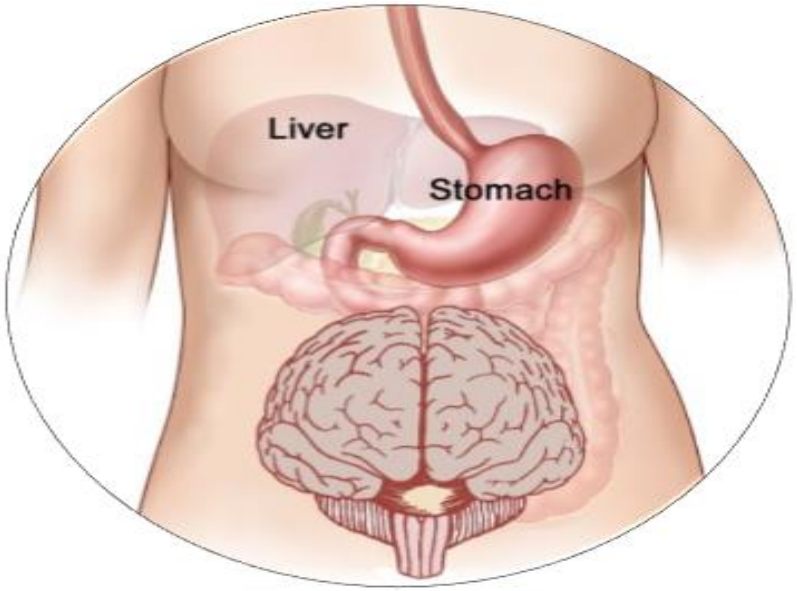
ALKOL DIŞI STEATOHEPATİT SÜRECİNDE İNTESTİNAL MİKROBİYOTA ve SAFRA ASİTLERİNİN ÖNEMİ



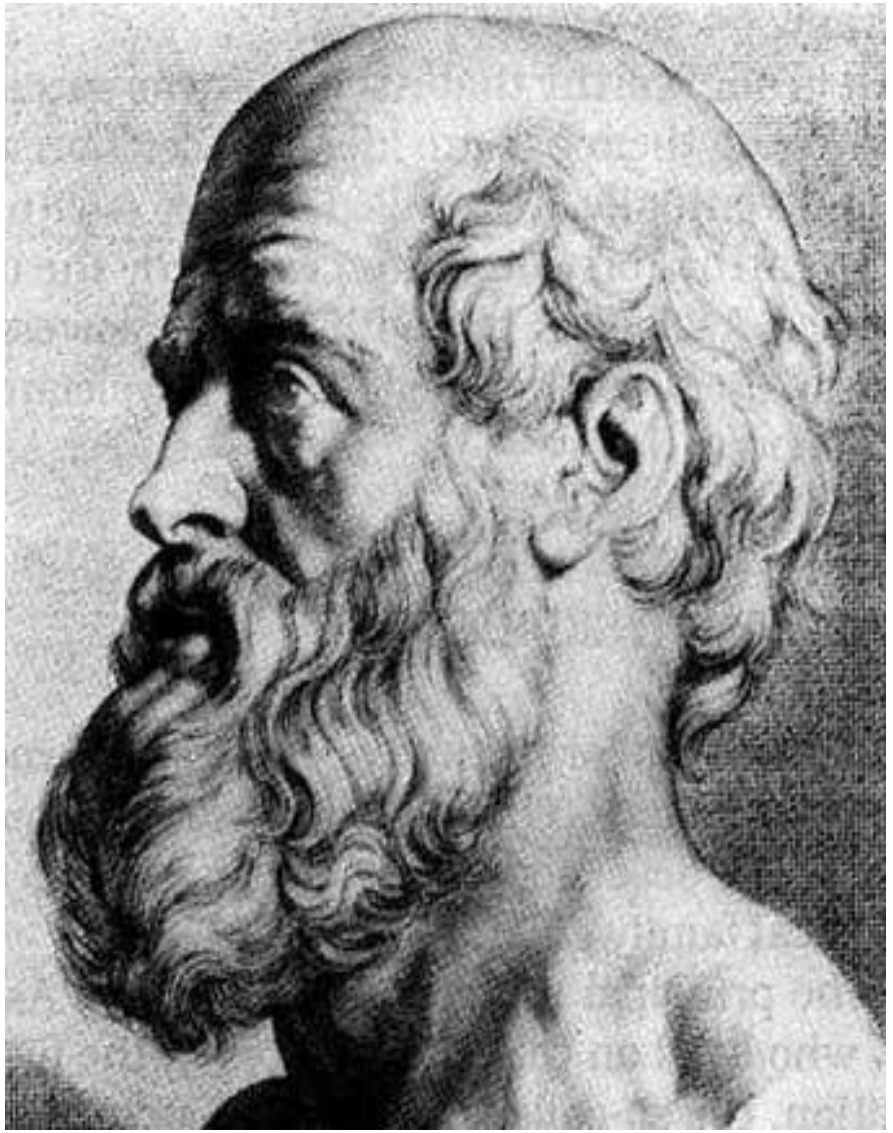
Doç.Dr. Hüseyin KAYADİBİ
Hitit Üniversitesi Tıp Fakültesi
Tıbbi Biyokimya AbD

24 Ocak 2018, Ankara

“Bütün hastalıklar barsaktan başlar.

Barsak hasta ise vücudun geri kısmı da hastadır.”

Hipokrat



SON 35 YILDIR

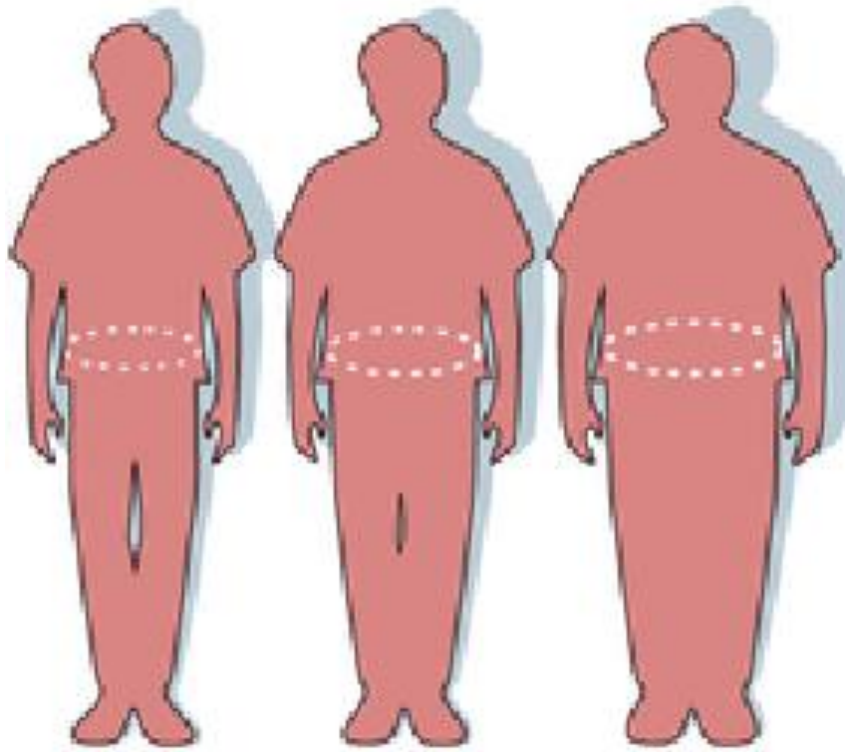
DİYET

YAPIYORUZ

SON 35 YILDIR

KİLO

ALIYORUZ



SUNUM PLANI

- **NASH Patogenezi**
- **NASH Gelişimindeki İntestinal Mikrobiyota Kaynaklı Faktörler**
- **NASH Sürecinde Safra Asitlerinin Önemi**

NASH Tanımı

- Karaciğerde yağlanma ile birlikte alkolik karaciğer hastalığında olduğu gibi hepatositlerde balonlaşma, iltihabi infiltrasyon, Mallory cisimcikleri, megamitokondri ve fibrozis gibi bulguların görüldüğü hastalıktır.

NASH Tarihçe

- 1968;

  "Alcohol-induced hepatic injury in nonalcoholic volunteers“

  New England Journal of Medicine

- 1979;

  "Non-alcoholic liver disease mimicking alcoholic hepatitis and cirrhosis"

  Gastroenterology

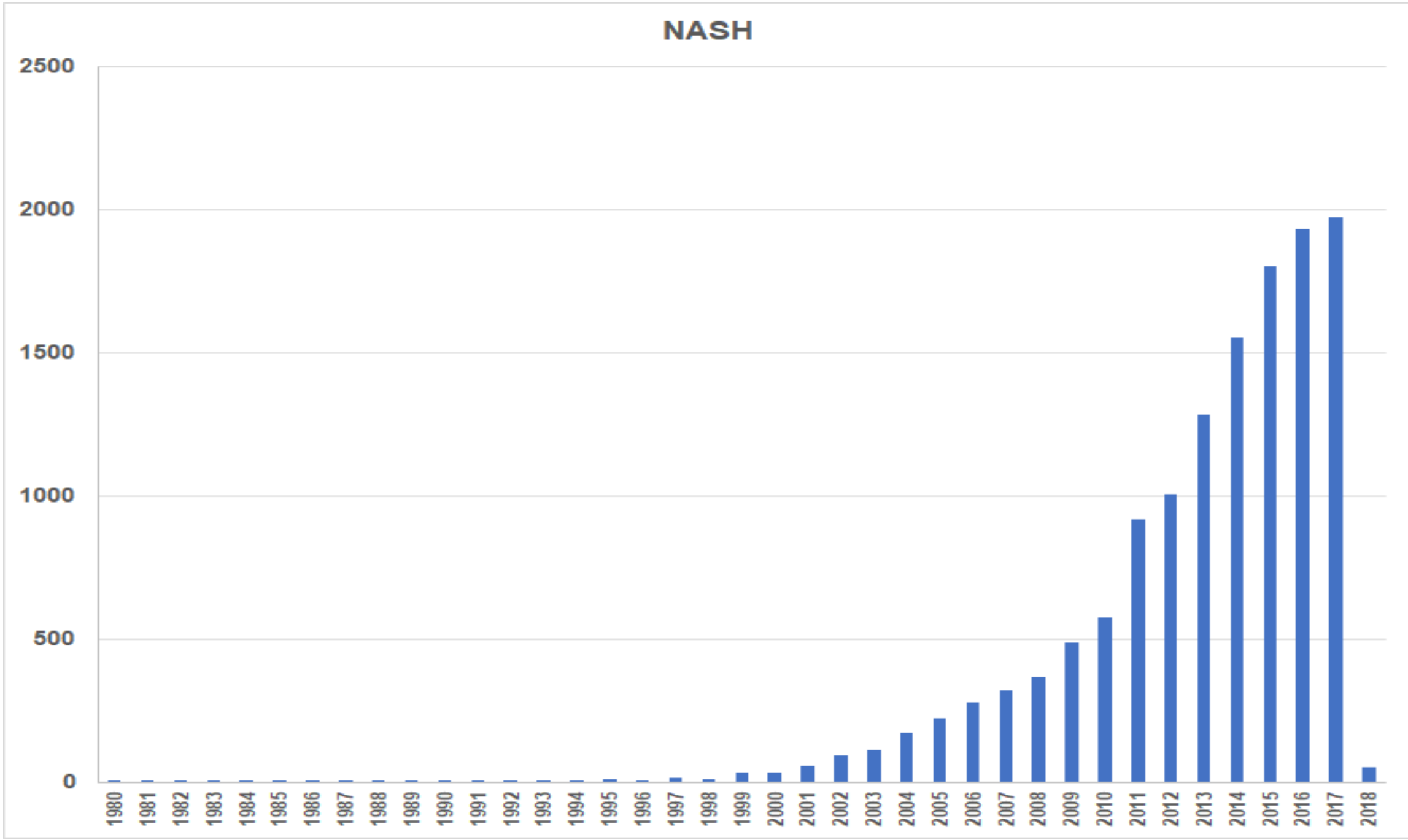
Mayo Clin Proc. 1980 Jul;55(7):434-8.

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.

Ludwig J, Viggiano TR, McGill DB, Oh BJ.

Abstract

Nonalcoholic steatohepatitis is a poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Described here are findings in 20 patients with nonalcoholic steatohepatitis of unknown cause. The biopsy specimens were characterized by the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates, and, in most instances, Mallory bodies; Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings. Currently, we know of no effective therapy.


