Non Alcoholic Fatty Liver Disease

(2019.02.20)

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- Assessment of Fatty liver disease
- Therapeutic approach of Fatty liver disease
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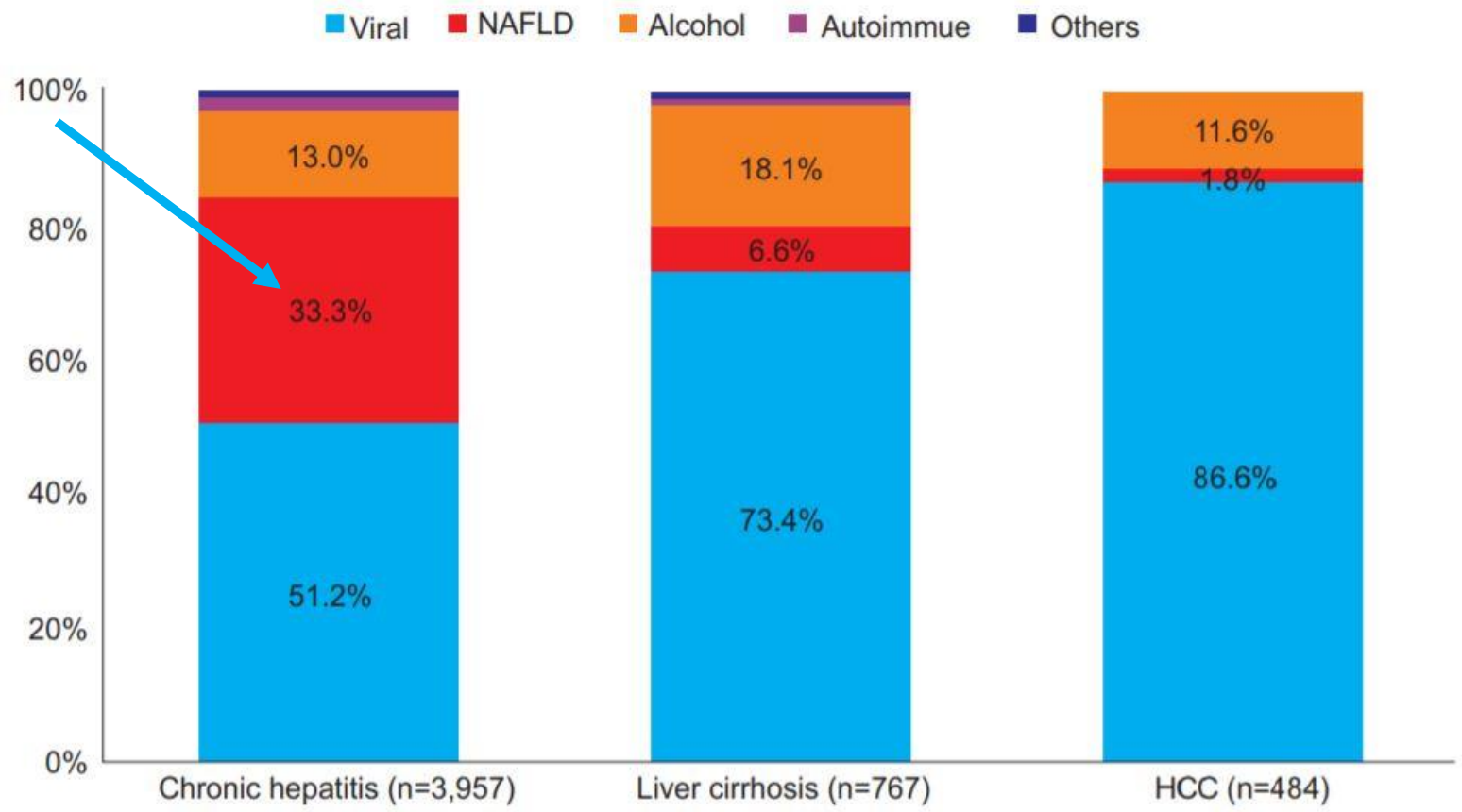
Introduction



Lee SS, et al. Clin Mol Hepatol 2012

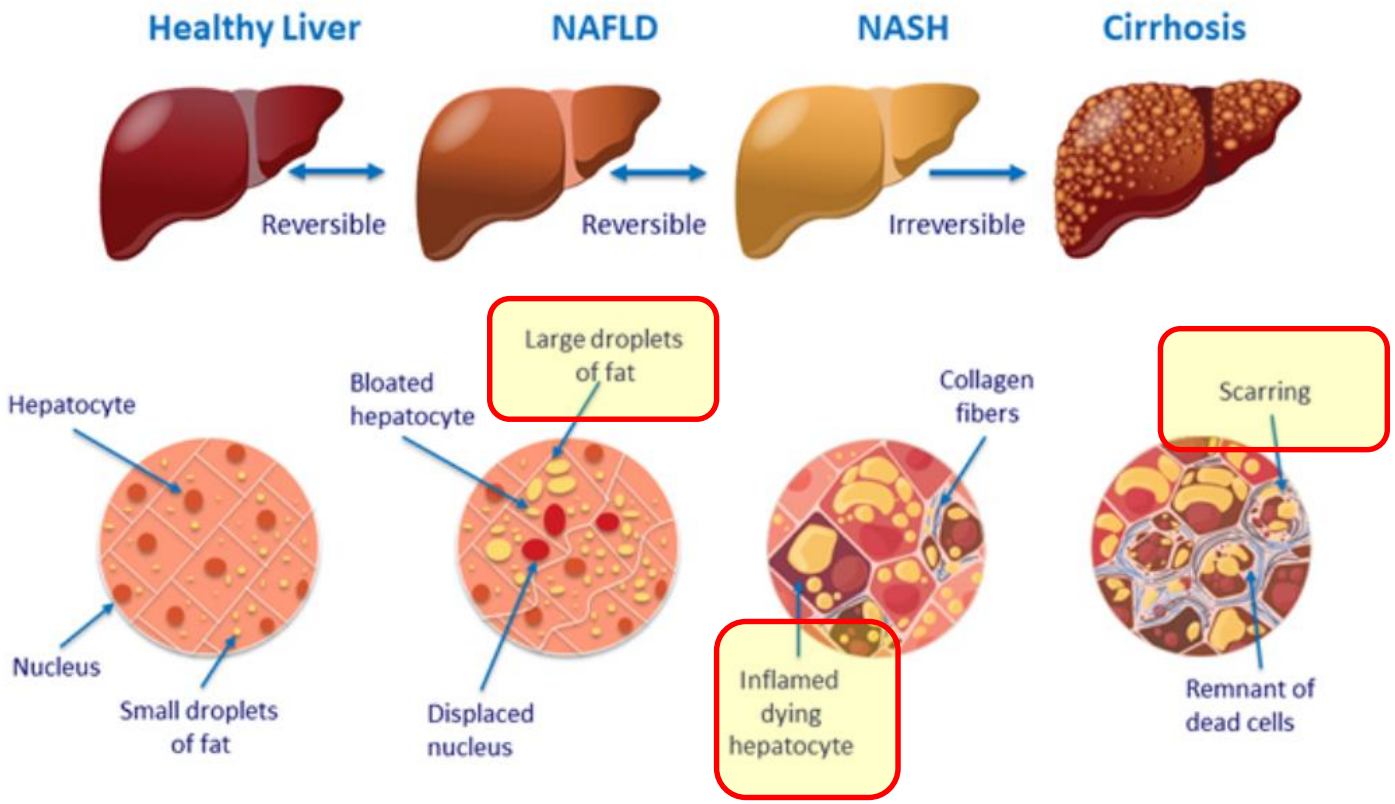
Introduction

TABLE 2. NAFLD and Related Definitions

NAFLD	Encompasses the entire spectrum of FLD in individuals without significant alcohol consumption, ranging from fatty liver to SH to cirrhosis
NAFL	Presence of ≥5% HS without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal.
NASH	Presence of ≥5% HS with inflammation and hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer.
NASH cirrhosis	Presence of cirrhosis with current or previous histological evidence of steatosis or SH

Chalasani N et al. Hepatology 2018

Introduction



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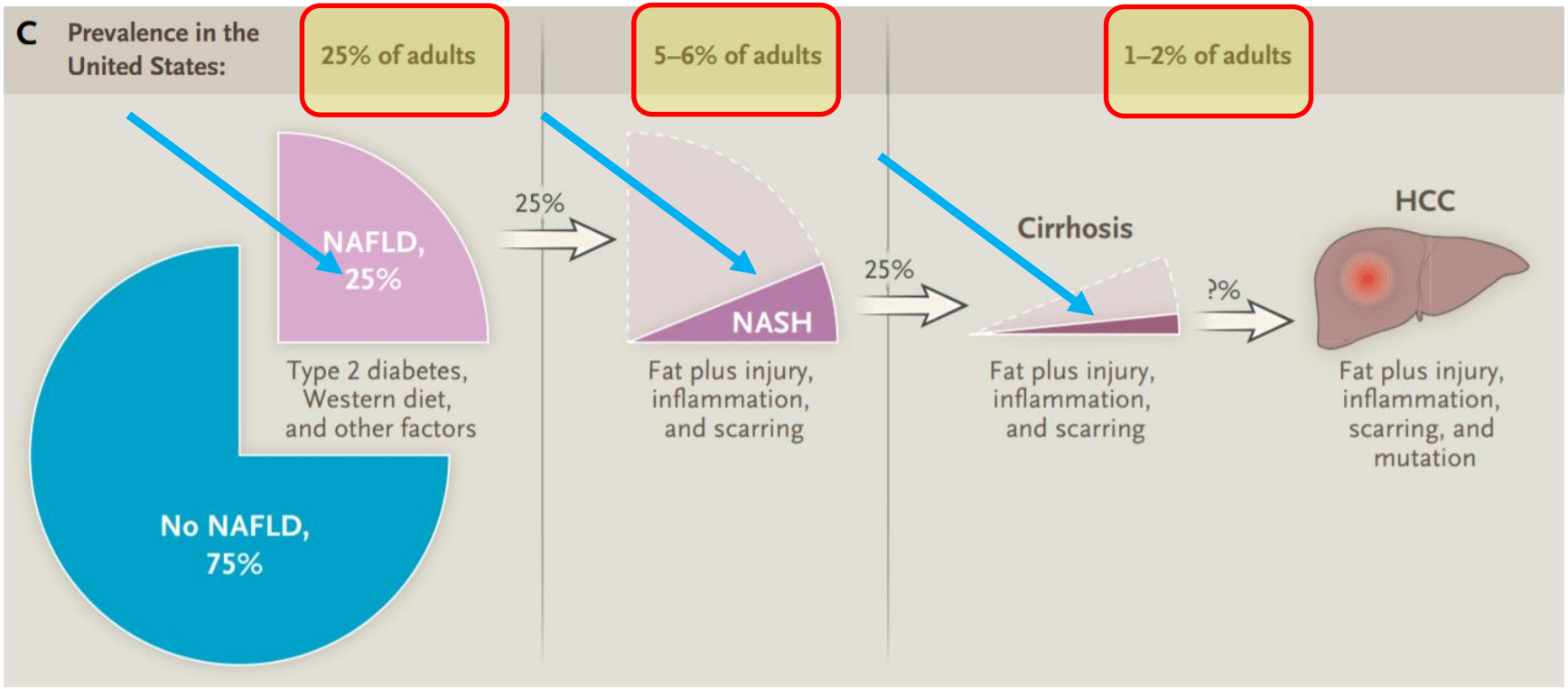

