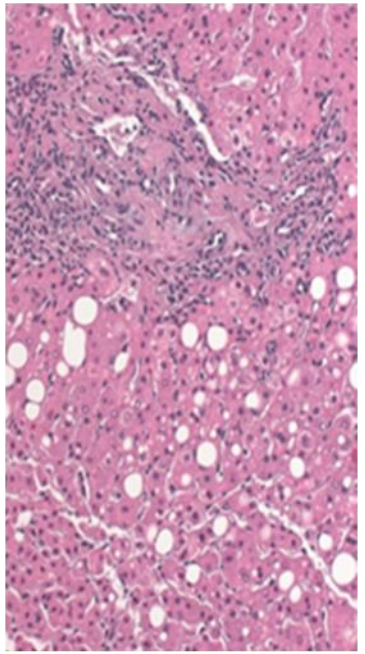
.- Patients were excluded if they had acute infammatory, or infectious diseases. Patients receiving ursodeoxycholic acid treatment were also excluded.

.- The use of antibiotics, probiotics, or prebiotic supplements that could modify microbiota in the previous 3 months was grounds for exclusion.

• Histologycal analysis

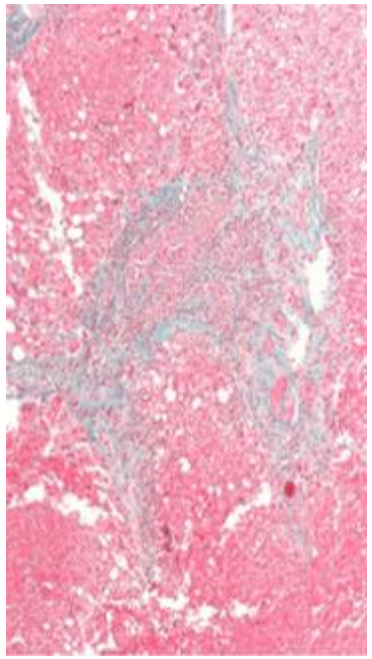
- Liver steatosis:
- ---grade 0 (<5%),
- ---grade 1 (5%–33%),
- ---grade 2
- (33%–66%),
- ---grade 3 (>66%) [17].





- Necroinfammatory activity is manifested by two factors:
- ---the infammatory lobular: no infammation (grade 0), scattered neutrophils with or without lymphocytes (<2 groups) (grade 1), intralobular neutrophils (2–4 groups) (grade 2), marked lobular infammation (>4 groups neutrophils) (grade 3),
- ---the presence of hepatocyte ballooning degeneration: no ballooned cells (grade 0), few ballooned cells (grade 1), and many ballooned cells (grade 2)

• Histologycal analysis



- **Liver fbrosis was graded based on the increase in connective tissue deposition and architectural remodelling noted:**
- **perisinusoidal or pericellular fbrosis (stage 1),**
- **perisinusoidal or pericellular fbrosis with focal or extensive periportal fbrosis (stage 2),**
- **perisinusoidal/pericellular fbrosis and portal fbrosis with focal or extensive bridging fbrosis (stage 3),**
- **and cirrhosis, progression of collagen deposits to severe fbrosis: pericellular, portal, and extensive bridging fbrosis (stage 4)**

• Histologycal analysis

- Patients were classifed according to the histological study into three groups:
- ---control group (patients with morbid obesity and non-fbrosis, non-steatosis, and non-necroinfammatory activity)
- ---patients with morbid obesity plus steatosis grade≥1 (non-fbrosis and non-necroinfammatory activity),
- ---patients with morbid obesity and steatosis grade≥1 plus NASH (necroinfammatory activity grade≥1 with/without fbrosis).

• Results

- **---70% were female**
- **---mean age of 46.76+8.91 years**
- **---Age, glucose levels, insulin levels, HOMA-IR values, cholesterol, and triglyceride levels were signifcantly higher in steatosis plus NASH group than in the control group. –**
- **---There were no statistically signifcant diferences between groups in the other variables that evaluated hydrocarbon and lipid metabolism or liver enzymes**