NASH
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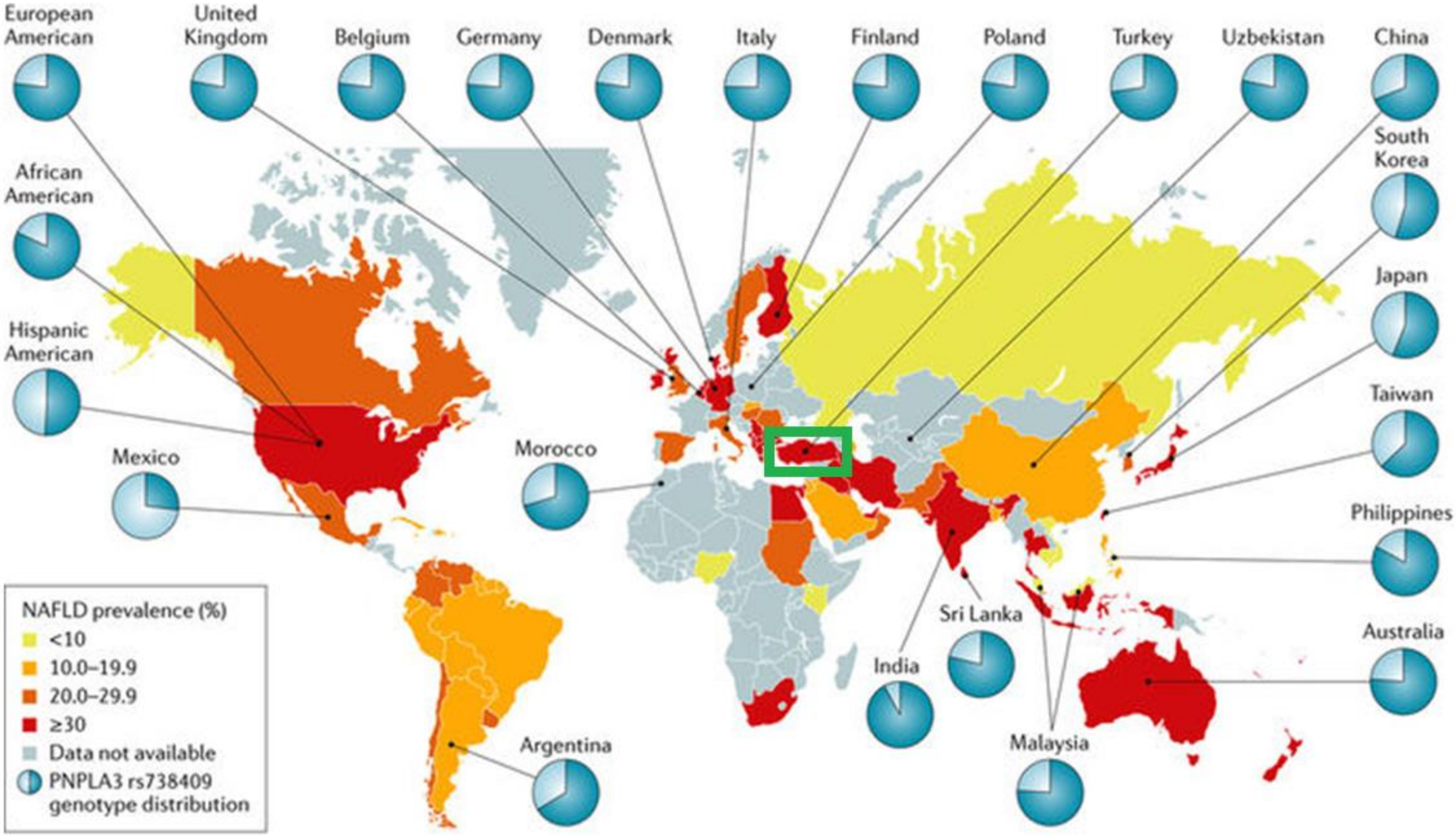
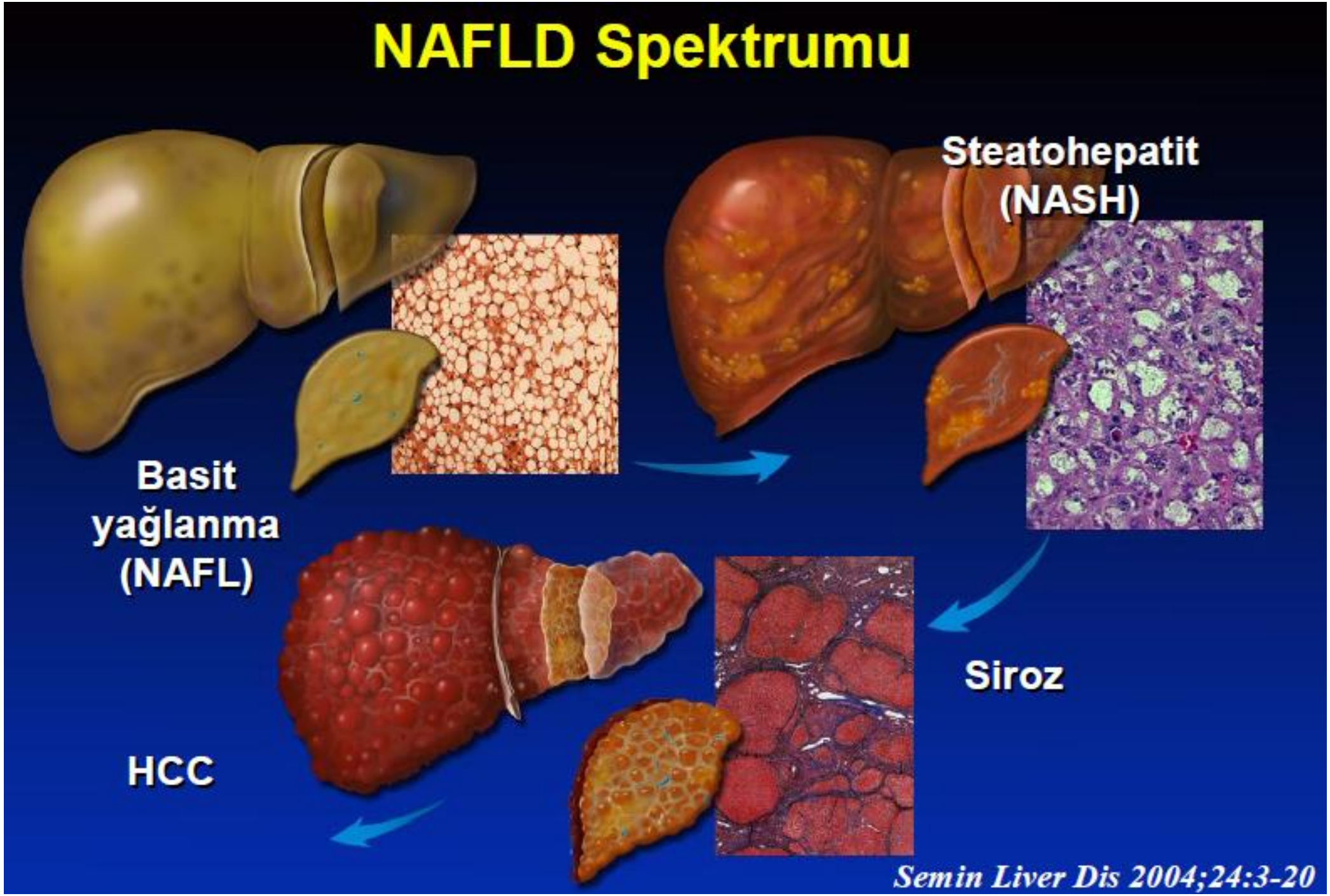

European American
United Kingdom
Belgium
Germany
Denmark
Italy
Finland
Poland
Turkey
Uzbekistan
China
South Korea
African American
Japan
Hispanic American
Taiwan
Mexico
Morocco
Philippines
Sri Lanka
Australia
India
Malaysia
Argentina
NAFLD prevalence (%)
<10
10.0–19.9
20.0–29.9
≥30
Data not available
PNPLA3 rs738409 genotype distribution

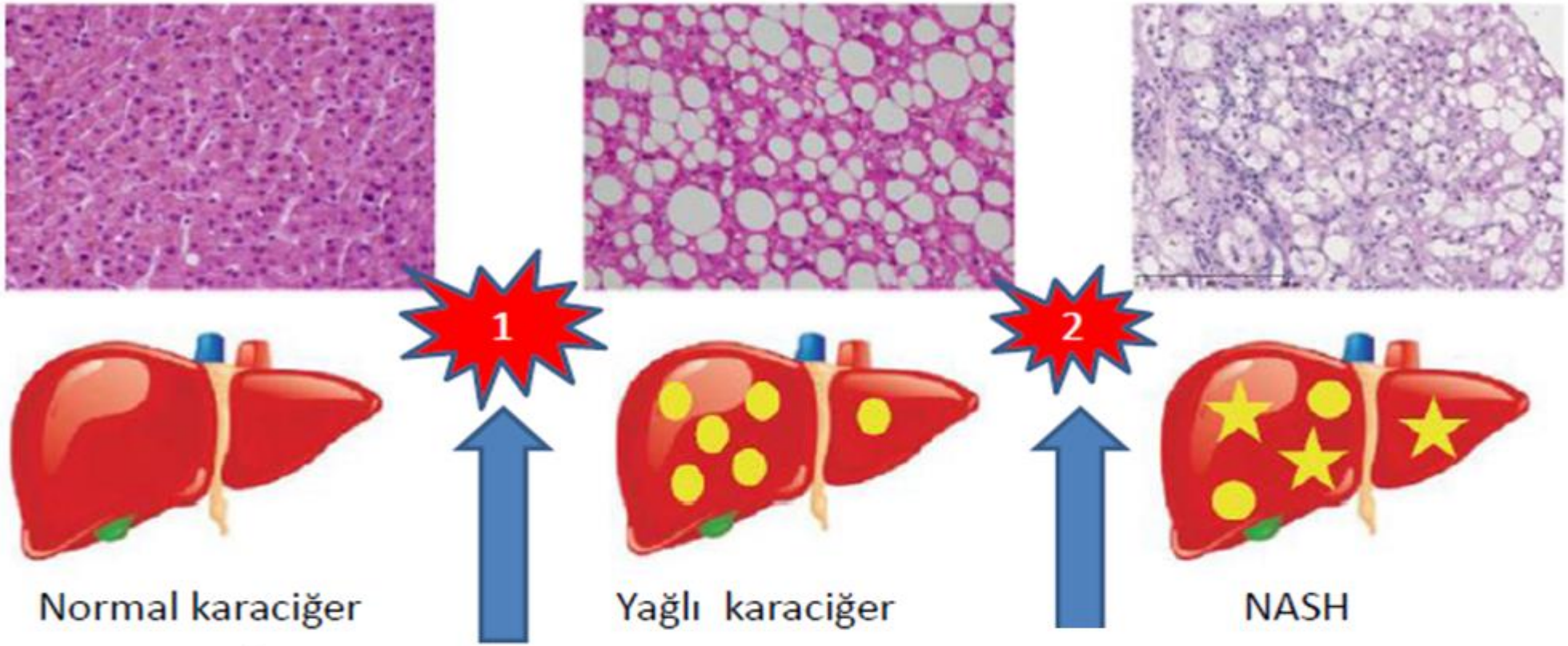
2020

Prevalence of NAFLD and NASH

- Too much fat in the liver (NAFLD)
  - > 30% of adults
  - 13% of children
- Fat plus significant injury (NASH)
  - 3-4% of all adults
  - 15-20% of obese adults
  - 25-70% of people having bariatric surgery

NAFLD Spektrumu





İnsülin direnci

Obezite

Genetik faktörler

Çevresel faktörler

Nekroinflamatuvar Aktivite

İnflamatuvar sitokinler

Oksidatif stres, lipid peroksidasyonu

Mitokondrial disfonksiyon

Adipositokin dengesizliği

Kuppfer hücre disfonksiyonu

Stellat hücre aktivasyonu

Day C, James O. Steatohepatitis: A tale of two “hits”? Gastroenterology 1998;114: 842.