Diehl AM, Day C. NEJM 2017

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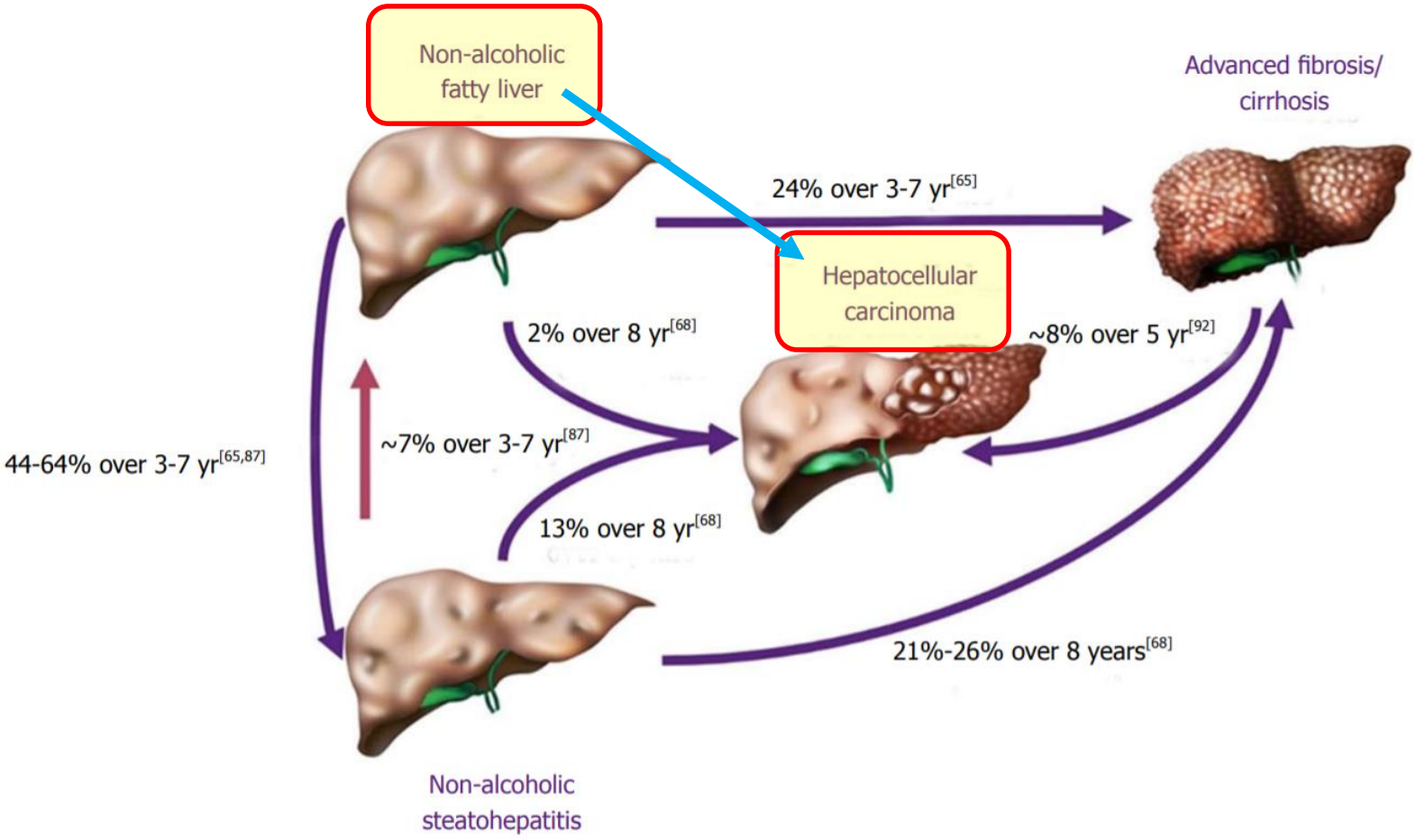

Perumpail BJ et al. World J Gastroenterol 2017

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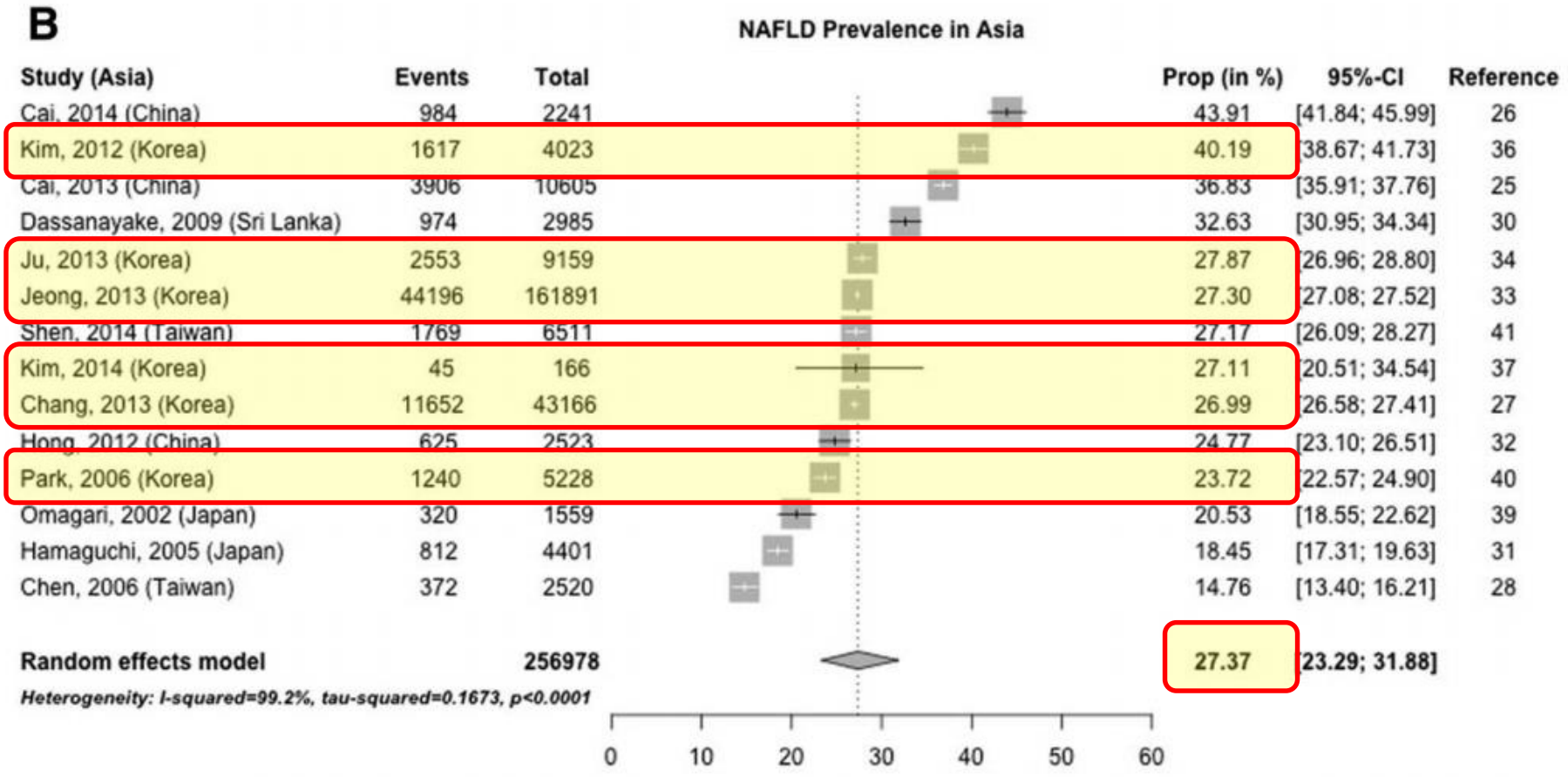


Younossi ZM et al. Hepatology 2016

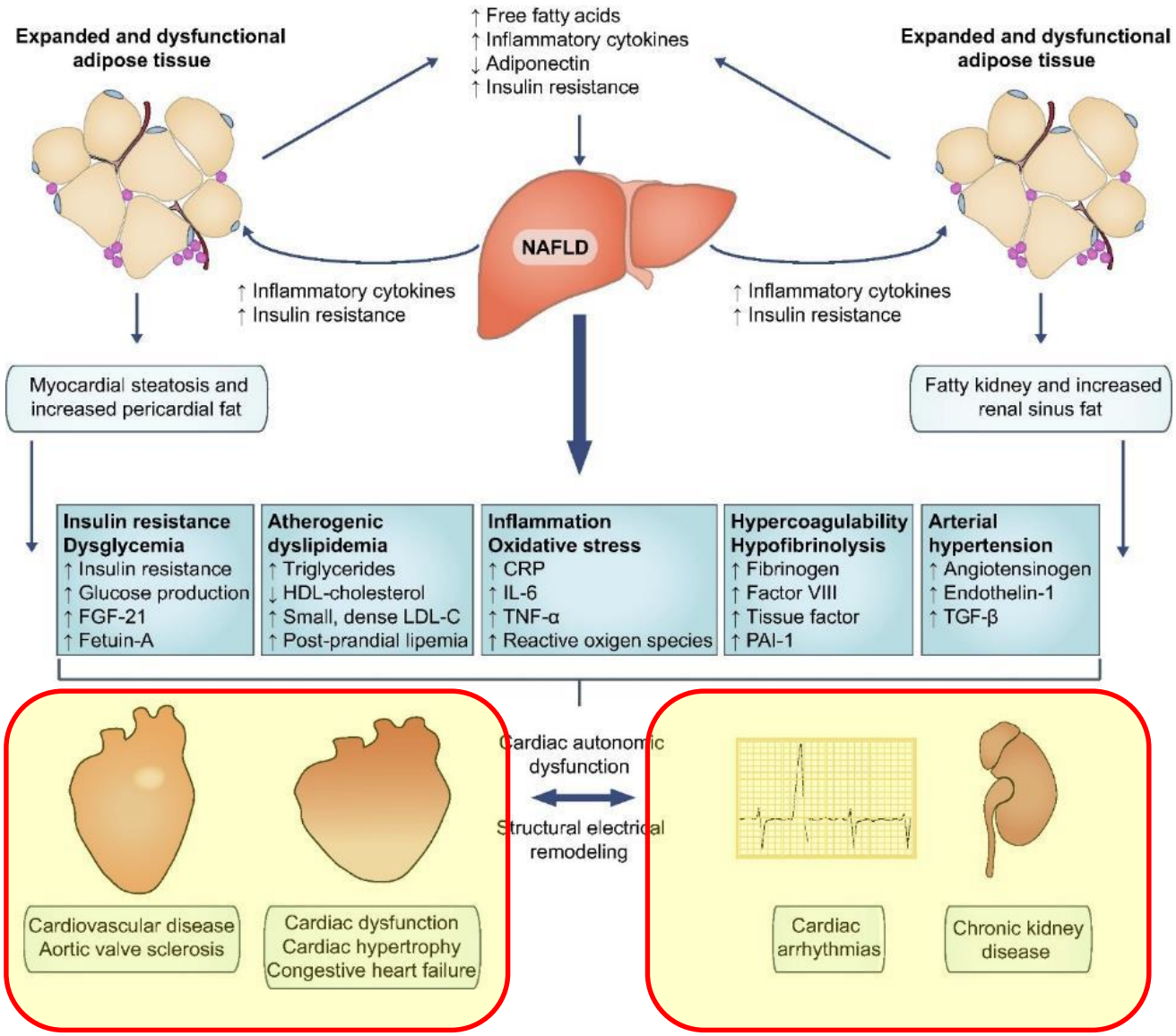
Introduction

TABLE 3. Incidence and IRR for Progression of NAFLD and NASH

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI	I^2 (%)	Follow-up (Years)
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29-0.66)	0.00	5.82
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)	91.84	13.17
NAFLD	Overall mortality	15.44	7	(11.73-20.34)	97.17	13.17
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)	9.80	4.05
NASH	HCC	5.29	1	(0.75-37.56)	NA	4.50
NASH	Liver-specific mortality	11.77	3	(7.1-19.53)	0.00	8.08
NASH	Overall mortality	25.56	2	(6.29-103.8)	73.85	6.17
		IRR*				
NAFLD	Liver-specific mortality	1.94	5	(1.28-2.92)	26.78	13.38
NAFLD	Overall mortality	1.05	5	(0.7-1.56)	97.99	13.38
NASH	Liver-specific mortality	64.6	3	(35.43-117.8)	0.00	8.08
NASH	Overall mortality	2.56	2	(0.63-10.39)	73.76	6.17
		AHR Ratio*				
NAFLD	Liver-specific mortality	2.6	5	(0.91-7.42)	76.66	13.23
NAFLD	Overall mortality	1.04	5	(1.03-1.04)	0.08	13.23
		Fibrosis Progression				
NASH	Percent fibrosis progression†	40.76	4	(34.69-47.13)	5.70	4.91
NASH	Mean fibrosis annual progression rate†	0.09	2	(0.06-0.12)	0.00	4.01