- **Table 1 Anthropometric and**
- **biochemical variables**

	Control	Steatosis	NASH + steatosis
Sex (F/M)	24/12	15/5	38/16
Age (years)	44.31 ± 9.51	46.30 ± 8.09	48.57 ± 8.51*
Weight (kg)	132.95 ± 20.23	130.32 ± 20.42	136.43 ± 24.26
BMI (kg/m^2)	46.95 ± 6.18	47.26 ± 6.97	49.67 ± 6.71
Glucose (mg/dl)	103.17 ± 22.50	103.95 ± 13.99	116.79 ± 33.46*
Insulin (μUI/ml)	14.35 ± 7.35	19.05 ± 10.38	26.21 ± 32.22*
HOMA-IR	3.72 ± 2.01	4.89 ± 2.59	7.48 ± 8.00*
Cholesterol (mg/dl)	181.57 ± 35.48	190.63 ± 40.70	195.53 ± 42.62*
Triglycerides (mg/dl)	124.14 ± 64.35	161.63 ± 46.51	183.02 ± 106.42*
HDL-cholesterol (mg/dl)	44.03 ± 13.45	45.32 ± 13.73	45.08 ± 11.82
LDL-cholesterol (mg/dl)	113.74 ± 30.96	119.00 ± 29.87	115.44 ± 33.71
GGT (U/l)	30.54 ± 21.71	28.79 ± 17.75	37.91 ± 30.09
AST (U/l)	24.06 ± 9.30	25.89 ± 11.07	30.14 ± 13.28
ALT (U/l)	29.09 ± 13.04	28.79 ± 17.75	35.13 ± 16.42
SBP (mm Hg)	134.56 ± 25.18	127.25 ± 16.03	132.75 ± 16.58
DBP (mm Hg)	84.58 ± 14.53	81.35 ± 8.55	84.42 ± 10.75
Histological parameters (*n*)			
Steatosis grade score (0/1/2/3)	36/0/0/0	0/17/0/3	0/31/14/9
Necroinflammatory activity grade (0/1/2/3)	36/0/0/0	20/0/0/0	0/38/16/0
Fibrosis state (0/1/2/3/4)	36/0/0/0/0	20/0/0/0	18/22/9/5

BMI Body mass index, *GGT* gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HOMA-IR* homeostasis model assessment of insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*Kruskal–Wallis test adjusted by Bonferroni, $p < 0.05$, between control group and steatosis + NASH group

*$p < 0.05$ between control group and NASH + steatosis group using Mann–Whitney *U* test