BMI ≥30

BASİT YAĞLI KARACİĞER

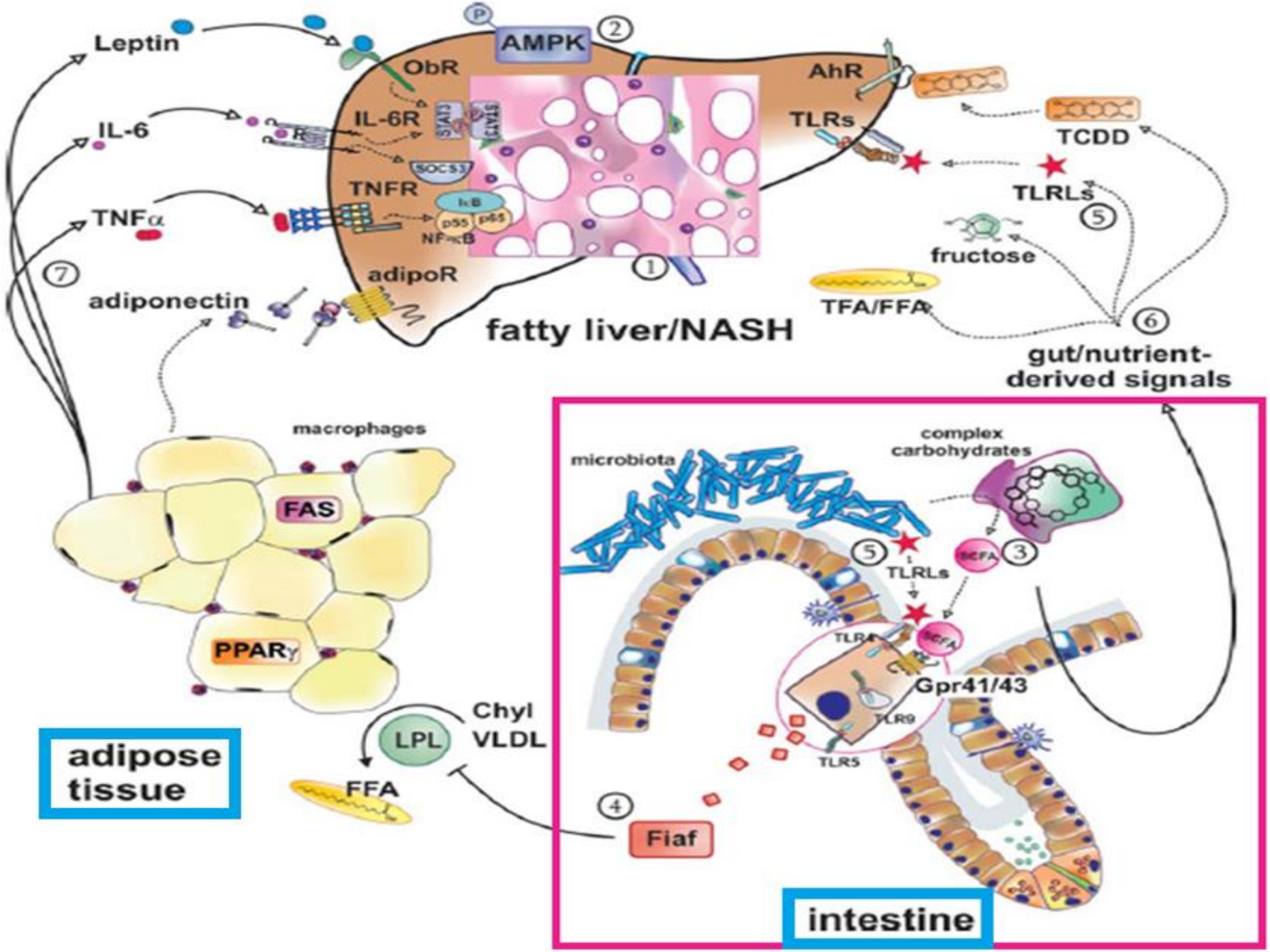
BMI <25

NASH

Evolution of Inflammation in Nonalcoholic Fatty Liver Disease: The Multiple Parallel Hits Hypothesis

Herbert Tilg and Alexander R. Moschen

Whereas in most cases a fatty liver remains free of inflammation, 10%-20% of patients who have fatty liver develop inflammation and fibrosis (nonalcoholic steatohepatitis [NASH]). Inflammation may precede steatosis in certain instances. Therefore, NASH could reflect a disease where inflammation is followed by steatosis. In contrast, NASH subsequent to simple steatosis may be the consequence of a failure of antilipotoxic protection. In both situations, many parallel hits derived from the gut and/or the adipose tissue may promote liver inflammation. Endoplasmic reticulum stress and related signaling networks, (adipo)cytokines, and innate immunity are emerging as central pathways that regulate key features of NASH. (HEPATOLOGY 2010;52:1836-1846)

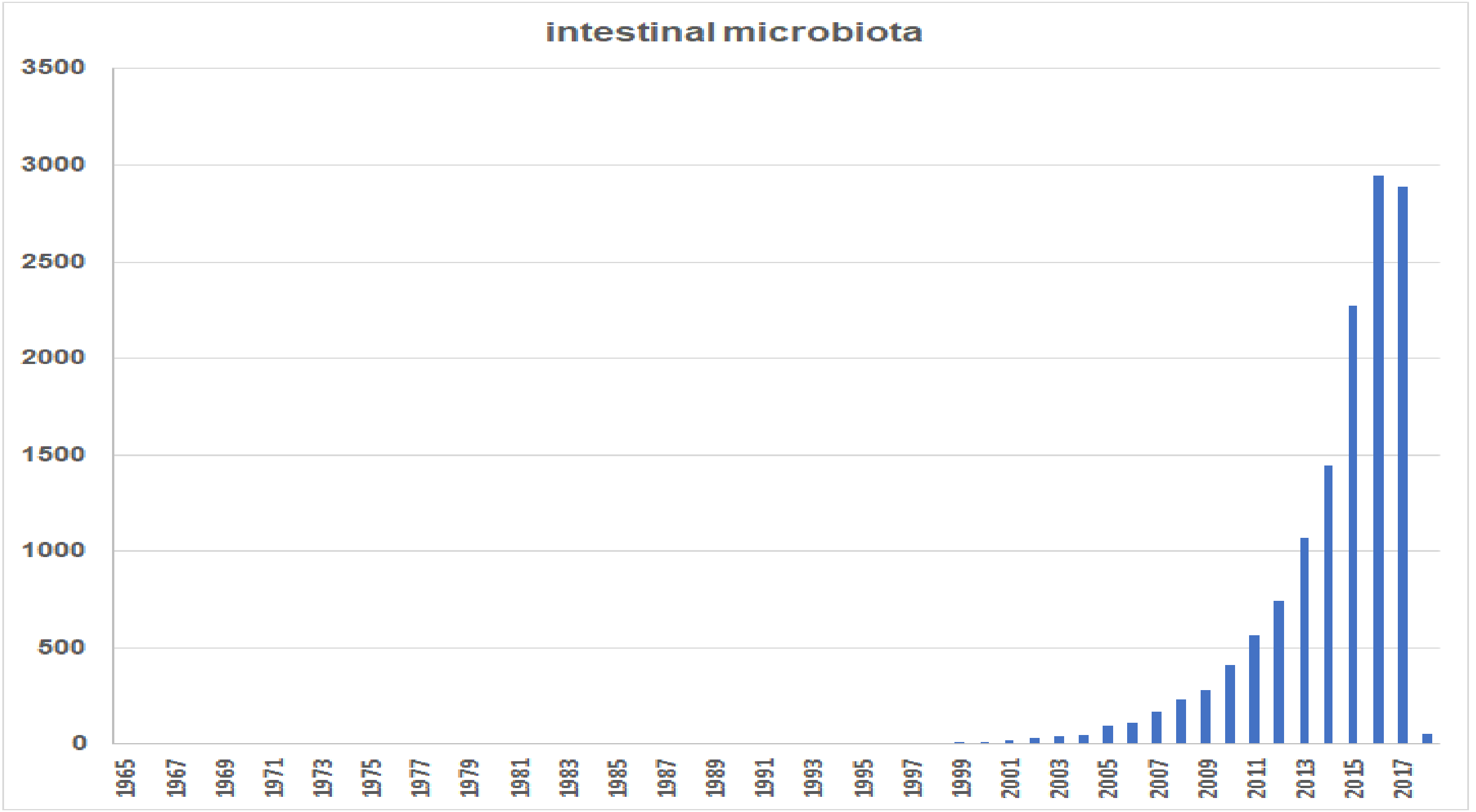

Leptin
IL-6
TNFα
adiponectin
ObR
IL-6R
TNFR
adipoR
AMPK
AhR
TLRs
TCDD
TLRLs
fructose
TFA/FFA
gut/nutrient-derived signals
fatty liver/NASH
macrophages
FAS
PPARγ
adipose tissue
LPL
Chyl VLDL
FFA
Fiaf
microbiota
complex carbohydrates
SCFA
TLR4
TLR9
TLR5
Gpr41/43
intestine

Siz ne yediğinizsiniz.

Siz annenizin ne yediğisiniz.

Siz büyükannenizin ne yediğisiniz.

Siz mikrobiomunuzun ne yediğisiniz.


intestinal microbiota
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2017

The Nobel Prize in Physiology or Medicine 1958

George Wells Beadle
Prize share: 1/4

Edward Lawrie Tatum
Prize share: 1/4

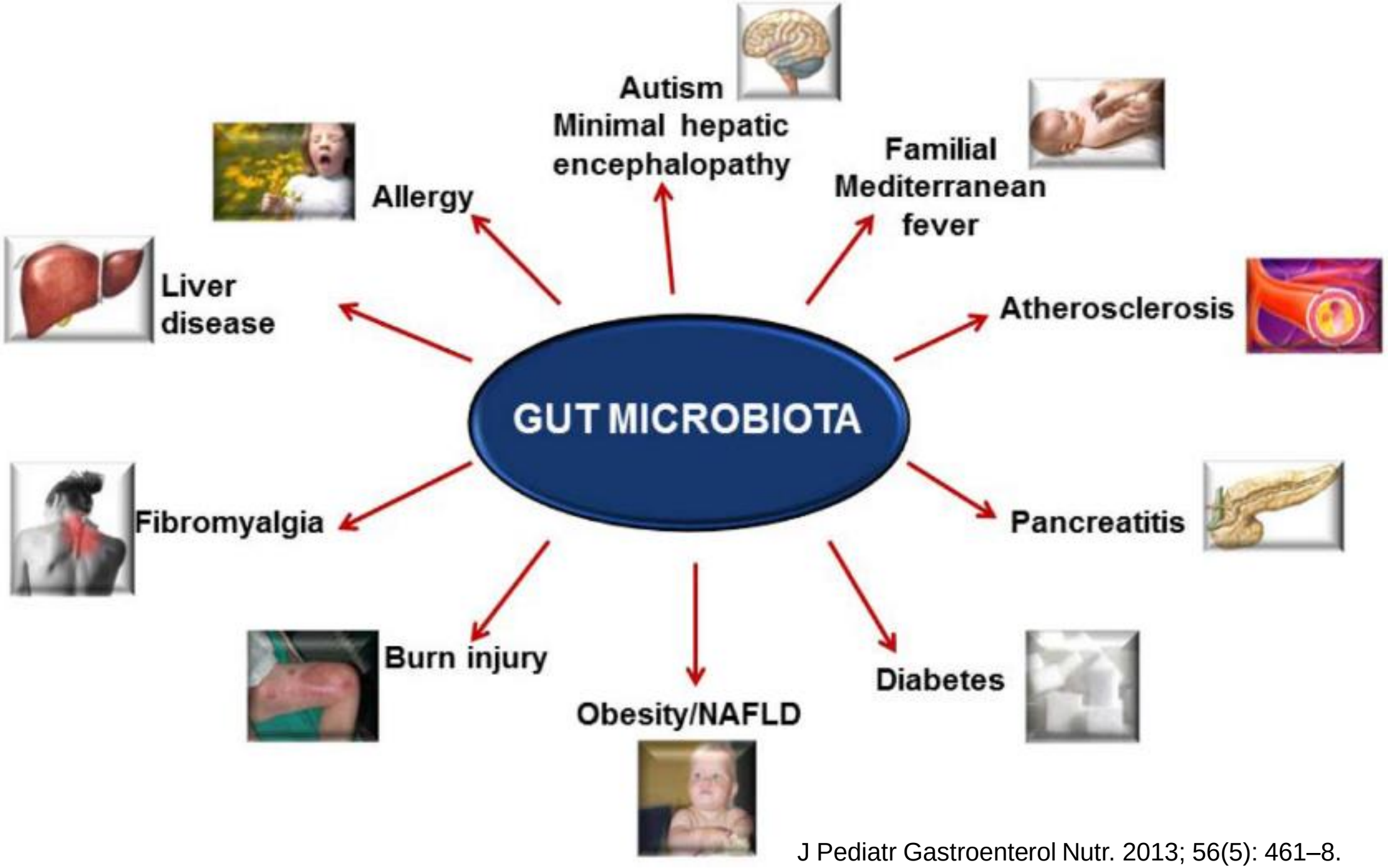
Joshua Lederberg
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1958 was divided, one half jointly to George Wells Beadle and Edward Lawrie Tatum *"for their discovery that genes act by regulating definite chemical events"* and the other half to Joshua Lederberg *"for his discoveries concerning genetic recombination and the organization of the genetic material of bacteria"*.