Younossi ZM et al. Hepatology 2016

Introduction



Byrne CD, Targher G. J Hepatol 2015

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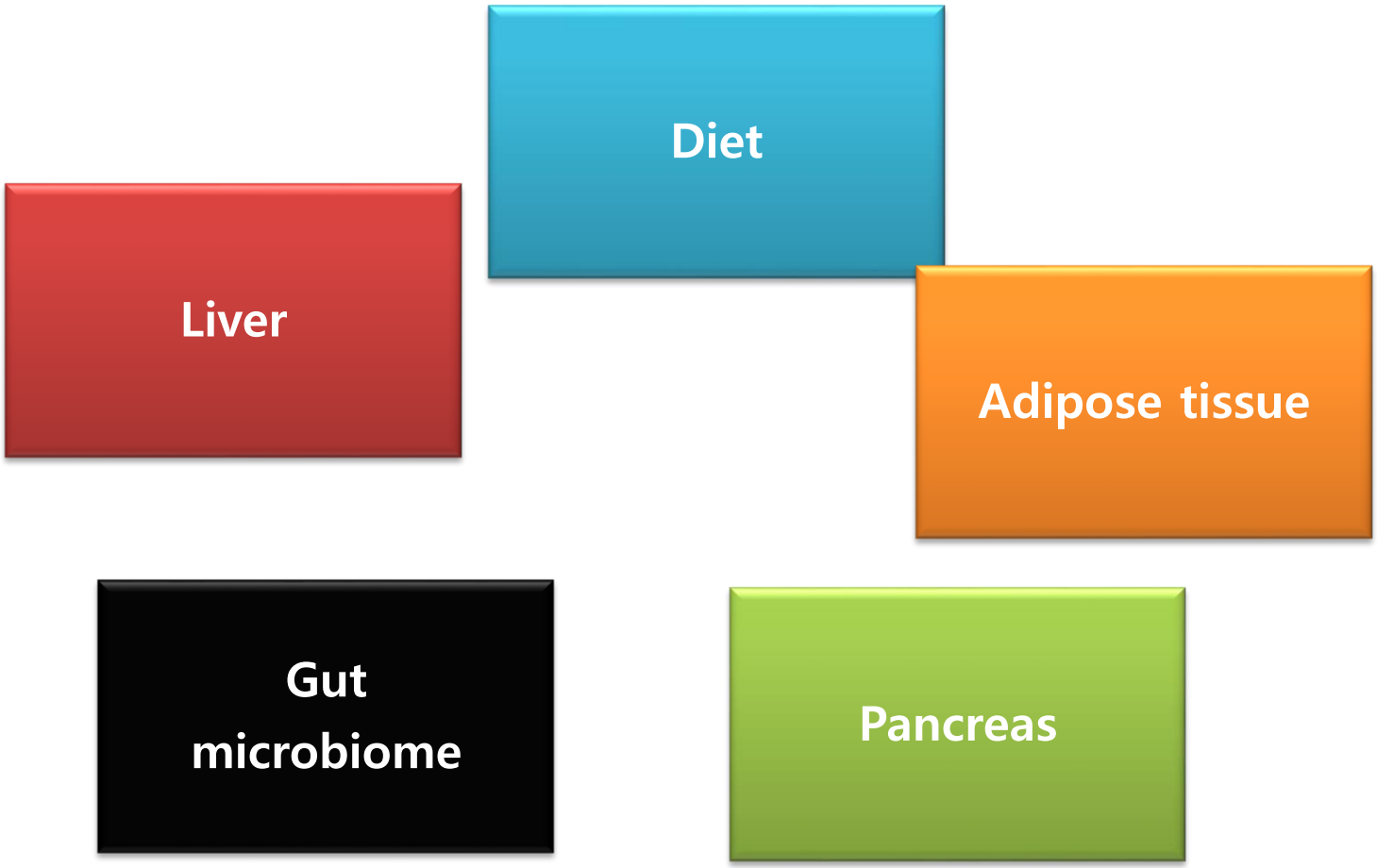


Cheung K et al. Clin Gastroenterol Hepatol 2012

Etiology and Mechanism

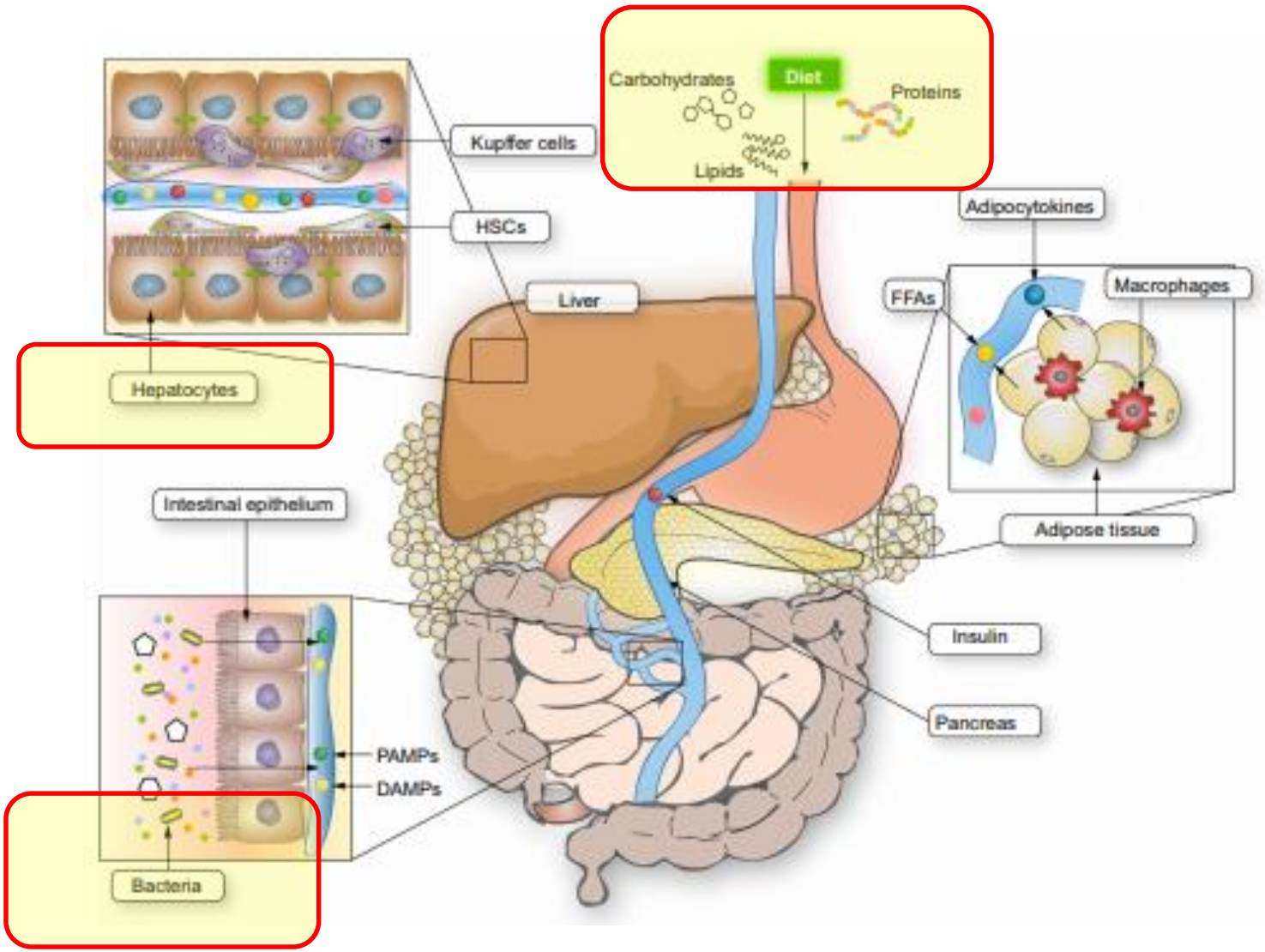
TABLE 3. Risk Factors Associated With NAFLD

Common Conditions With Established Association	Other Conditions Associated With NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
MetS*	Hypogonadism
Polycystic ovary syndrome	Pancreatoduodenal resection
	Psoriasis

*The Adult Treatment Panel III clinical definition of MetS requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) TG level 150 mg/dL or greater; (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.[287]