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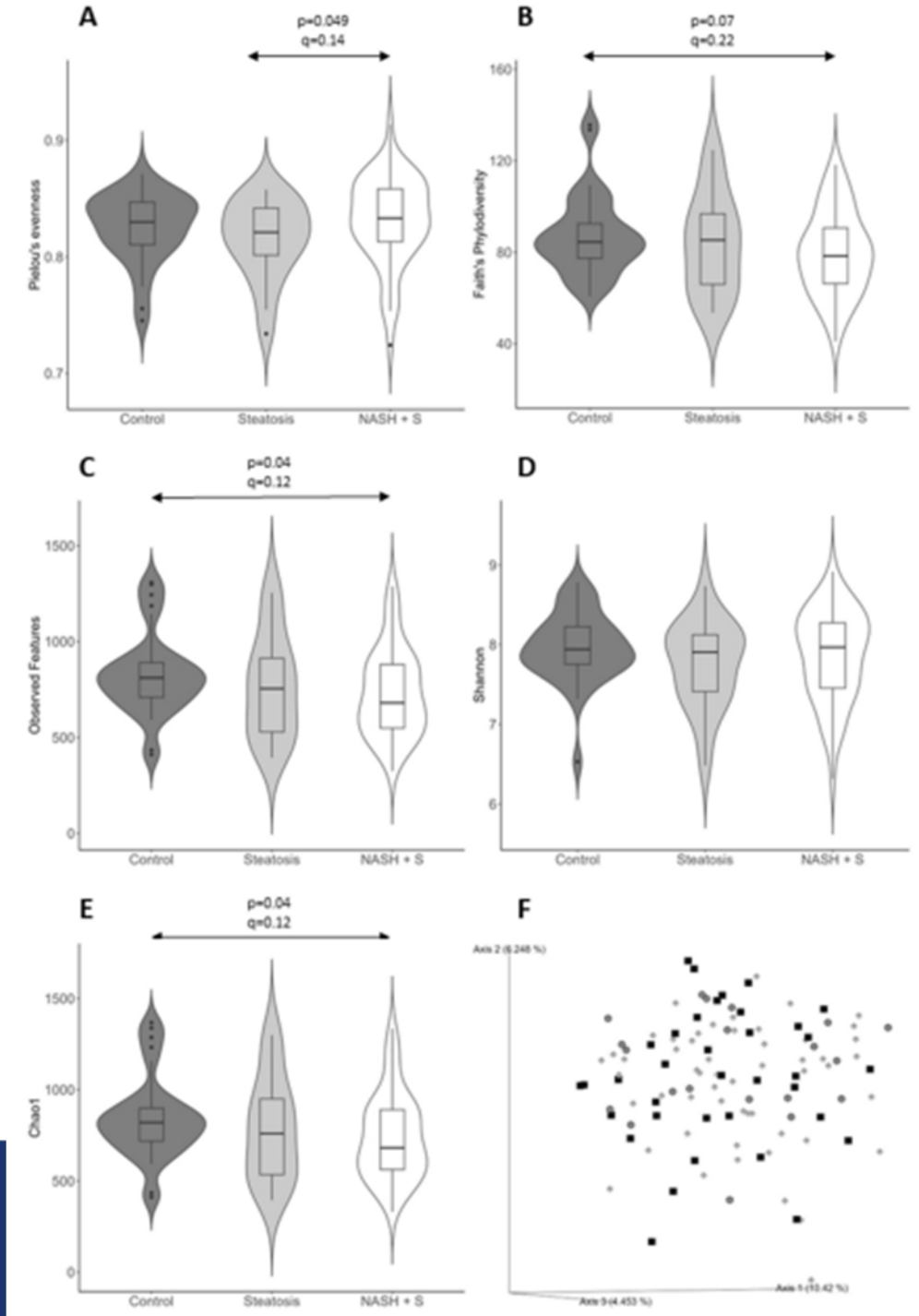
Age (years)	44.31 ± 9.51	46.30 ± 8.09	48.57 ± 8.51*
Weight (kg)	132.95 ± 20.23	130.32 ± 20.42	136.43 ± 24.26
BMI (kg/m^2)	46.95 ± 6.18	47.26 ± 6.97	49.67 ± 6.71
Glucose (mg/dl)	103.17 ± 22.50	103.95 ± 13.99	116.79 ± 33.46*
Insulin (μUI/ml)	14.35 ± 7.35	19.05 ± 10.38	26.21 ± 32.22*
HOMA-IR	3.72 ± 2.01	4.89 ± 2.59	7.48 ± 8.00*
Cholesterol (mg/dl)	181.57 ± 35.48	190.63 ± 40.70	195.53 ± 42.62*
Triglycerides (mg/dl)	124.14 ± 64.35	161.63 ± 46.51	183.02 ± 106.42*
HDL-cholesterol (mg/dl)	44.03 ± 13.45	45.32 ± 13.73	45.08 ± 11.82
LDL-cholesterol (mg/dl)	113.74 ± 30.96	119.00 ± 29.87	115.44 ± 33.71
GGT (U/l)	30.54 ± 21.71	28.79 ± 17.75	37.91 ± 30.09
AST (U/l)	24.06 ± 9.30	25.89 ± 11.07	30.14 ± 13.28
ALT (U/l)	29.09 ± 13.04	28.79 ± 17.75	35.13 ± 16.42
SBP (mm Hg)	134.56 ± 25.18	127.25 ± 16.03	132.75 ± 16.58
DBP (mm Hg)	84.58 ± 14.53	81.35 ± 8.55	84.42 ± 10.75
Histological parameters (*n*)			
Steatosis grade score (0/1/2/3)	36/0/0/0	0/17/0/3	0/31/14/9
Necroinflammatory activity grade (0/1/2/3)	36/0/0/0	20/0/0/0	0/38/16/0
Fibrosis state (0/1/2/3/4)	36/0/0/0/0	20/0/0/0	18/22/9/5