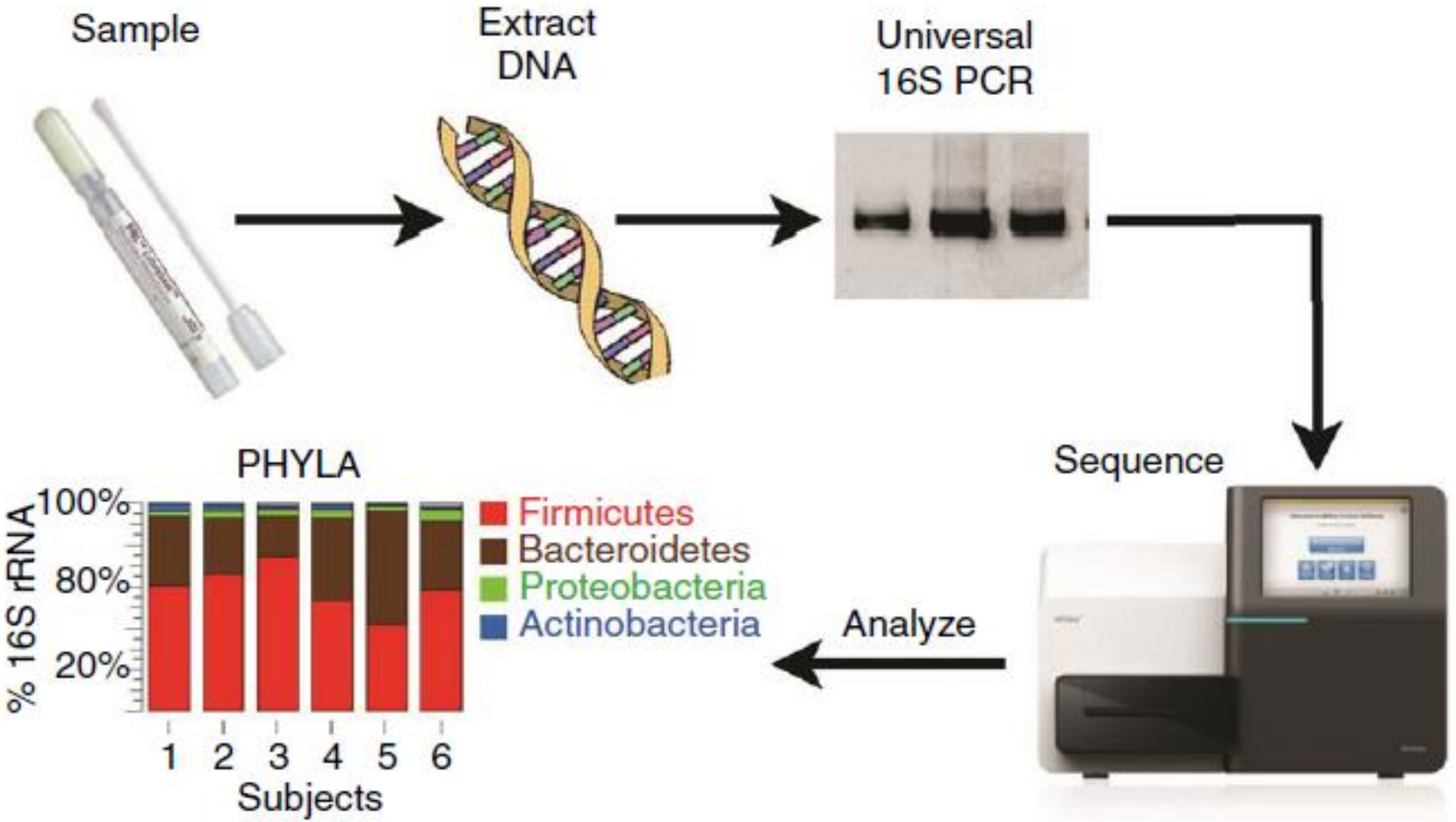
Mikrobiyota terimi

Alkol dışı yağlı karaciğer gelişiminde mikrobiyotanın rolü ilk defa **1982** yılında Drenick ve ark. tarafından belirtiliyor.

Drenick, E.J.,et al. Hepatic steatosis after intestinal bypass e prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. Gastroenterology 1982;82(3):535e548.



J Pediatr Gastroenterol Nutr. 2013; 56(5): 461–8.



Wieland A. Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2015; 42: 1051–63.

NASH Gelişimindeki İntestinal Mikrobiyota Kaynaklı Faktörler

1. İnce barsakta aşırı bakteri üremesi (SIBO)
2. Barsak mikrobiyotasının bozulması (Disbiyozis)
3. İntestinal bariyer disfonksiyonu ve permeabilite artışı
4. İnflamasyon
5. Endotoksinler
6. Etanol
7. Metabolik bozukluklar

1. İnce Barsakta Aşırı Bakteri Üremesi (SIBO)

ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2016/n2/a7
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.252.iwg

Small Intestinal Bacterial Overgrowth Is Associated with Non-Alcoholic Fatty Liver Disease

Andrea Fialho[1], Andre Fialho[1], Prashanthi Thota[2], Arthur J. McCullough[2], Bo Shen[2]

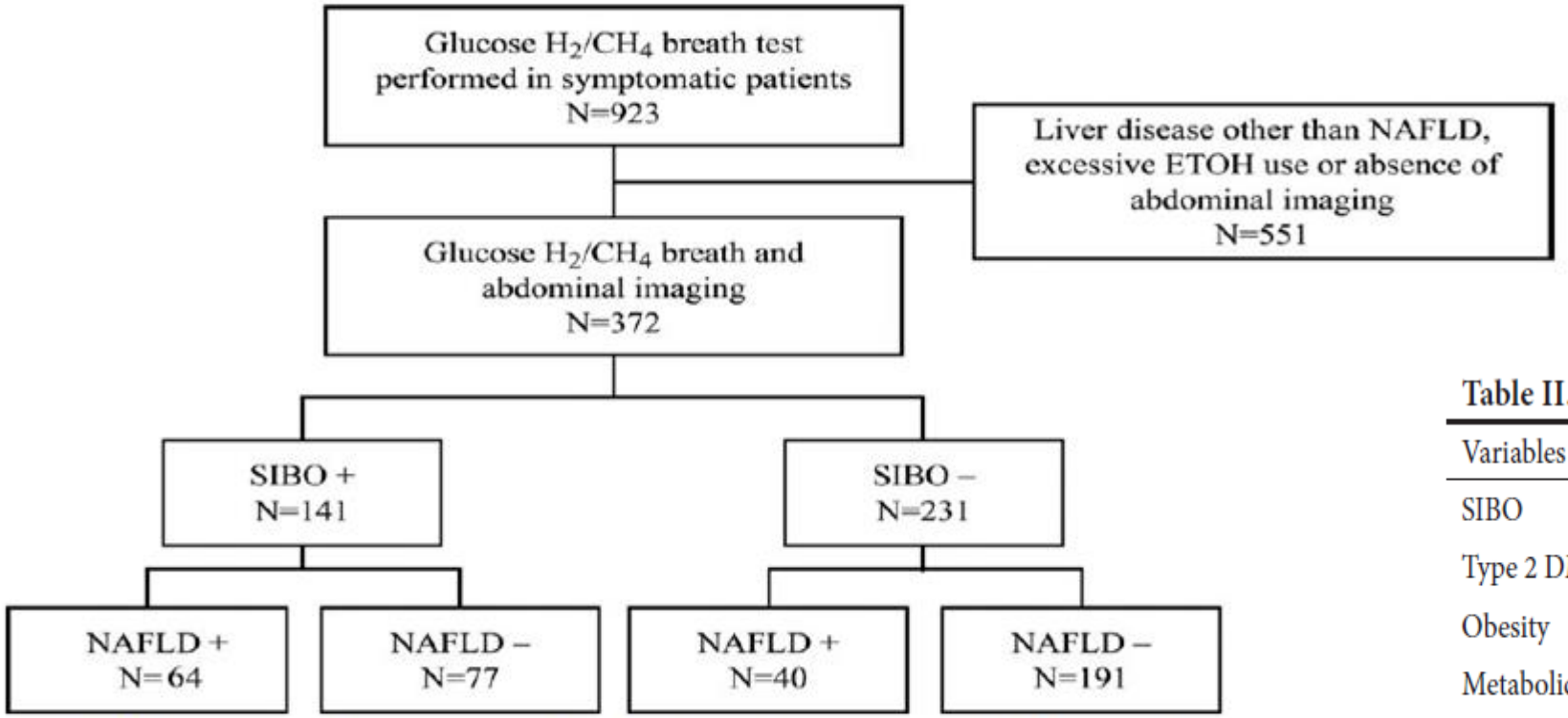
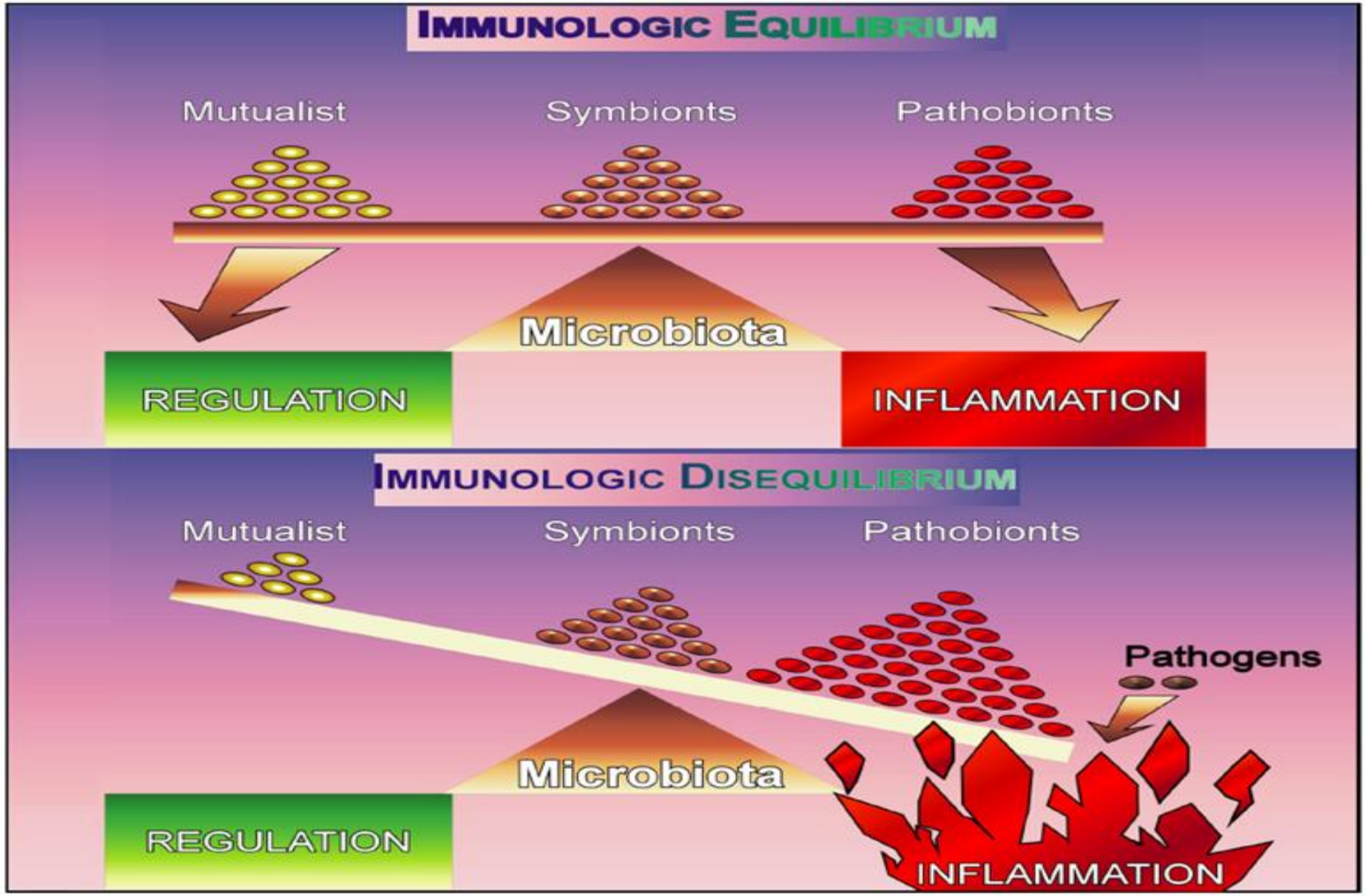


Fig. 1. Distribution of patients according to breath test results and abdominal imaging.

Table II. Multivariate analysis of the risk factors associated with NAFLD

Variables	Adjusted OR	95%CI	P
SIBO	1.95	1.14-3.31	0.014
Type 2 DM	3.04	1.57-5.90	0.001
Obesity	3.58	1.70-7.54	0.001
Metabolic syndrome	2.15	0.79-5.84	0.131
Hypertension	1.14	0.55-2.39	0.716

2. Barsak Mikrobiyotasının Bozulması (Disbiyozis)



- >2000 farklı tür
- Trilyonlarca mikroorganizma
- 1,5-2 kg

Round and Mazmanian
Nat Rev Immunol. 2009 May ; 9(5): 313–323.