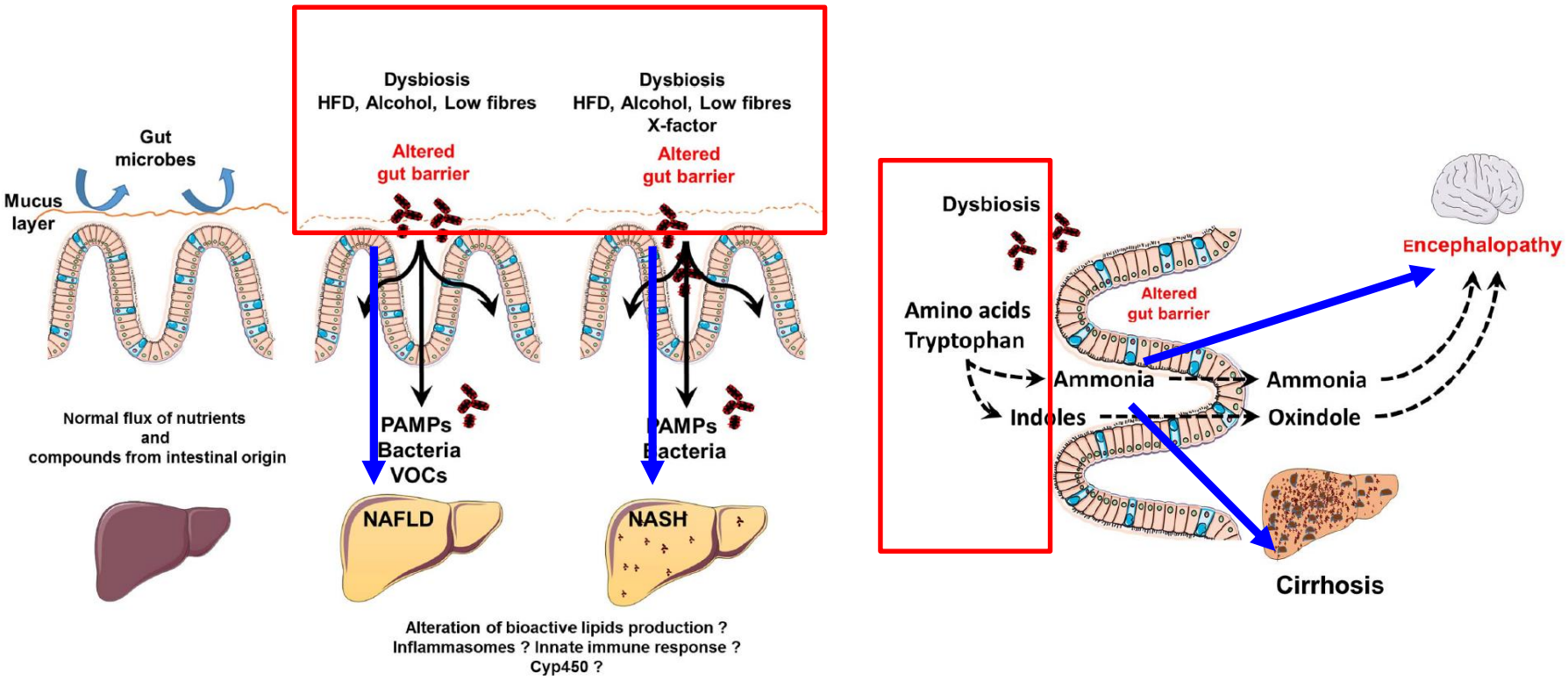
Chalasani N et al. Hepatology 2018

Etiology and Mechanism



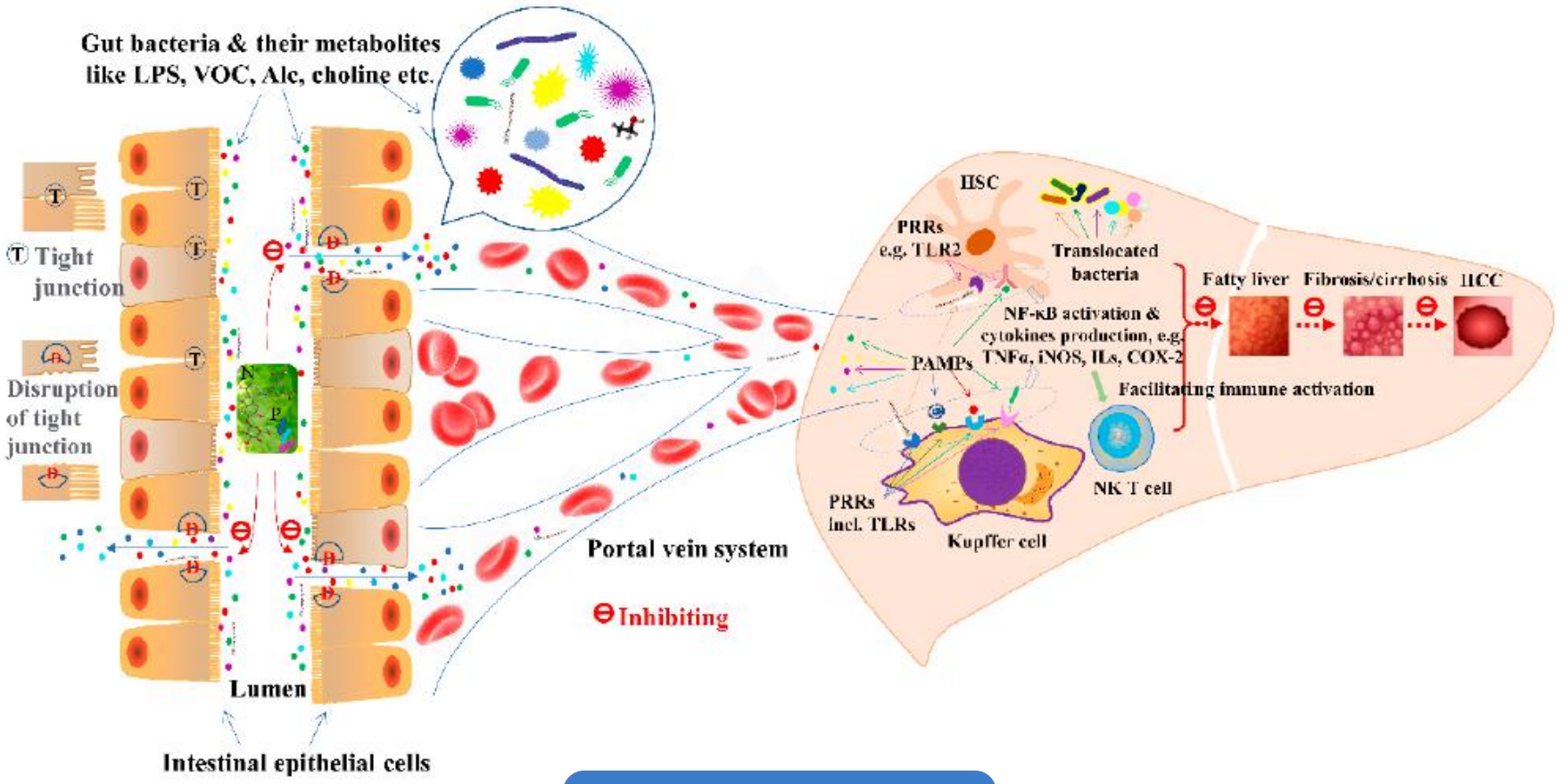
Nobili, V et al. J Hepatol 2013

Etiology and Mechanism



Tilg H et al. Gut 2016

Etiology and Mechanism



Leaky Gut

Meng X et al. Nutrients 2018

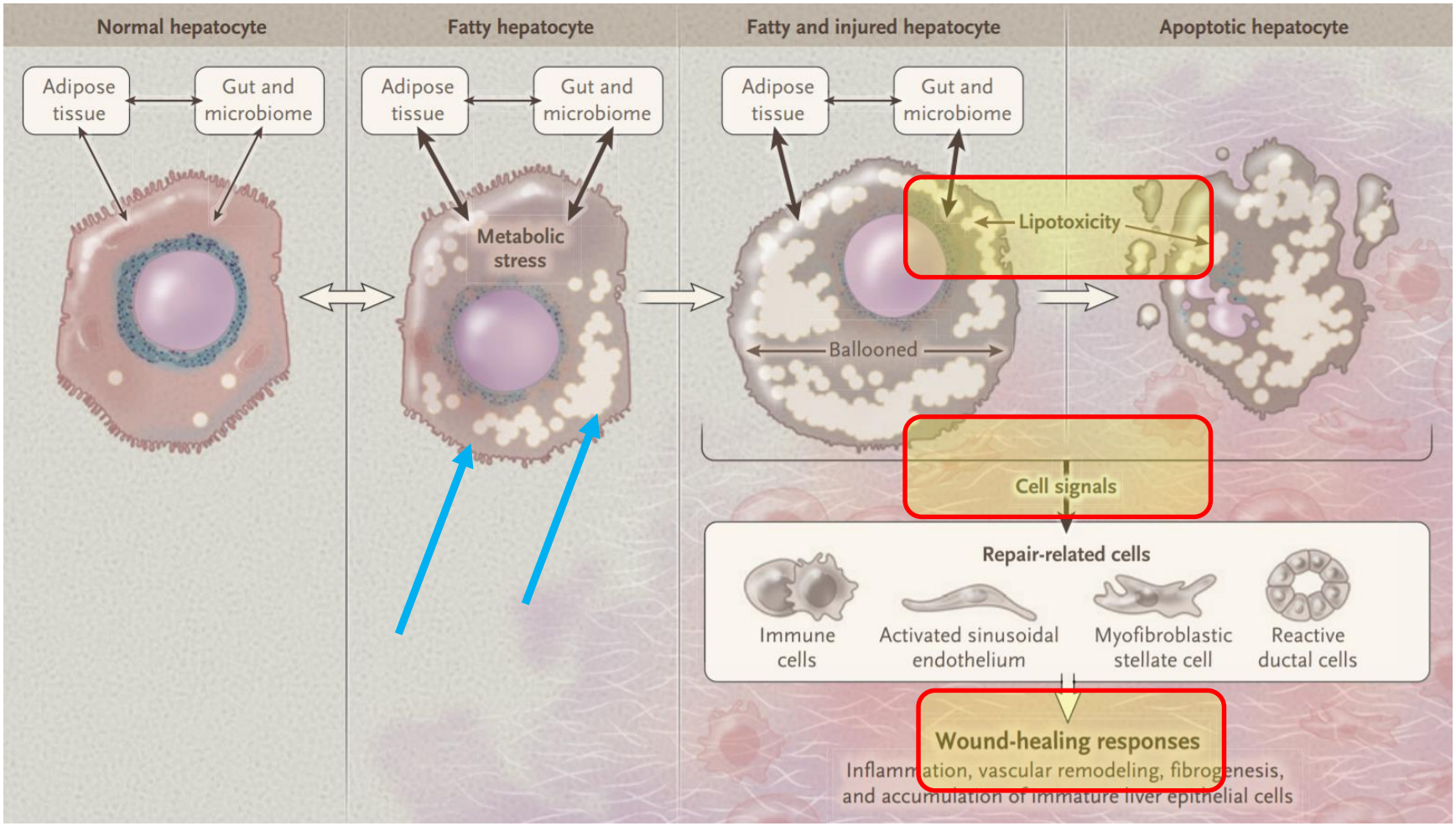
Etiology and Mechanism

Table 1. Effects and mechanisms of natural products and probiotics on non-alcoholic fatty liver disease (NAFLD) by modulating gut microbiota.

Factors that Affect NAFLD	Study Type	Effects and Mechanisms
Probiotics		
Lactobacillus johnsonii BS15 (2×10^7 colony-forming units (CFU)/0.2 mL or 2×10^8 CFU/0.2 mL)	In vivo (in mice)	Enhancing antioxidant defense system, suppressing insulin resistance, restoring mitochondrial functions, improving intestinal permeability, and modulating gut flora
Lactobacillus rhamnosus GG (5×10^7 CFU/g body weight)	In vivo (in mice)	Altering the beneficial bacteria in the distal small intestine, improving the intestinal barrier, reducing lipopolysaccharide (LPS) levels in portal venous blood, attenuating inflammation, and inhibiting fatty acid accumulation in the liver
A combination of live *Bifidobacterium infantis* and *Lactobacillus acidopilus* (0.5×10^6 CFU) and live *Bacillus cereus* (0.5×10^5 CFU)	In vivo (in rats)	Ameliorating gut microbiota dysbiosis, restoring intestinal barrier integrity, decreasing serum inflammatory cytokines, improving liver pathology, attenuating increased serum liver enzymes and glycometabolic biomarkers, possibly through the LPS/toll-like receptor 4 (TLR4) signaling pathway
A synbiotic comprising *Lactobacillus fermentum* CECT5716 and fructo-oligosaccharides	In vivo (in rats)	Preventing hepatic steatosis and mitigating insulin resistance through modulation of gut microbiota, accompanying markedly improved dysbiosis and barrier function.