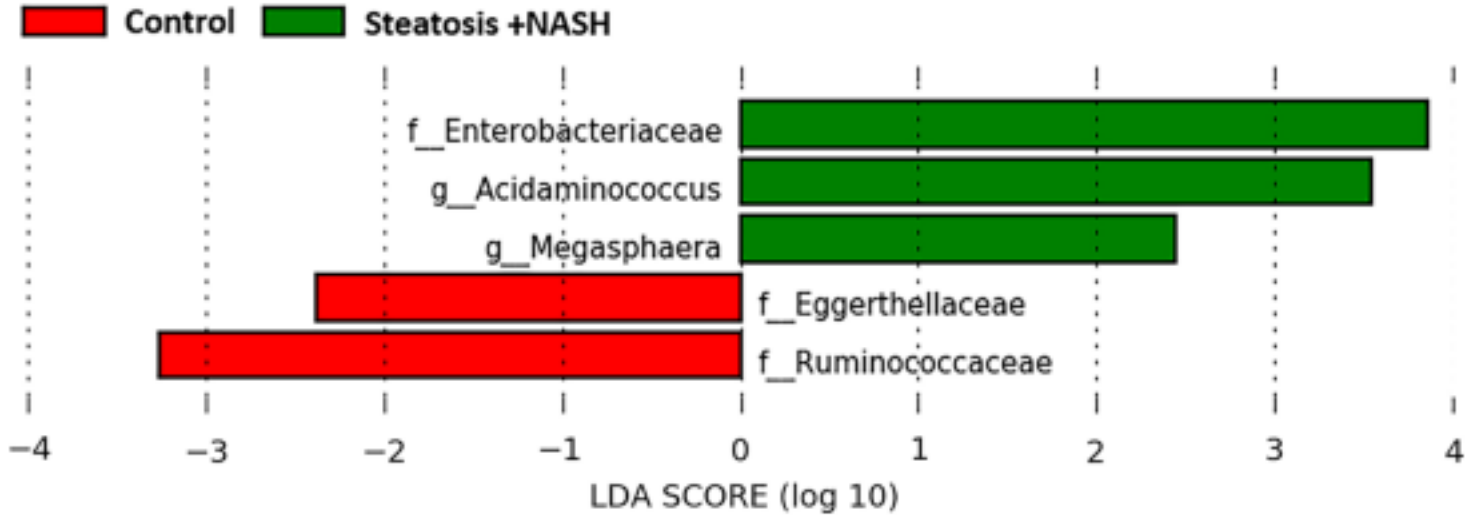
BMI Body mass index, *GGT* gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *HOMA-IR* homeostasis model assessment of insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*Kruskal–Wallis test adjusted by Bonferroni, $p < 0.05$, between control group and steatosis + NASH group

*$p < 0.05$ between control group and NASH + steatosis group using Mann–Whitney *U* test

- Fig. 1 Gut microbiota diversity.
- A Pielou's evenness.
- B Faith's phylodiversity.
- C Observed features.
- D Shannon.
- E Chao1.
- F Principal coordinates analysis plot of the unweighted UniFrac distance. Black squares: control group. Grey circles: steatosis group. Light grey diamonds: steatosis+NASH group





- **Gut microbiota composition and its predicted functional properties in MAFLD progression:**

---steatosis plus NASH was enriched in Enterobacteriaceae family and Acidaminococcus and Megasphaera genera,

---control group was enriched in Eggerthellaceae and Ruminococcaceae families (Fig. 2).

---However, no signifcant enrichment was observed in steatosis group

• Conclusions

.- Our fndings showed that patients with morbid obesity, steatosis, -us NASH (diagnosed by liver biopsies) were characterized by an altered microbial pattern with:

------an increase in Enterobacteriaceae family, an ethanol-producing bacteria,

-----and the depletion of Ruminococcaceae family, a healthpromoting bacteria: SCFA-producing bacteria.

- **MAFLD was also associated with enrichment in pathways related to proteinogenic amino acid degradation and succinate production, biosynthesis of menaquinol-7 (K2 vitamin), and saccharolytic and proteolytic fermentation.**
- **These metabolic pathways mainly produce harmful products, such as ethanol or succinate, resulting in possible mechanisms for the pathogenesis and progression of MAFLD.**

- Thus, we established a link between the altered microbiota patterns and histological injury in the liver. (GUT LIVER AXIS)

- Gut microbiota analysis and their metabolic pathways could add information to the classical predictors of MAFLD severity and suggest novel metabolic targets.-

- FUTURE Perspectives:
- New targets and new tratments
- The role of non-absorbable antibiotics
- How to feed the microbiota thinking in the species promoting liver changes
- How to protect de enterocyte mucosa barrier to avoid the circulation of harmful species throu de portal vein ti the liver

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