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Intestinal Microbiota in Patients With Nonalcoholic Fatty Liver Disease

Marialena Mouzaki,[1,2] Elena M. Comelli,[3] Bianca M. Arendt,[2] Julia Bonengel,[2] Scott K. Fung,[2,4] Sandra E. Fischer,[2,5] Ian D. McGilvray,[2,4] and Johane P. Allard[2,3,4]

(HEPATOLOGY 2013;58:120-127)

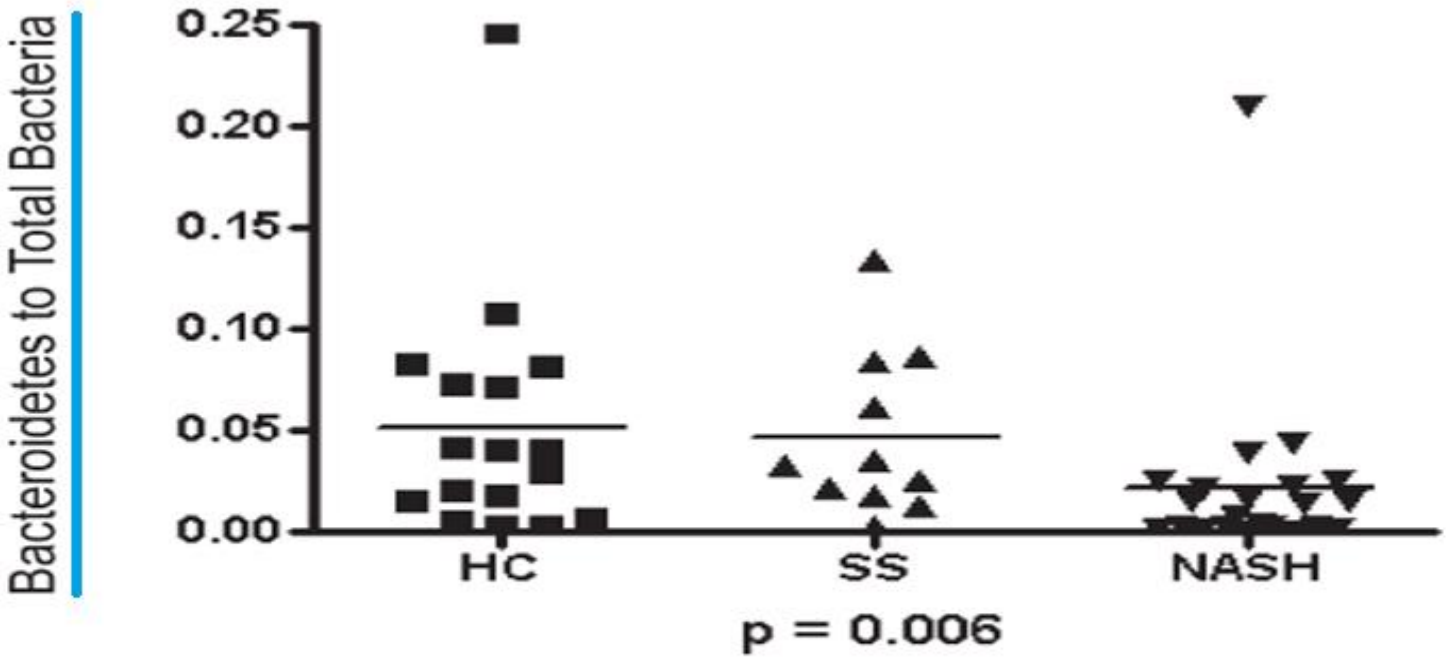
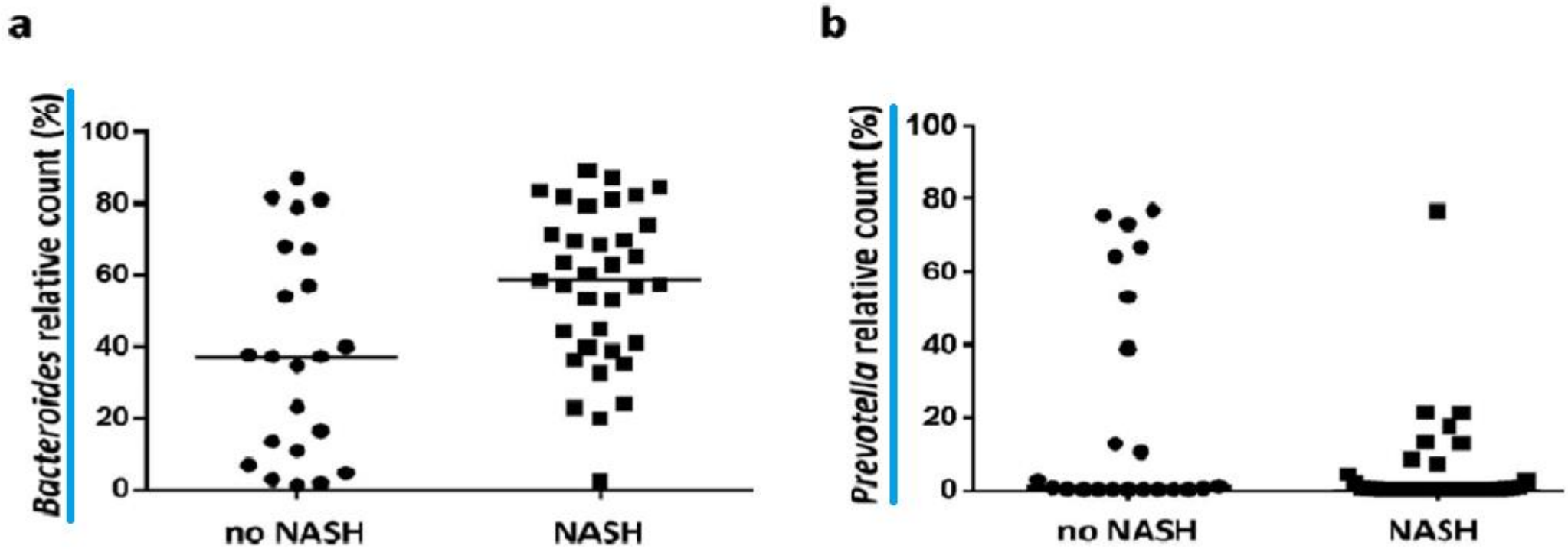


Fig. 2. Comparisons for percentage Bacteroidetes (Bacteroidetes to total bacteria ratio) in stool between the groups. Patients with NASH have lower fecal percentage Bacteroidetes compared to both patients with SS and HC. N = 17 HC, 11 SS, 22 NASH.

Published in final edited form as:
Hepatology. 2016 March ; 63(3): 764–775. doi:10.1002/hep.28356.

The severity of NAFLD is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota

Jérôme Boursier[1,2], Olaf Mueller[3], Matthieu Barret[4], Mariana Machado[5], Lionel Fizanne[2], Felix Araujo-Perez[6], Cynthia D. Guy[7], Patrick C. Seed[3,4,5,6], John F. Rawls[3], Lawrence A. David[3], Gilles Hunault[2], Frédéric Oberti[1,2], Paul Calès[1,2], and Anna Mae Diehl[5]



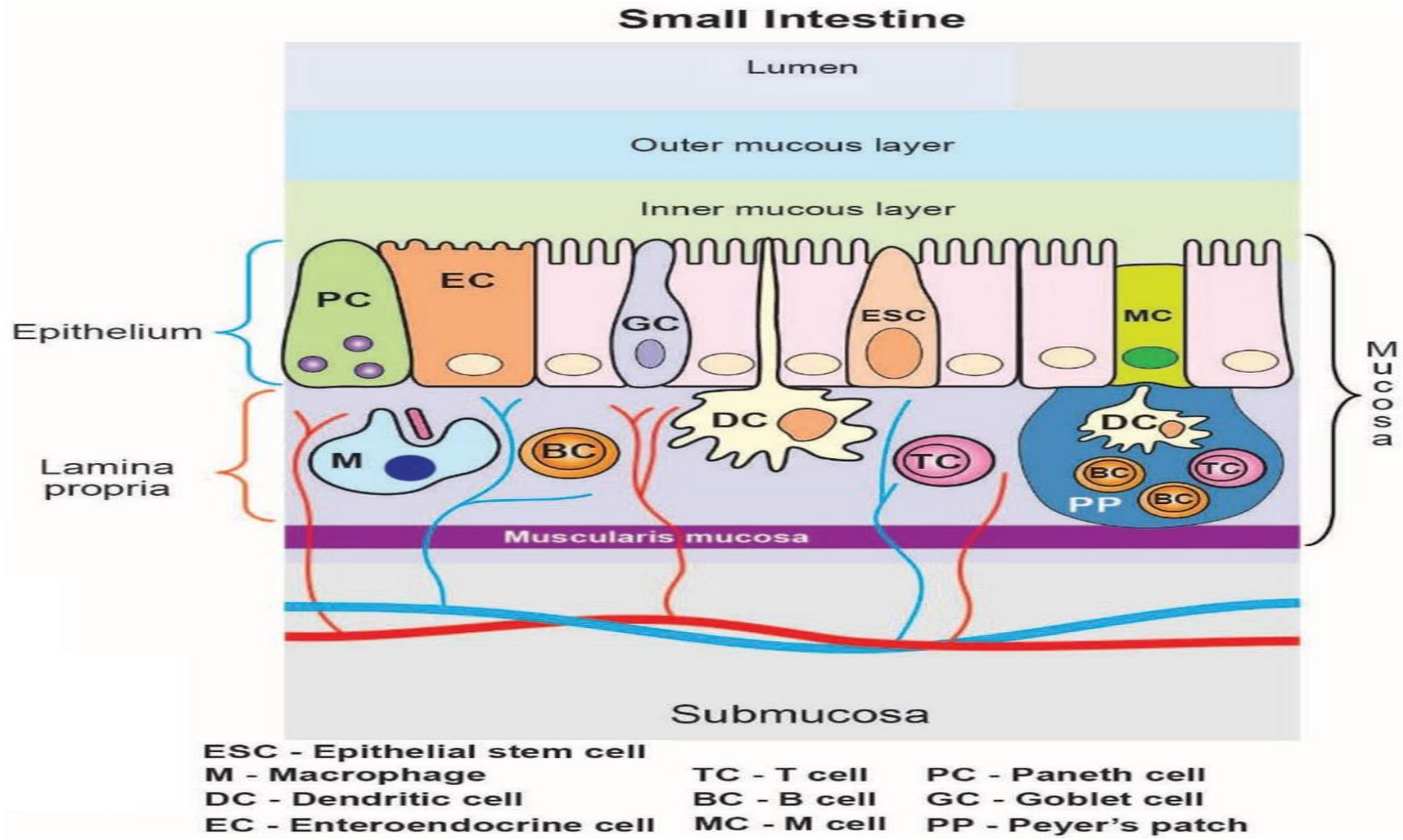
Figures 2a/2b: NASH patients had higher abundance of gut *Bacteroides* (p=0.013) and lower abundance of *Prevotella* (p=0.053).

Table 1 | Human studies of microbiota composition in NAFLD

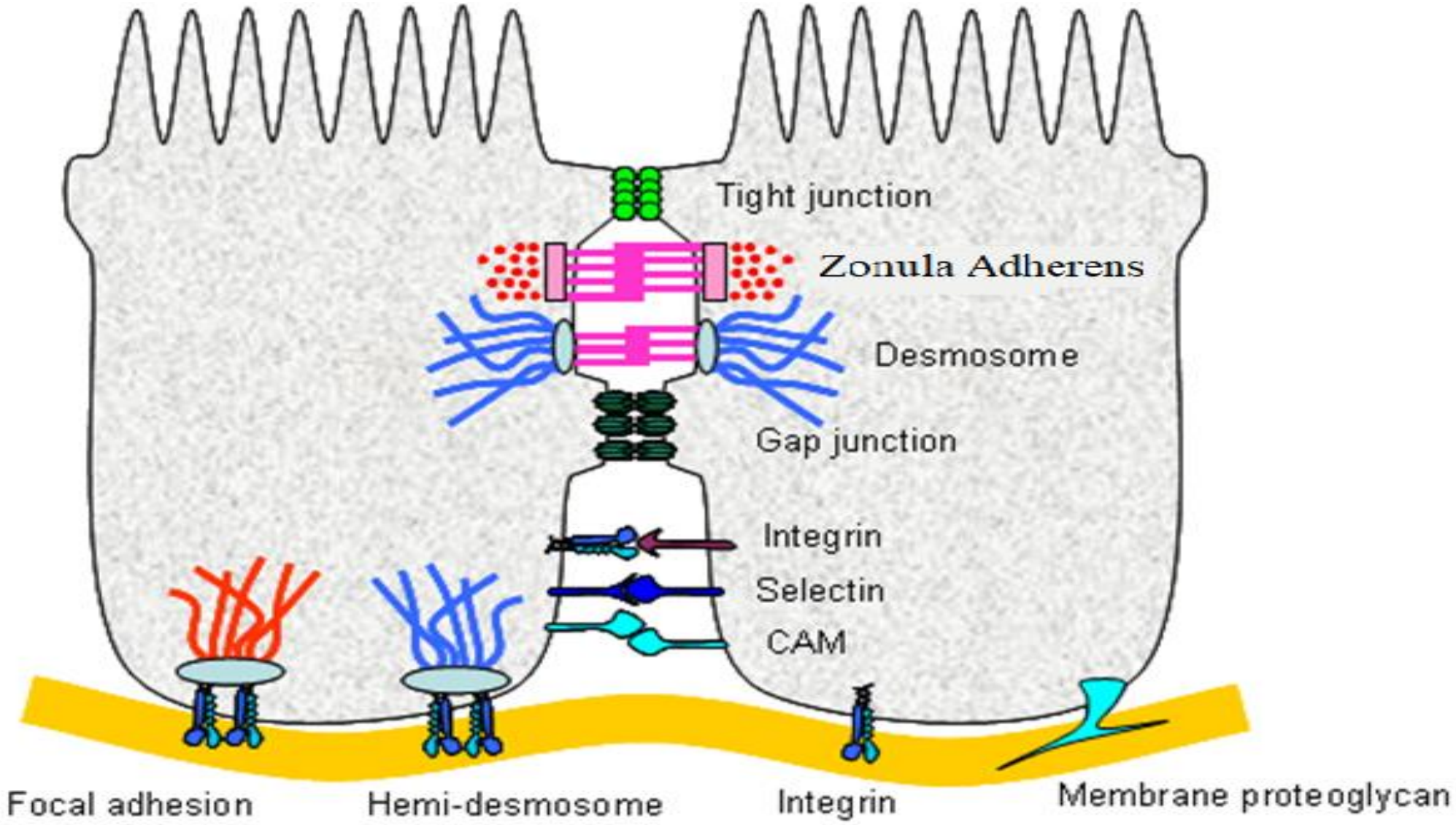
Study	Population	Serial Samples	Biopsy-proven NASH	Phyla differences	Other important differences	Hypothesised mechanism
Zhu *et al.*[56]	Sample size: 63 children 22 NASH by biopsy 25 obese (normal liver tests, no biopsy) 16 Healthy Control (no liver biopsy)	No	Yes	Actinobacteria: Increased in Obese and NASH vs. Healthy Control Bacteroidetes: Increased in Obese and NASH vs. Healthy Control Firmicutes: Decreased in Obese and NASH vs. Healthy Control Proteobacteria: increased in Obese vs. NASH vs. Healthy Control	Escherichia: Increased in NASH vs. obese	Increased alcohol bloo levels measured in NASH vs. Obese and Controls No difference in endotoxin levels[61]
Mouzaki *et al.* 2013[57]	Sample size: 50 adults 11 Simple Steatosis on biopsy 22 NASH on biopsy 17 Healthy Control (normal liver on biopsy)	No	Yes	Bacteroidetes: decreased in NASH vs. Simple Steatosis and Healthy Control	NASH increased C. coccoides compared with Simple steatosis (not significant after adjust for BMI and fat intake)	–
Raman *et al.* 2013[58]	Sample size: 60 adults 30 Obese with clinical diagnosis of NAFLD 30 Non-obese Healthy Control	No	No	Firmicutes: selective subgroups increased in NAFLD	Increased lactobacillus in NAFLD Decreased Ruminacoccaceae within Firmicutes	Increased volatile organic compounds in NAFLD
Wong *et al.* 2013[59]	Sample size: 38 adults 16 NASH on biopsy 7 treated with 6 months probiotics 9 standard of care 22 Healthy Control (no liver biopsy)	Yes: in NASH patients only Baseline stool samples. Repeat stool samples after 6 months of probiotic therapy vs. standard of care	Yes	*Baseline:* Bacteroidetes: remained the same between groups Firmicutes: Decreased in NASH vs. controls *After 6 months:* Bacteroidetes: increased percentage correlated with reduced hepatic fat content Firmicutes: Decreased percentage correlated with reduced hepatic fat content	*Baseline:* *Class:* Clostridia: Decreased in NASH vs. control Unclassified Firmicutes: decreased in NASH vs. control *Order:* Aeromonadales: increased in NASH vs. control Clostridiales: decreased in NASH vs. control	–