Meng X et al. Nutrients 2018

Etiology and Mechanism



Diehl AM, Day C. NEJM 2017

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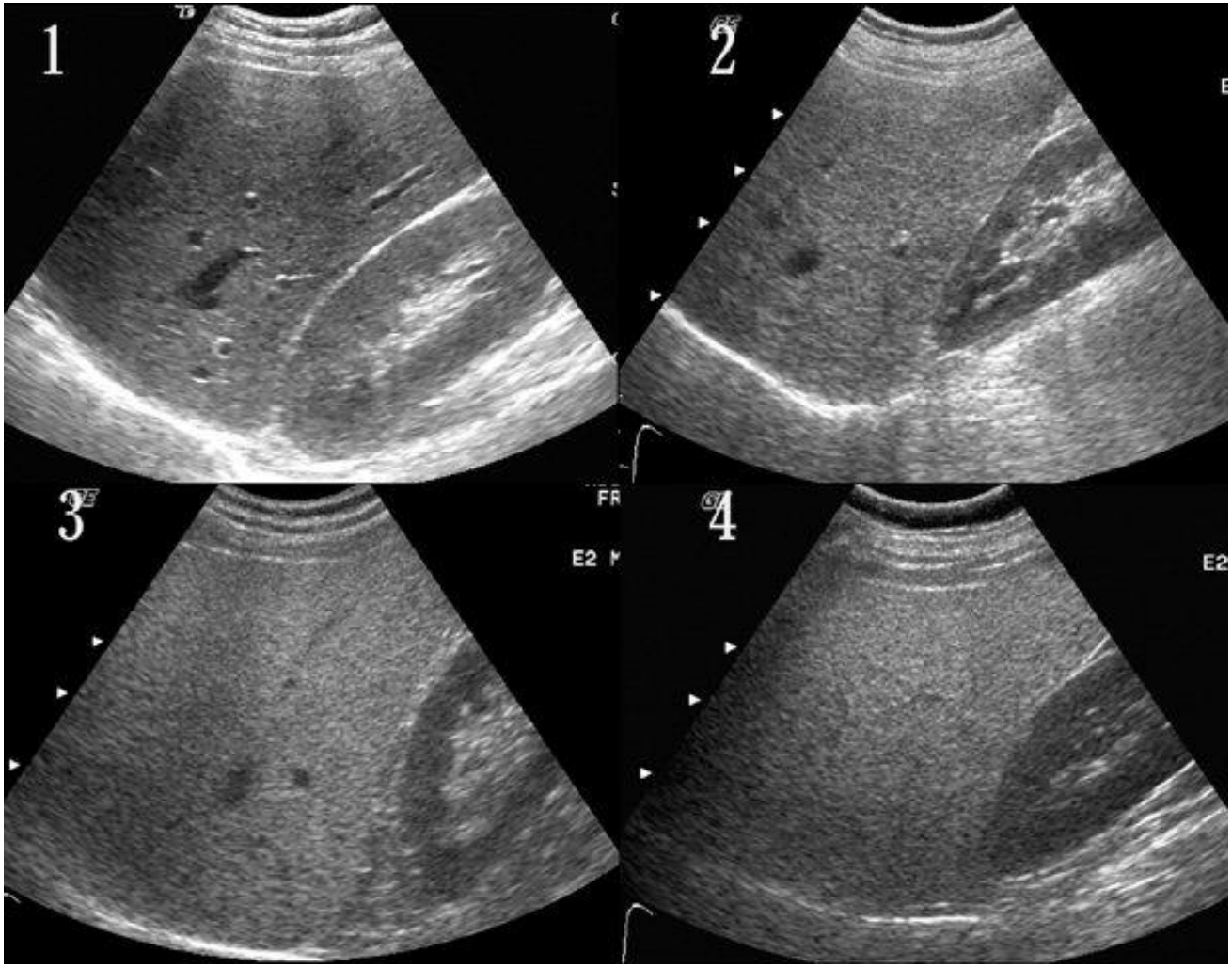
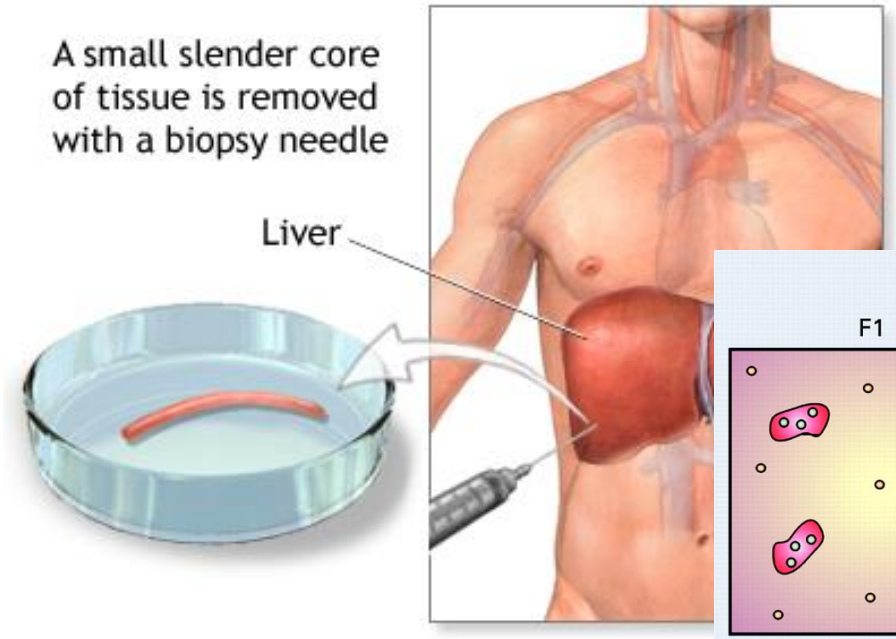
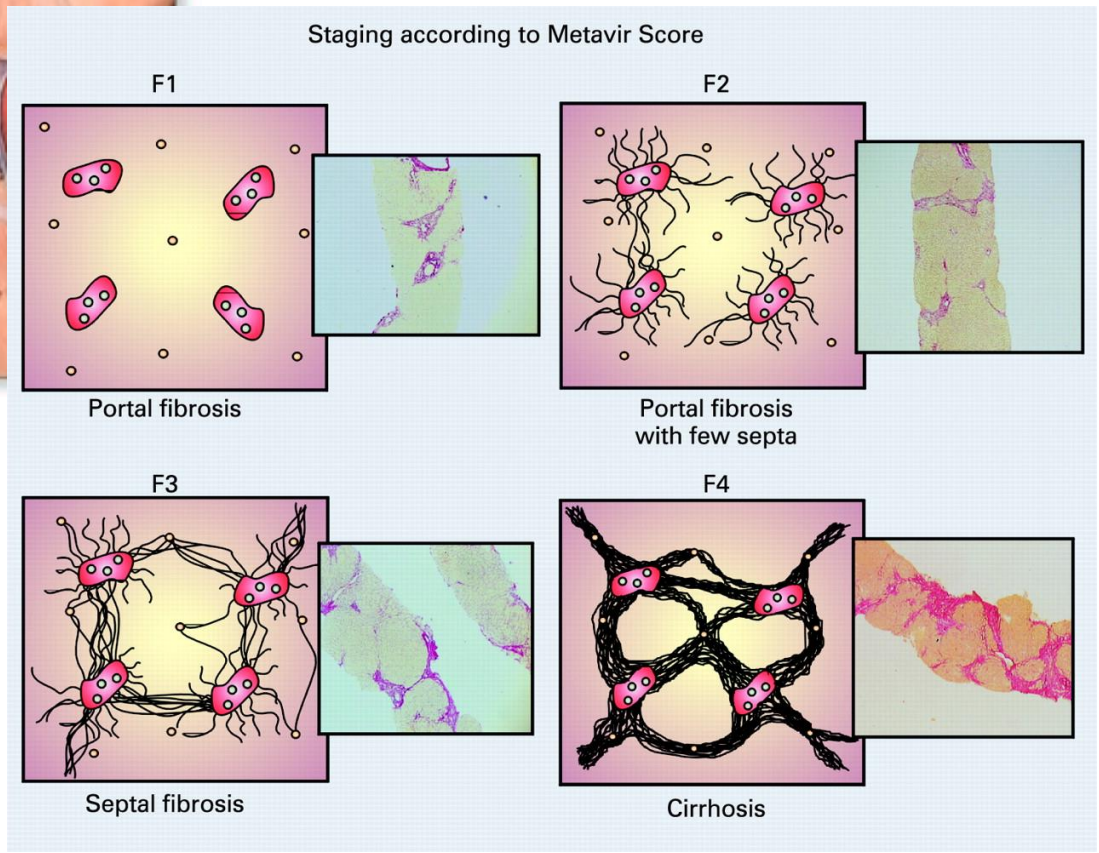
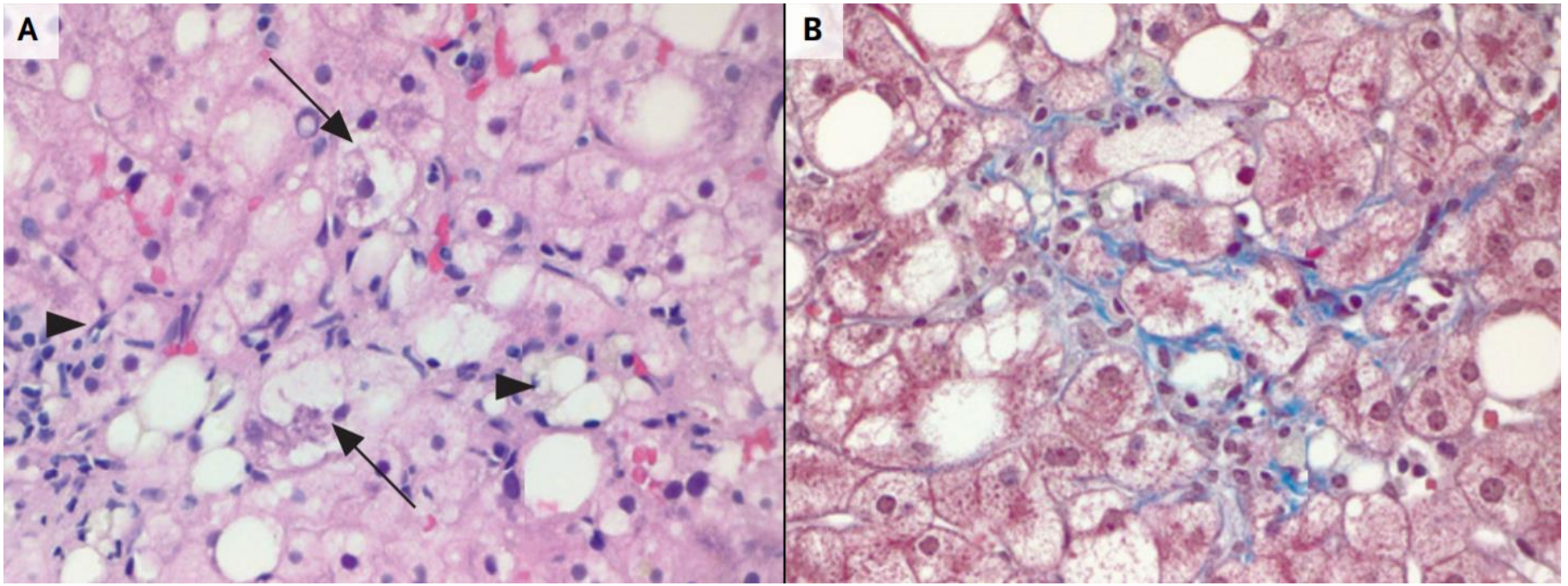


Assessment


A small slender core of tissue is removed with a biopsy needle
Liver


Staging according to Metavir Score
F1
Portal fibrosis
F2
Portal fibrosis with few septa
F3
Septal fibrosis
F4
Cirrhosis