Wieland A, et al. Aliment Pharmacol Ther 2015; 42: 1051–1063

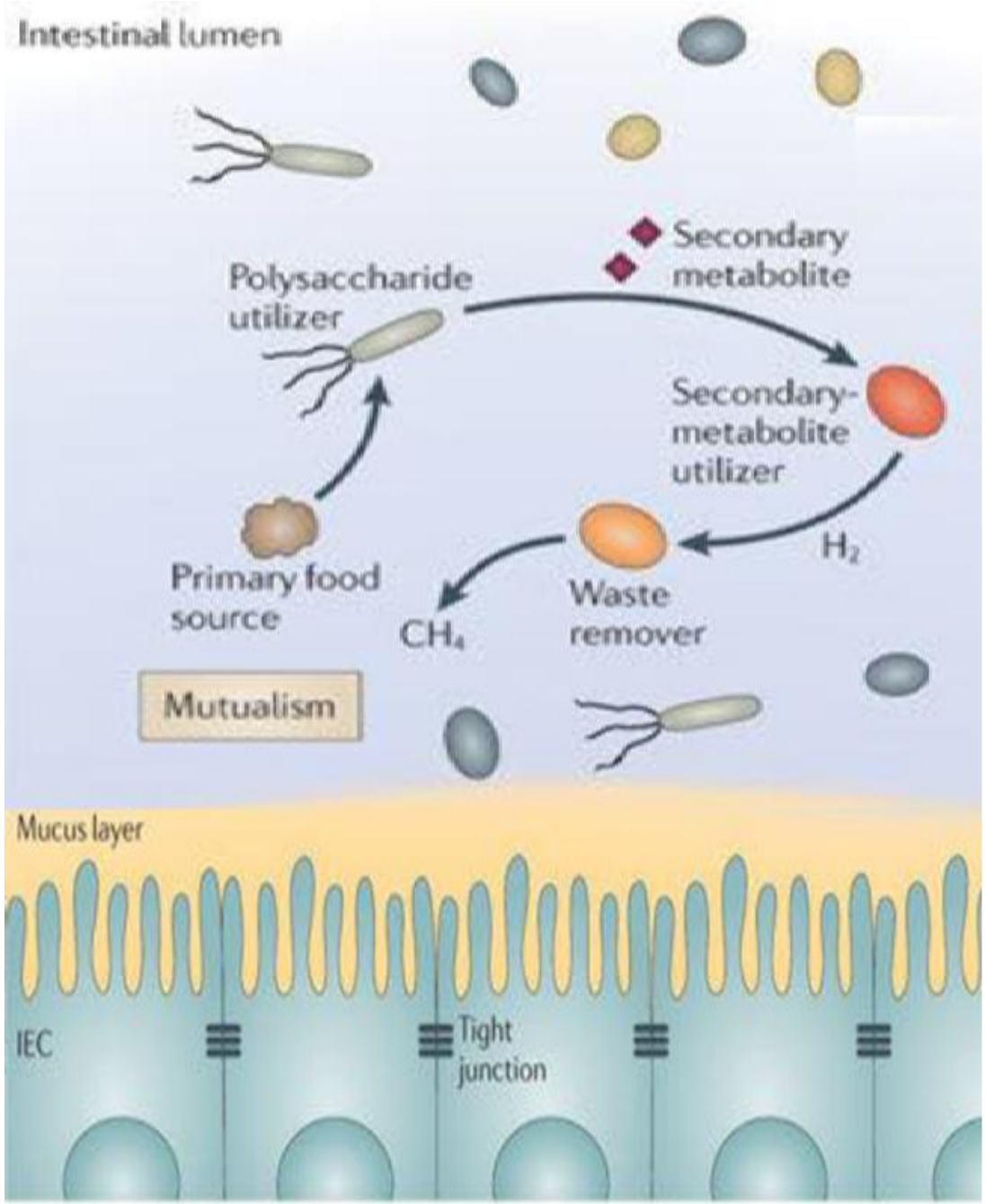
3. İntestinal Bariyer Disfonksiyonu



3. İntestinal Bariyer Disfonksiyonu

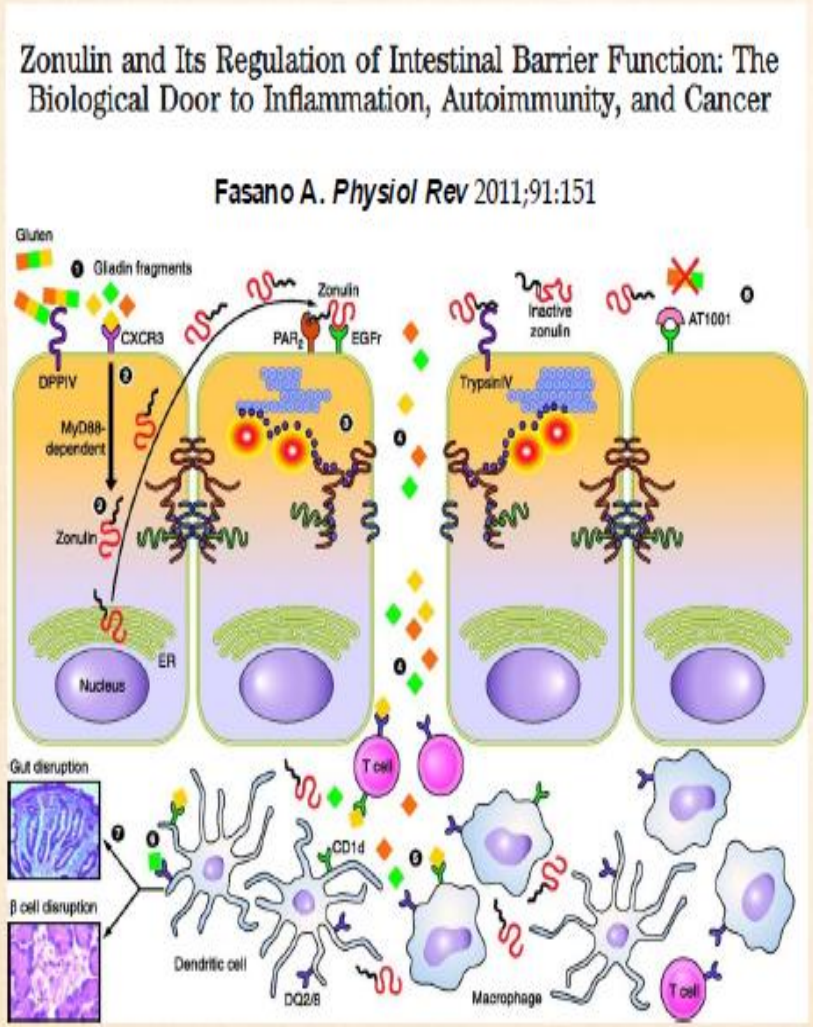


Glucagon-like peptide 2 is a regulator of TJ protein expression



Leaky Gut

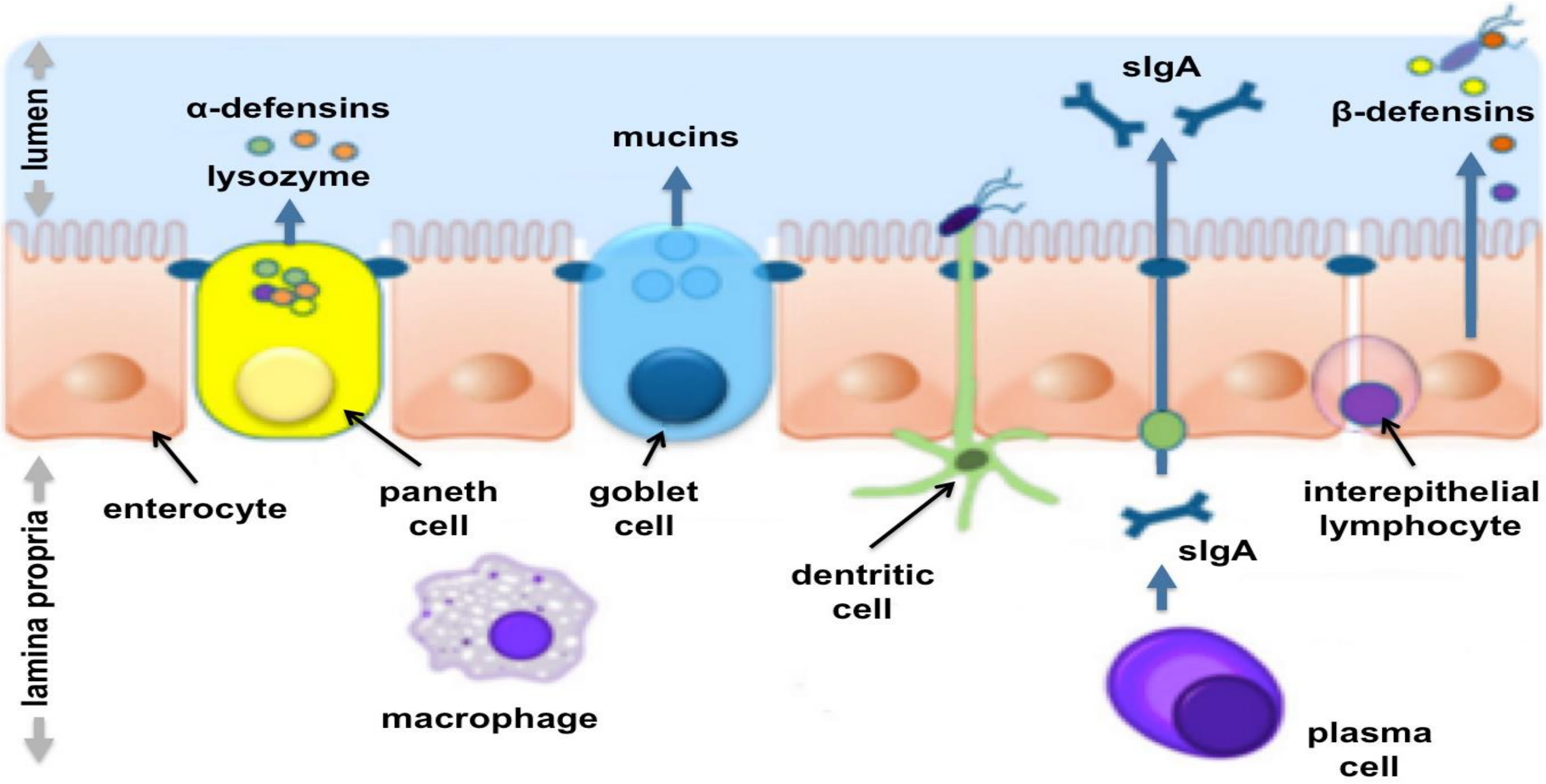
Loss of Tight Junction Functional Integrity

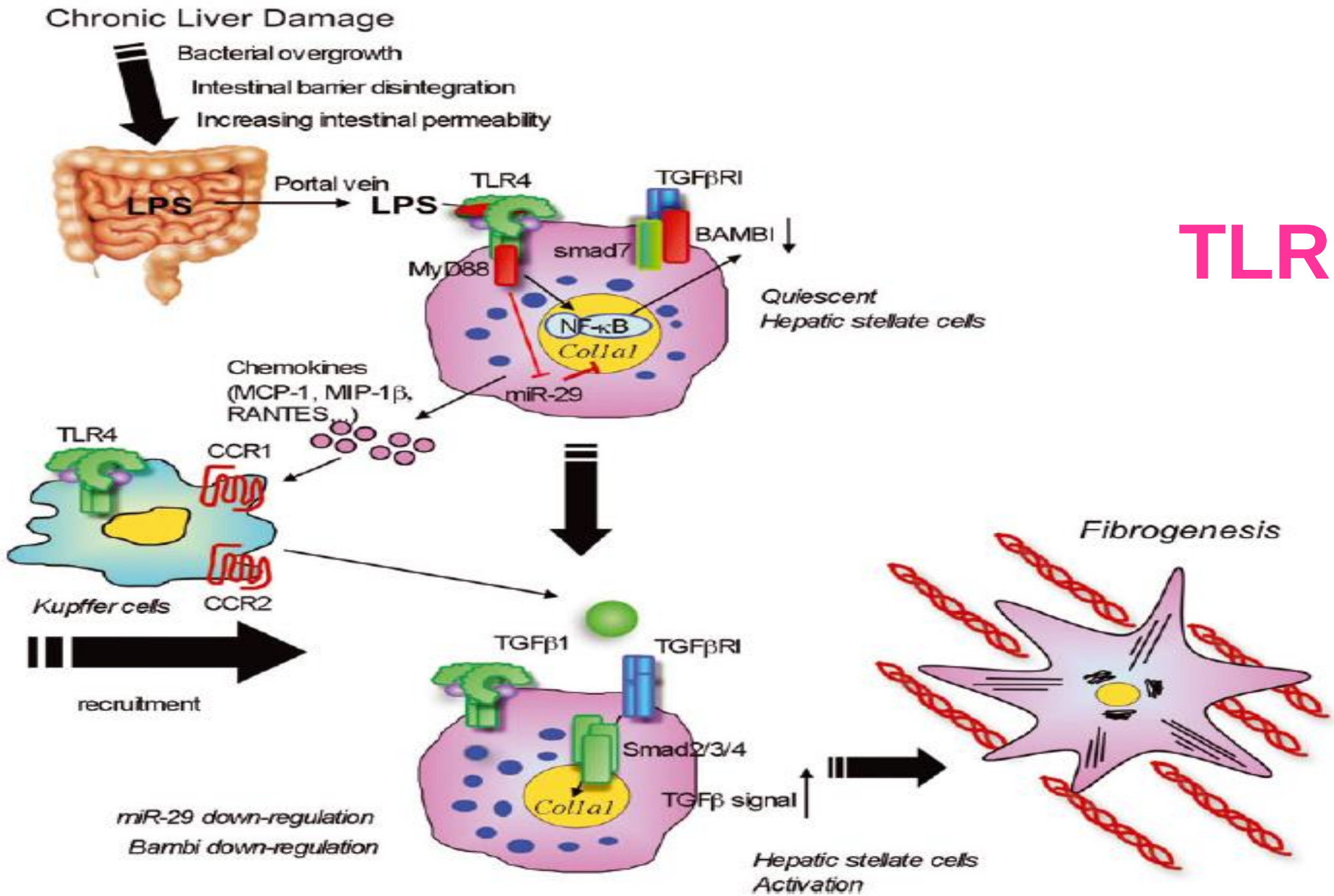


Cascade Effects

- Maldigestion
- Gluten sensitivity
- Delayed food sensitivities
- Dysbiosis
- Nutrient malabsorption
- Bacterial overgrowth
- Yeast overgrowth
- Bacterial translocation
- Metabolic endotoxemia
- Systemic inflammation
- Neuro-inflammation
- Autoimmune disorders
- Chronic toxicity

4. İnflamasyon





TLR

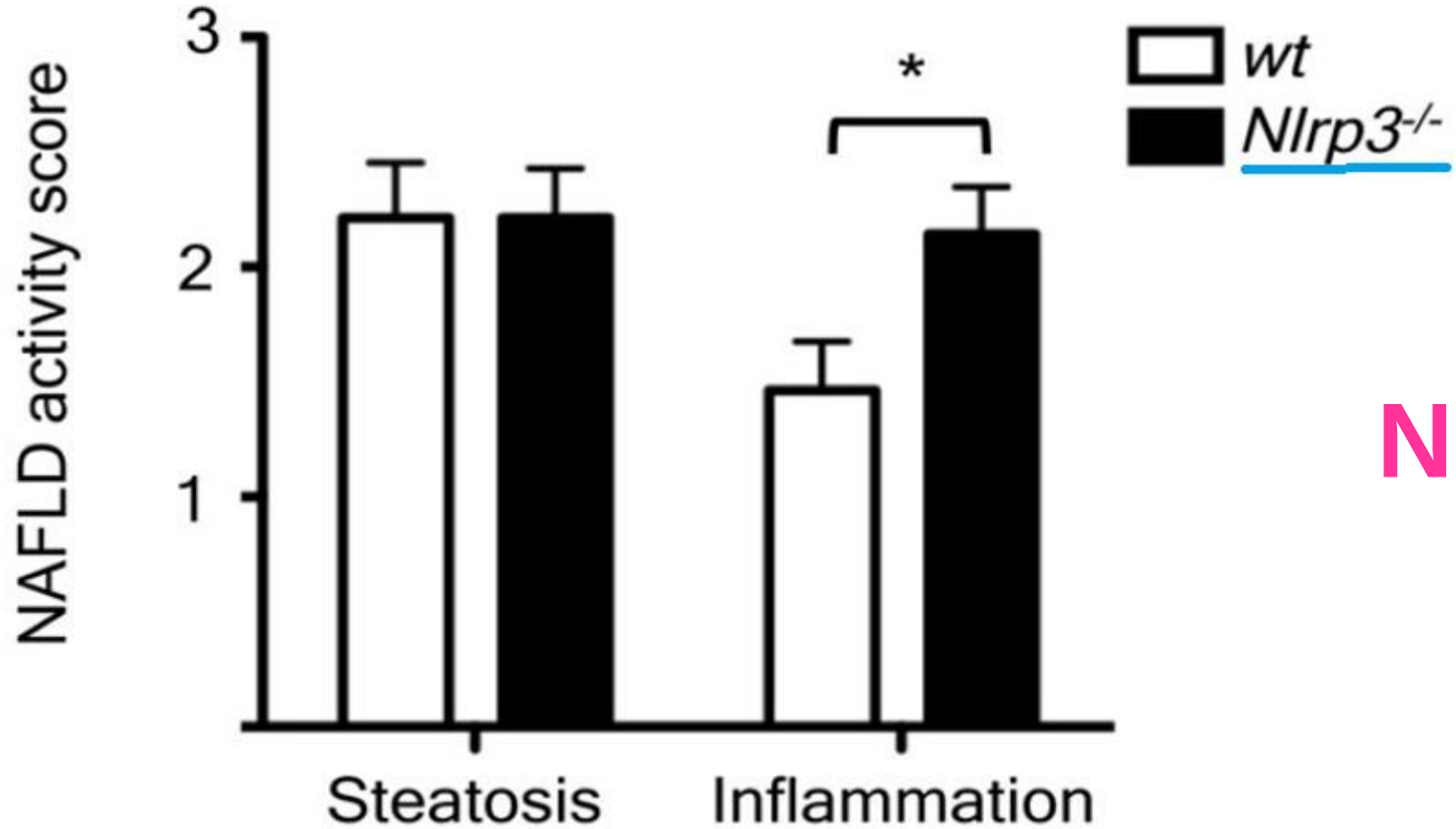
Ekihiro Seki and Bernd Schnabl. *J Physiol* 590.3 (2012) pp 447–58

Nature. ; 482(7384): 179–185. doi:10.1038/nature10809.

Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity

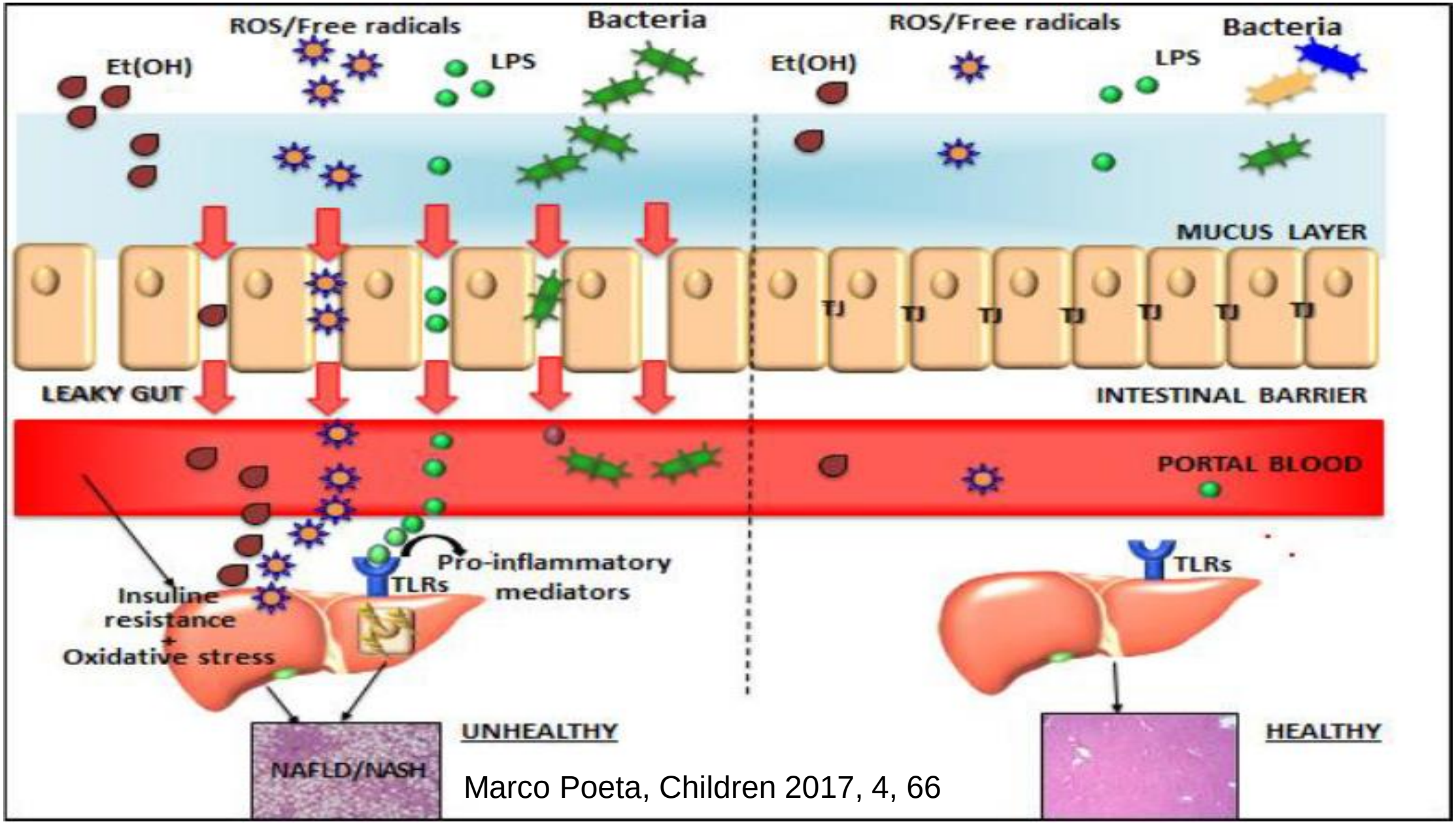
Jorge Henao-Mejia[1,*], **Eran Elinav**[1,*], **Cheng-Cheng Jin**[1,2,*], **Liming Hao**[3], **Wajahat Z. Mehal**[4], **Till Strowig**[1], **Christoph A. Thaiss**[1], **Andrew L. Kau**[5,6], **Stephanie C. Eisenbarth**[7], **Michael J. Jurczak**[4], **Joao-Paulo Camporez**[4], **Gerald I. Shulman**[4,9], **Jeffrey I. Gordon**[5], **Hal M. Hoffman**[8], and **Richard A. Flavell**[1,9,**]

[1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520



NLR

5. Endotoksinler



Marco Poeta, Children 2017, 4, 66

6. Etanol

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Characterization of Gut Microbiomes in Nonalcoholic Steatohepatitis (NASH) Patients: A Connection Between Endogenous Alcohol and NASH

Lixin Zhu,[1] Susan S. Baker,[1] Chelsea Gill,[2] Wensheng Liu,[1] Razan Alkhouri,[1] Robert D. Baker,[1] and Steven R. Gill[2]

(HEPATOLOGY 2013;57:601-609)