Assessment



ballooned hepatocytes

inflammatory infiltrate

fibrosis

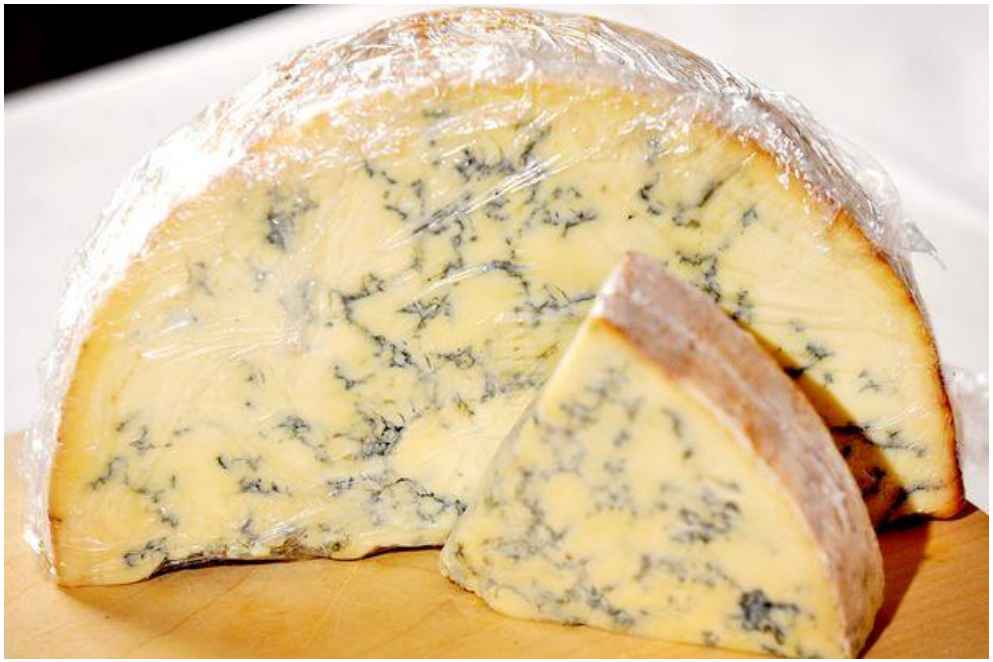
Diehl AM, Day C. NEJM 2017

Assessment

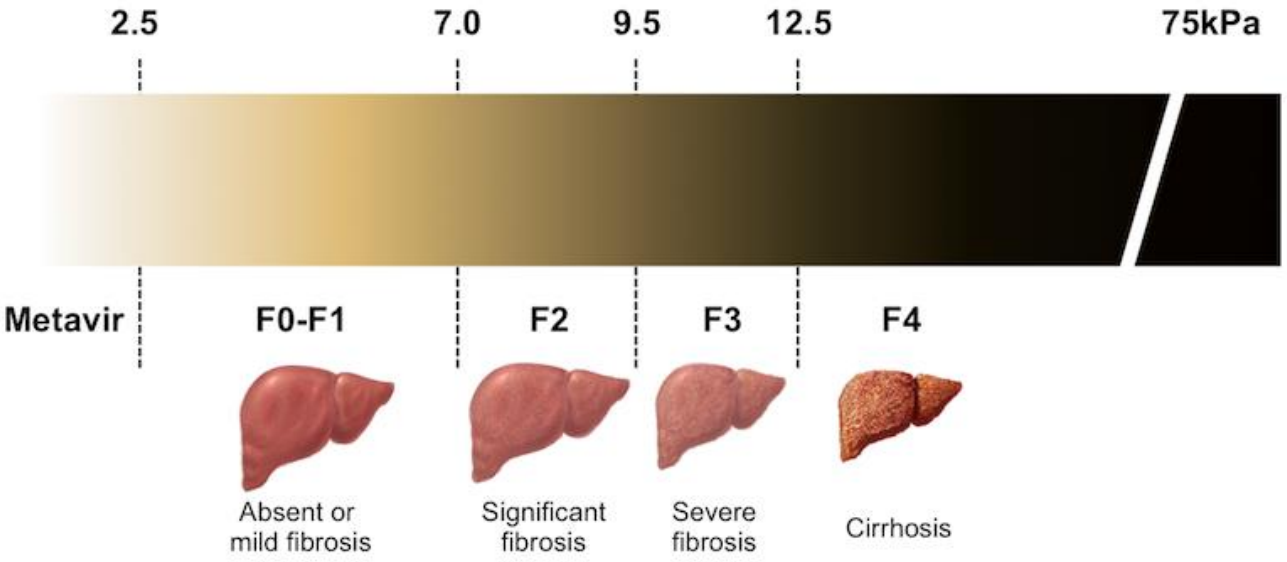

2.9
3.5
3.6
4.9
4.3
3.6
3.7
3.1
3.2
3.5
Invalid measures
Success rate
100 %
202 dB/m
3.6 kPa
CAP (dB/m)
IQR
16
MEDIAN
204
IQR/med.
8 %
E (kPa)
MEDIAN
3.5
IQR
0.4
IQR/med.
11 %

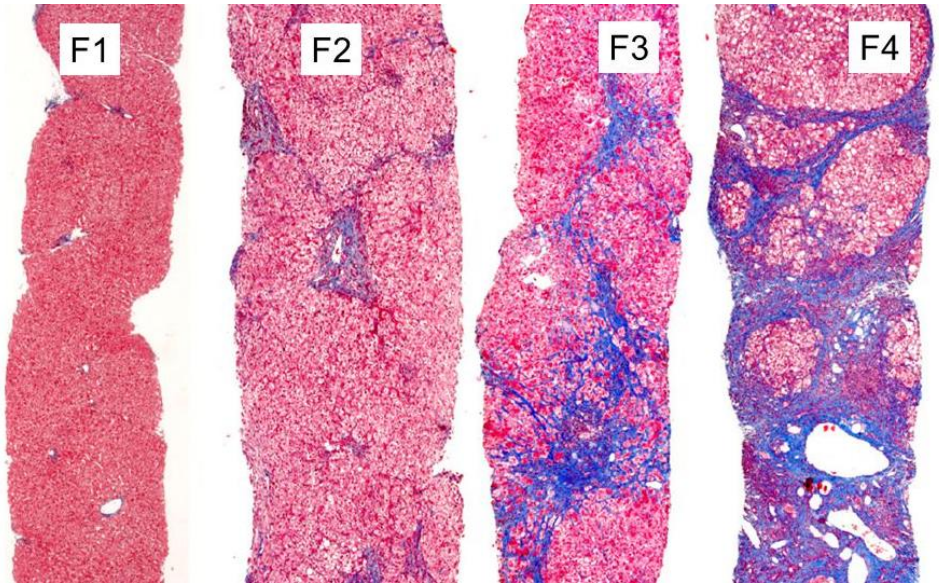
Assessment

- **Cutting wedge technology : CHEESE scanner**
- Originally developed for farmers to test the **ripeness** of their product

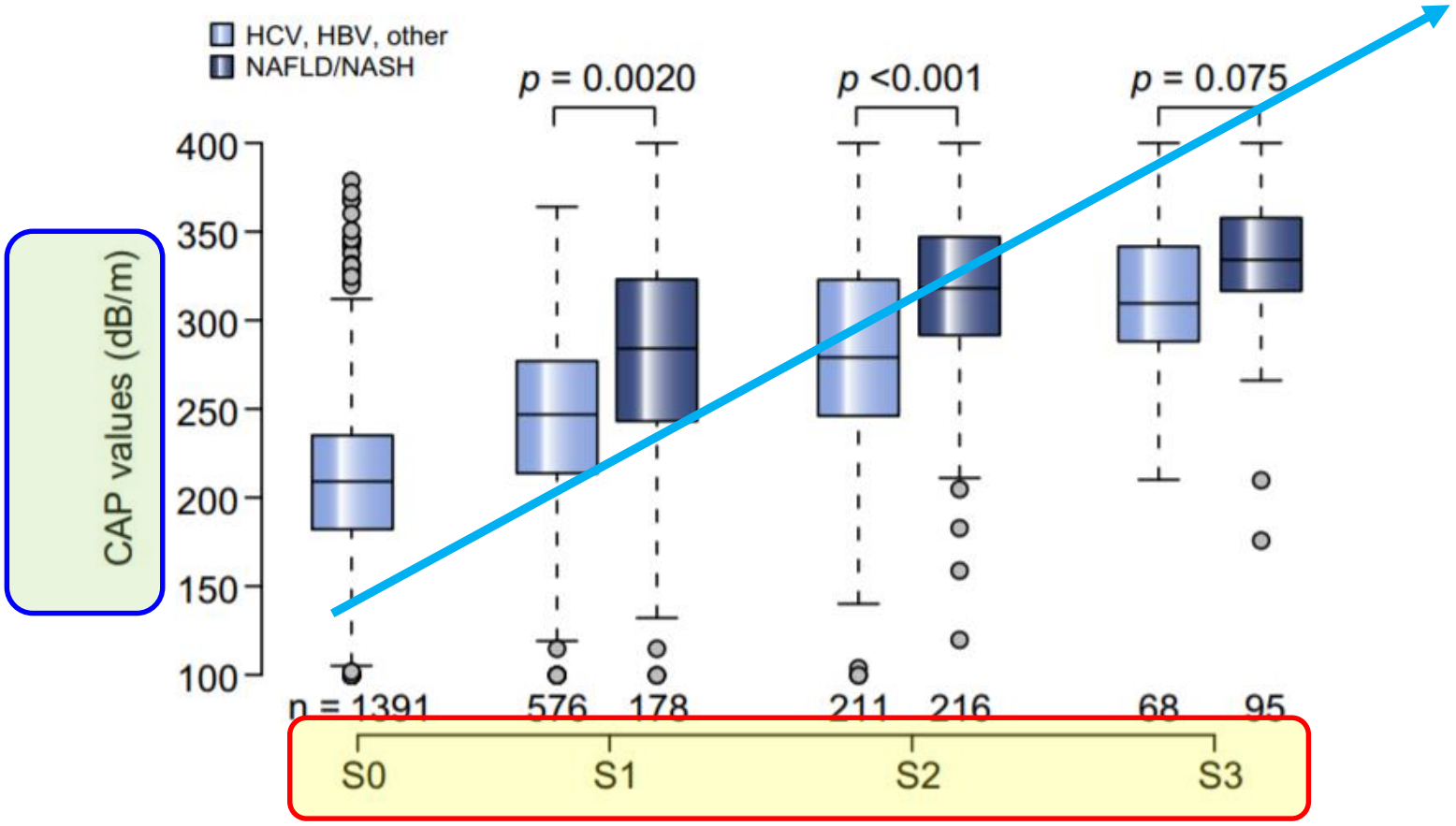


Assessment


2.5
7.0
9.5
12.5
75kPa
Metavir
F0-F1
F2
F3
F4
Absent or mild fibrosis
Significant fibrosis
Severe fibrosis
Cirrhosis


F1
F2
F3
F4

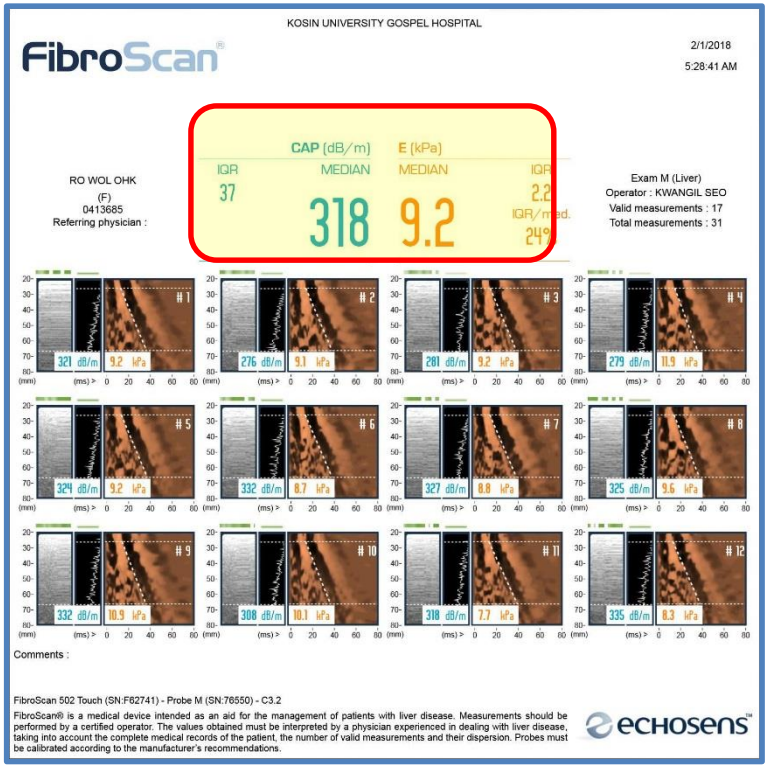
Assessment



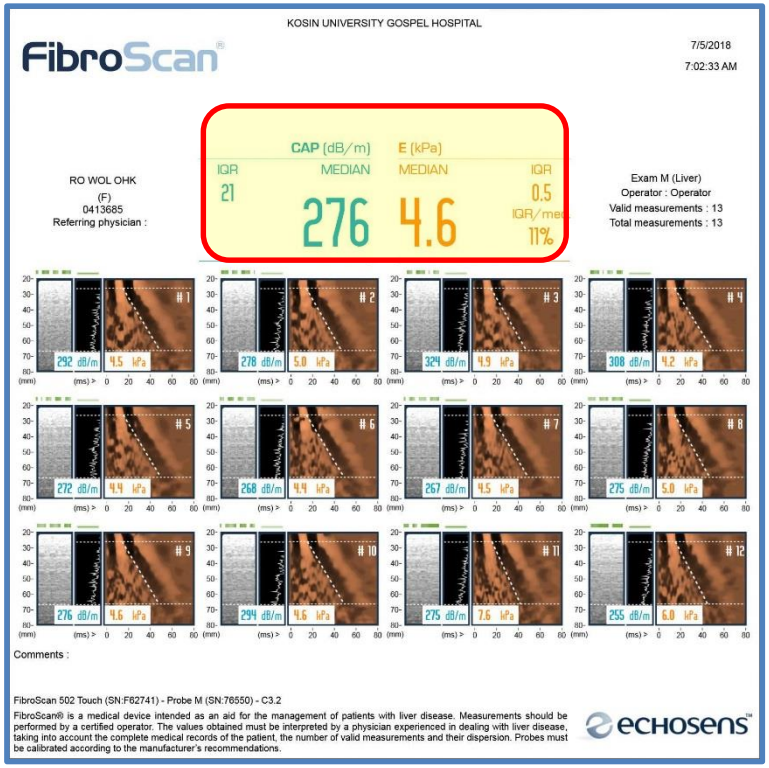
Karlas T et al. Hepatol. 2017

Assessment

64 kg



59 kg



Stage 1 - 5~33% : 238 이상
Stage 2 - 34~66% : 260 이상
Stage 3 - >66% : 293 이상

Contents

Therapeutic approach

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016

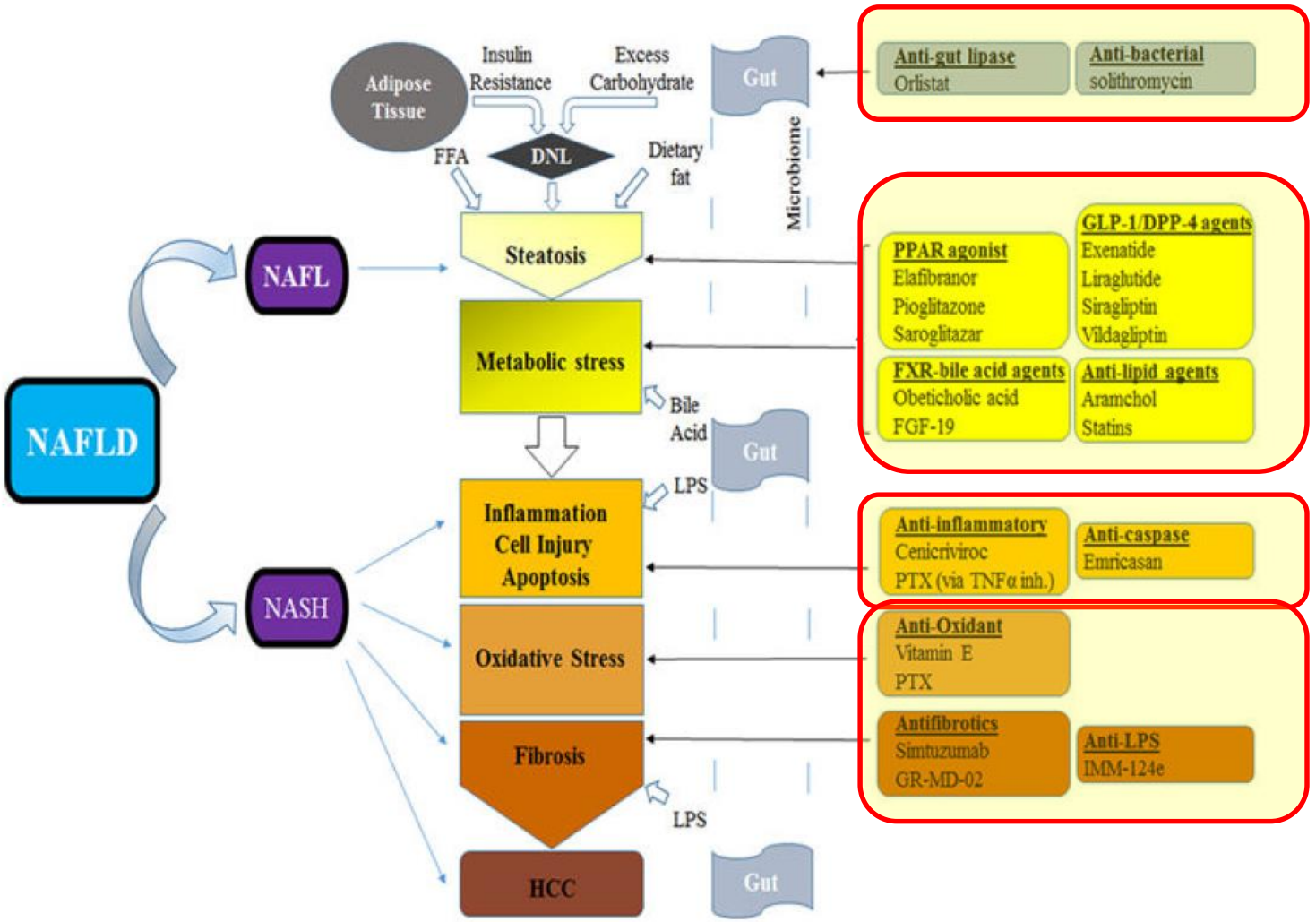
Therapeutic approach

Table 1. Lifestyle Modifications to Mitigate Nonalcoholic Steatohepatitis.*

Lose 7% of body weight if overweight or obese
Limit consumption of fructose-enriched beverages
Limit consumption of alcohol (≤1 drink/day for women and ≤2 drinks/day for men)
Drink two or more cups of caffeinated coffee daily

Diehl AM, Day C. NEJM 2017

Therapeutic approach



Oseini A et al. Liver int 2017

Therapeutic approach

Table 2. Pharmacotherapies for Nonalcoholic Steatohepatitis Evaluated in Phase 2 or 3 Clinical Trials.*

Pharmacologic Agent	Therapeutic Target		
	Metabolic Stress	Inflammation	Fibrosis
Vitamin E†	Yes	Yes	No
Pioglitazone (PPAR-γ agonist)†	Yes	Yes	Yes
Obeticholic acid (FXR agonist)†	Yes	Yes	Yes
Chemokine receptor 2 and 5 antagonists	No	Yes	Yes
PPAR-α and PPAR-δ agonists	Yes	Yes	Yes
Lysyl oxidase–like 2 inhibitor	No	No	Yes
Galectin 3	No	Yes	Yes
Bovine milk colostrum	No	Yes	Yes
Stress-activated kinase 1 inhibitor	Yes	Yes	Yes
FGF-21	Yes	Yes	Yes
FGF-19–like agent	Yes	Yes	Yes

Diehl AM, Day C. NEJM 2017

Therapeutic approach

HEPATOLOGY

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PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

- **Treatment indication**
  - **biopsy-proven NASH and fibrosis**

- **Weight loss**
  - **3%-5% : improve steatosis**
  - **7%-10% : improve histopathological features of NASH, including fibrosis.**

Chalasani N et al. Hepatology 2018

Therapeutic approach

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- **Metformin**
  - **not recommended**
- **Pioglitazone**
  - **improves liver histology (in biopsy-proven NASH)**
- **GLP-1 agonists**
  - **premature to consider**
- **Vitamin E**
  - **with biopsy-proven NASH (without DM, without cirrhosis)**

Chalasani N et al. Hepatology 2018

Therapeutic approach

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- **BARIATRIC SURGERY**
  - **can be considered**
  - **premature to consider foregut bariatric surgery as an established option to specifically treat NASH**
  - **case-by-case basis by an experienced bariatric surgery program.**

Chalasani N et al. Hepatology 2018

Therapeutic approach

- **BARIATRIC SURGERY**
  - **an option in patients unresponsive to lifestyle changes and pharmacotherapy**
  - **reduces weight and metabolic complications**
  - **stable results in the long term**

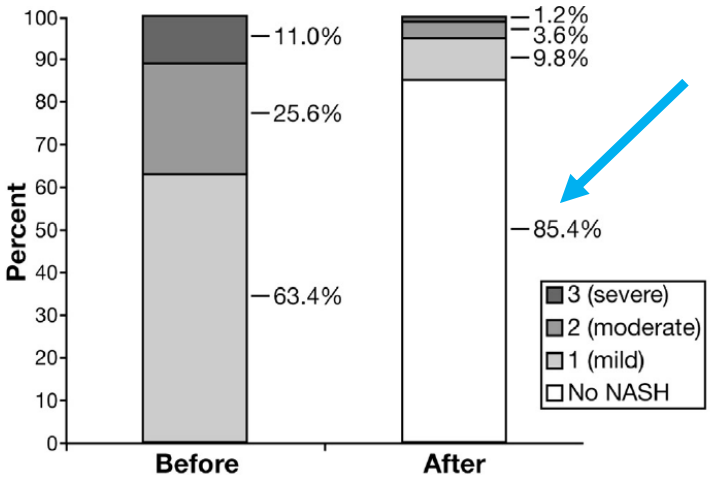
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016

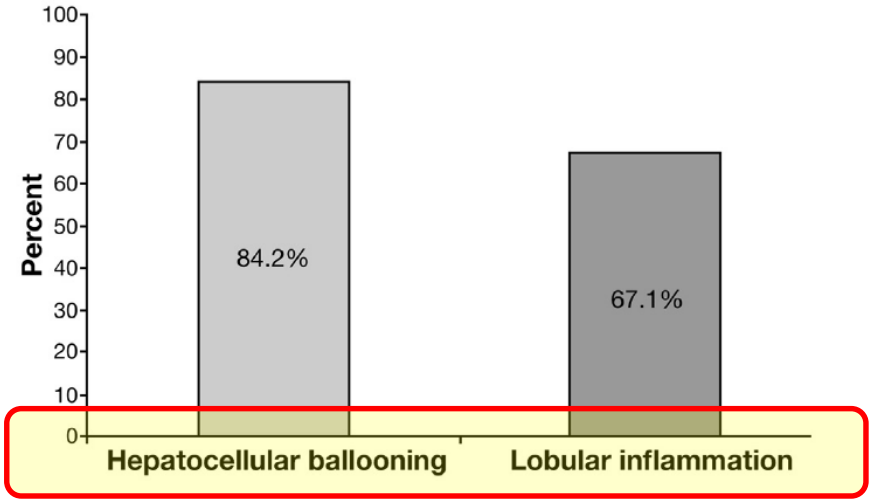
Therapeutic approach

Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients

Guillaume Lassailly,[1,2,*] **Robert Caiazzo**,[3,4,*] David Buob,[5] Marie Pigeyre,[6] Hélène Verkindt,[4] Julien Labreuche,[7] Violeta Raverdy,[4] Emmanuelle Leteurtre,[5] Sébastien Dharancy,[1,2] Alexandre Louvet,[1,2] Monique Romon,[6] Alain Duhamel,[7] François Pattou,[3,4] and Philippe Mathurin[1,2]

[1]Service d'Hépato-Gastroentérologie; [2]Unité Inserm U 995; [3]Unité Inserm U 1011, Services de [4]Chirurgie Endocrinienne; [5]d'Anatomie Pathologique; [6]de Nutrition, CHRU de Lille; and [7]Department of Biostatistics, Université Lille 2, France





Lassailly G, Caiazzo R et al. Gastroenterology 2015

Therapeutic approach

Prospective Study of the Long-Term Effects of Bariatric Surgery on Liver Injury in Patients Without Advanced Disease

PHILIPPE MATHURIN,[*,‡] ANTOINE HOLLEBECQUE,[*,‡] LAURENT ARNALSTEEN,[§,‖] DAVID BUOB,[¶] EMMANUELLE LETEURTRE,[¶] ROBERT CAIAZZO,[§,‖] MARIE PIGEYRE,[#] HÉLÈNE VERKINDT,[‖] SÉBASTIEN DHARANCY,[*,‡] ALEXANDRE LOUVET,[*,‡] MONIQUE ROMON,[#] and FRANÇOIS PATTOU[§,‖]

Service d'Hépato-Gastroentérologie, ‡Unité Inserm U 795, §Unité Inserm U 859, Services de, ‖Chirurgie Endocrinienne, ¶d'Anatomie Pathologique, #de Nutrition, CHRU de Lille, Université Lille 2, France

Table 4. Effects of Bariatric Surgery on Clinical and Biological Parameters at 1 and 5 Years

Variables	Before surgery	1 Year	5 Years	*P* value, paired *t* test: Before vs 1 year	Before vs 5 years	1 Year vs 5 years
Age, mean ± SD, *y*	41.5 ± 9.6	NA	NA	NA	NA	NA
BMI, mean ± SD, kg/m^2	50 ± 7.6	39 ± 8.2	37.7 ± 8.4	.00001	.00001	.00001
Diabetes mellitus, n (%)	94 (24.8)	46 (12.1)	24 (10.8)	.00001	.00001	NS
Arterial hypertension, n (%)	185 (48.8)	139 (36.7)	85 (37)	.00001	.0005	NS
Systolic blood pressure, mean ± SD, *mm Hg*	135 ± 19	128 ± 15	129 ± 17	.00001	.0005	NS
Diastolic blood pressure, mean ± SD, *mm Hg*	73 ± 13	70 ± 11	70 ± 12	.00003	.0003	NS
Cholesterolemia, mean ± SD, *g/L*	2.04 ± 0.39	1.85 ± 0.44	1.89 ± 0.46	.00001	.00001	.01
Serum triglycerides, mean ± SD, *g/L*	1.67 ± 2.1	1.2 ± 0.76	1.06 ± 0.67	.00001	.00001	.00001
ALT, mean ± SD, *IU/L*	30.1 ± 21.7	21.4 ± 14	22.8 ± 14.1	.00001	.00003	NS
GGT, mean ± SD, *IU/L*	39.9 ± 42.4	30 ± 27.8	29.2 ± 32	.00001	.00001	.02
Fasting glucose, mean ± SD, *g/L*	1.18 ± 0.65	0.96 ± 0.3	0.94 ± 0.25	.00001	.00001	.05
Insulin resistance index, mean ± SD	3.2 ± 0.35	2.84 ± 0.35	2.83 ± 0.35	.00001	.00001	NS

ALT, alanine aminotransferase; BMI, body mass index; GGT, γ-glutamyl transferase; NA, not applicable; NS, not significant.

Mathurin P et al. Gastroenterology 2009

Therapeutic approach

Table 5. Effects of Bariatric Surgery on Histologic Parameters at 1 and 5 Years

Variables	Before surgery (n = 362)	1 Year (n = 267)	5 Years (n = 211)	*P* value, paired *t* test: Before vs 1 year	Before vs 5 years	1 Year vs 5 years
Amount of steatosis, mean ± SD, (%)	37.4 ± 25.5	15.3 ± 19.8	16 ± 27.3	.00001	.00001	.5
Severe steatosis, n (%)	106 (29)	15 (5.6)	18 (8.5)	.00001	.00001	.5
NAS, mean ± SD	1.97 ± 1.33	1.07 ± 1.26	1 ± 1.33	.00001	.00001	.07
NAS inflammation, mean ± SD	0.18 ± 0.41	0.196 ± 0.45	0.23 ± 0.45	.7	.1	.7
NAS ballooning, mean ± SD	0.20 ± 0.47	0.12 ± 0.36	0.1 ± 0.33	.001	.001	.07
Extent of fibrosis, mean ± SD	0.27 ± 0.55	0.41 ± 0.69	0.36 ± 0.59	.002	.001	.9
Fibrosis score						
F0	280 (77.4)	181 (67.8)	147 (69.7)			
F1	67 (18.5)	69 (25.8)	55 (26)			
F2	13 (3.6)	10 (3.7)	6 (2.8)			
F						
F						

Table 6. Specific Evolution of 99 Patients with Probable or Definite NASH (NAS ≥ 3)

Variables	Before surgery	1 Year	5 Years	*P* value, paired *t* test: Before vs 1 year	Before vs 5 years	1 Year vs 5 years
Extent of steatosis, mean ± SD, (%)	66.3 ± 18.3	28.8 ± 24.5	25.7 ± 25.2	.00001	.00001	.14
NAS, mean ± SD	3.71 ± 0.86	2.13 ± 1.48	1.92 ± 1.56	.00001	.0001	.04
NAS inflammation, mean ± SD	0.53 ± 0.55	0.49 ± 0.64	0.56 ± 0.56	.5	.2	1
NAS ballooning, mean ± SD	0.63 ± 0.67	0.33 ± 0.55	0.26 ± 0.48	.002	.001	.13
Extent of fibrosis, mean ± SD	0.71 ± 0.79	0.76 ± 0.86	0.66 ± 0.79	.65	.77	.5
Fibrosis score, n (%)						
F0	55 (56)	36 (47)	31 (51)			
F1	33 (33)	28 (36)	22 (37)			
F2	10 (10)	9 (12)	6 (10)			
F3	1 (1)	4 (5)	1 (2)			

NAS, nonalcoholic fatty liver disease score.

Mathurin P et al. Gastroenterology 2009

Therapeutic approach

OBES SURG (2015) 25:2280–2289
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ORIGINAL CONTRIBUTIONS

Bariatric Surgery and Non-Alcoholic Fatty Liver Disease: a Systematic Review of Liver Biochemistry and Histology

Guy Bower[1] · Tania Toma[1] · Leanne Harling[1] · Long R Jiao[1,3] · Evangelos Efthimiou[1,2] · Ara Darzi[1] · Thanos Athanasiou[1] · Hutan Ashrafian[1,2,3]

Bariatric surgery is associated with a significant reduction in the weighted incidence of a number of histological features of NAFLD including

- steatosis (50.2 and 95 %CI of 35.5–65.0),
- **fibrosis (11.9 and 95 %CI of 7.4–16.3 %),**
- hepatocyte ballooning (67.7 and 95 %CI 56.9–78.5)
- lobular inflammation (50.7 and 95 %CI 26.6–74.8 %)

OBES SURG 2015;25:2280–2289

Therapeutic approach

Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

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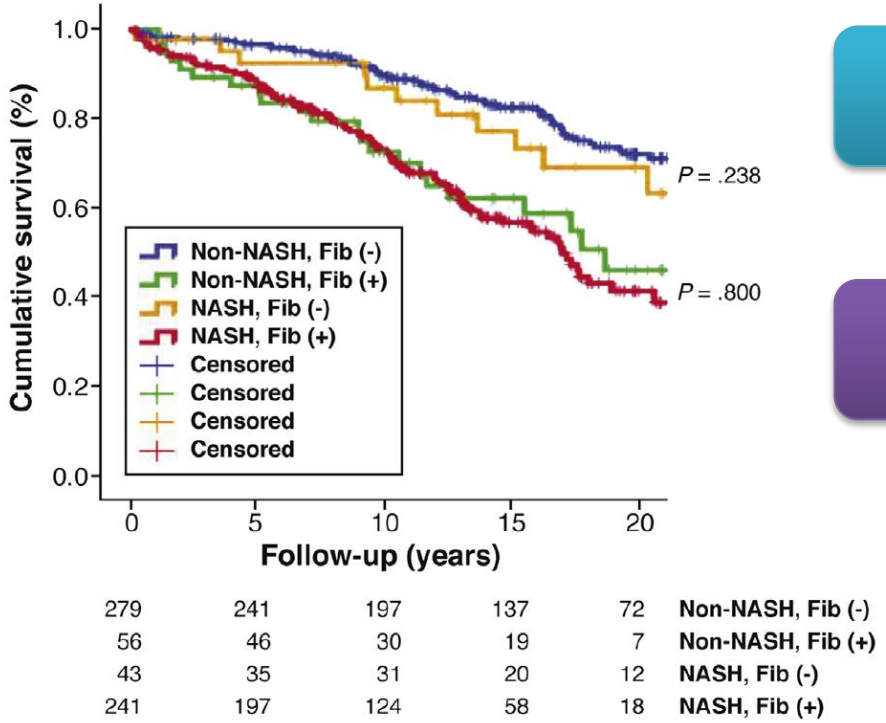

Fib (-)
Non-NASH vs. NASH

Fib (+)
Non-NASH vs. NASH

Angulo P et al. Gastroenterology. 2015

Therapeutic approach

Increased Perioperative Mortality Following Bariatric Surgery Among Patients With Cirrhosis

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Mortality

without LC : 0.3 %

compensated LC : 0.9 %

decompensated LC : 16.3 %

Table 2. Multivariate Analysis of Predictors of In-Hospital Mortality

	Adjusted odds ratio (95% confidence interval)	*P* value
Liver disease status		
No cirrhosis	Ref	
Compensated cirrhosis	2.2 (1.0–4.6)	.041
Decompensated cirrhosis	21.1 (5.4–82.3)	<.0001

Bariatric surgery in patients with cirrhosis should be performed while liver disease is well compensated.

Mosko JD et al. Clin Gastroenterol Hepatol 2011

Contents

Conclusion

1. 지방간 환자가 증가하고 있으며 향후 간질환의 주된 원인이 될 것이다.

2. 체중 감량과 식이 조절이 가장 중요한 치료 방법이다.

3. 간내 섬유화 소견이 가장 중요한 예후 인자이다.

4. 생활 습관 조절 등 내과적 치료에 반응하지 않는 지방간 환자들에서 수술적 치료를 고려할 수 있다.

5. 간경변이 동반된 환자에서 수술적 치료는 신중하게 고려해야 한다.

Thank you!