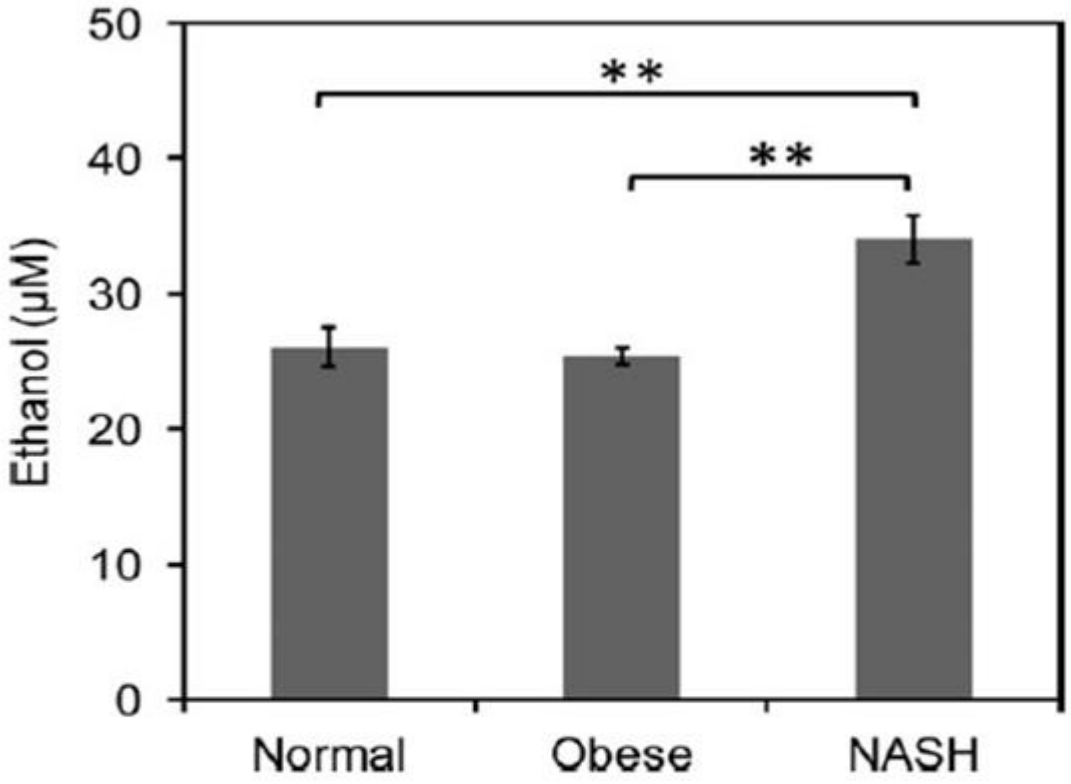
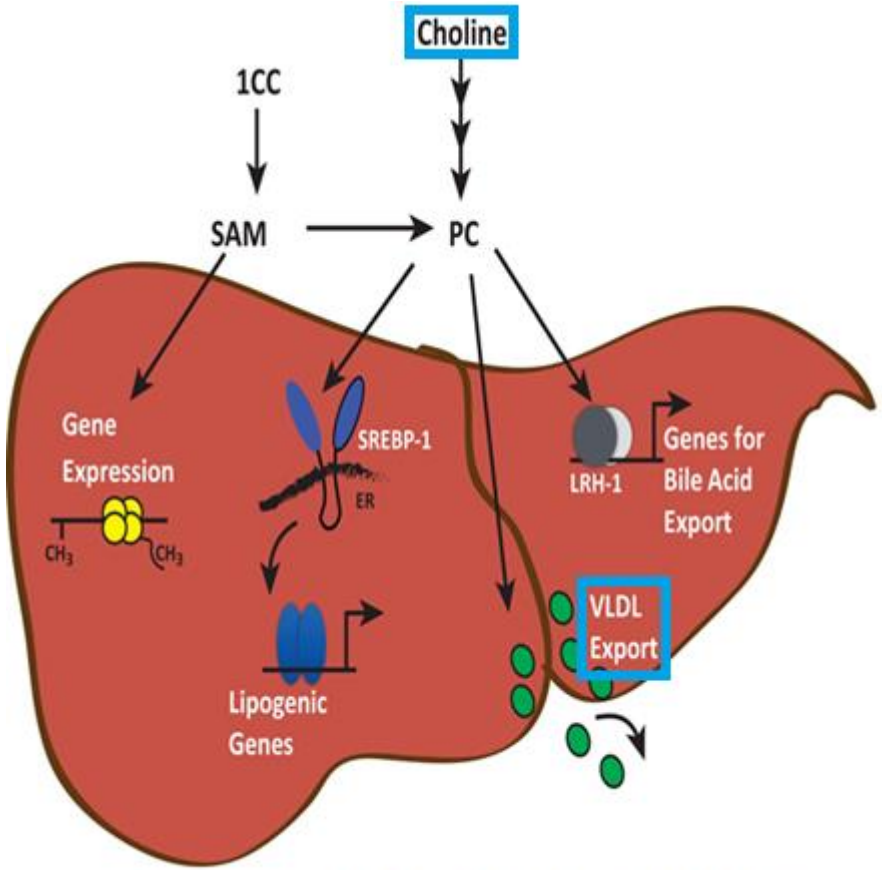
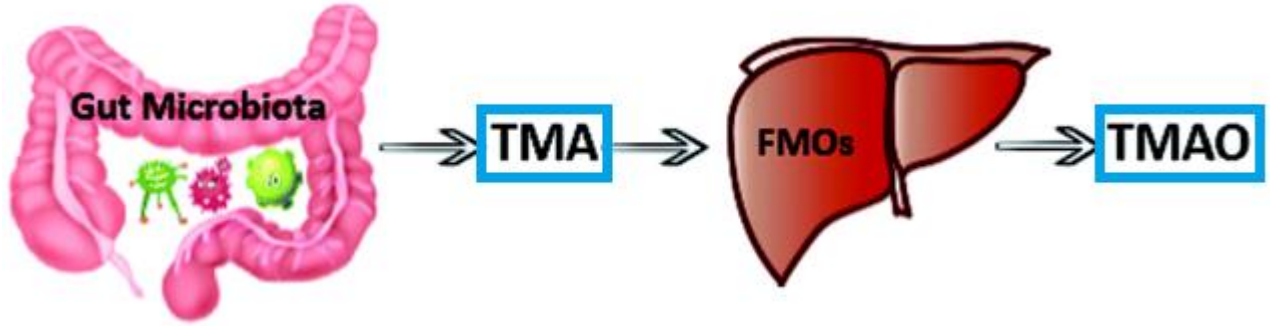


Fig. 4. Elevated serum ethanol concentration in NASH patients. Serum ethanol of healthy subjects (healthy; n = 10), obese patients (n = 7), and NASH patients (n = 13) were measured using an ethanol assay kit from BioVision (Milpitas, CA). Data represent mean ± standard error of the mean. Significant difference was detected among three groups ($P < 0.001$; ANOVA). $^{**}P < 0.01$ in Tukey's honest significance test.

7. Metabolik Bozukluklar



Walker AM. Trends in Endoc and Metabol. 2017;28:63



- Kolinden fakir diyet hepatosteatoz yapabilir. Çünkü VLDL'nin oluşumu ve karaciğerden sekresyonu için fosfatidil kolin gerekir.

- Disbiyozis durumunda diyetteki kolin toksik trimetilamine dönüşüp karaciğerde inflamasyonu indükleyen Trimetilamin-N-oksid'e dönüşür.

7. Metabolik Bozukluklar

PNAS

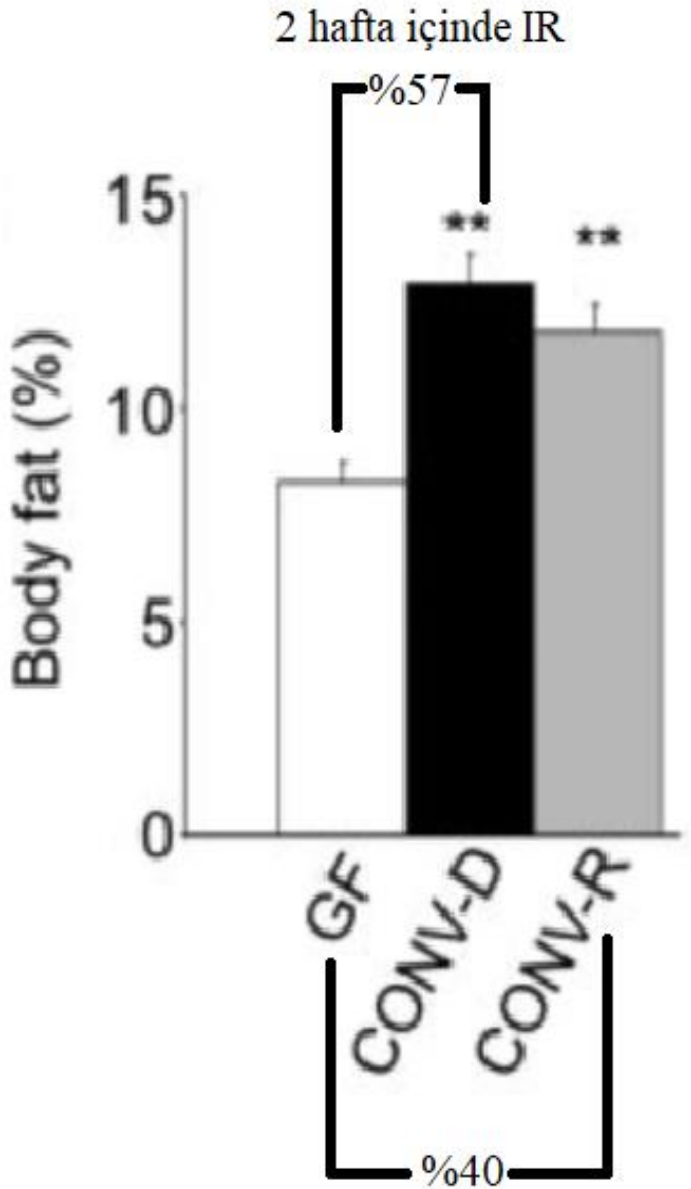
The gut microbiota as an environmental factor that regulates fat storage

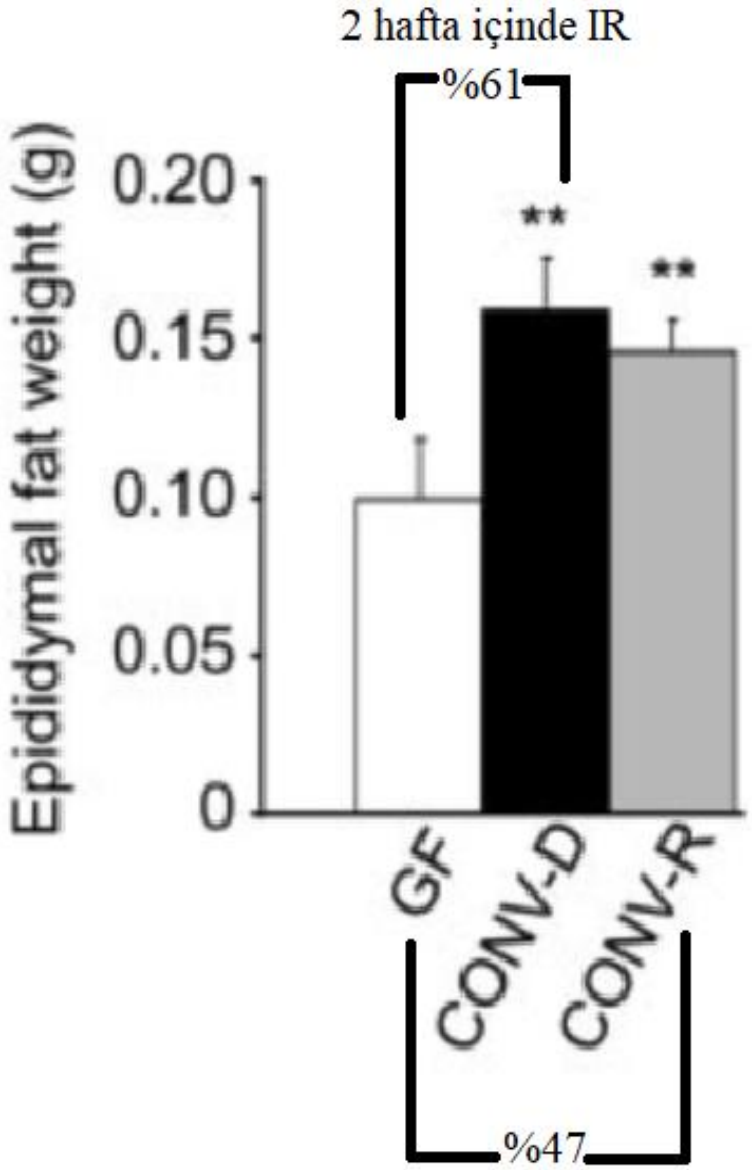
Fredrik Bäckhed*†‡, Hao Ding‡§¶, Ting Wang‖, Lora V. Hooper†**, Gou Young Koh††, Andras Nagy§‡‡, Clay F. Semenkovich§§, and Jeffrey I. Gordon*†¶¶

*Center for Genome Sciences and Departments of †Molecular Biology and Pharmacology, ‖Genetics, and §§Medicine, Cell Biology, and Physiology, Washington University School of Medicine, St. Louis, MO 63110; §Samuel Luenfeld Research Institute, Mount Sinai Hospital, Toronto, ON, Canada M5G 1X5; ††Biomedical Center, Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, 305-701, Republic of Korea; and ‡‡Department of Medical Genetics and Microbiology, University of Toronto, Toronto, ON, Canada M5S 1A8

Contributed by Jeffrey I. Gordon, September 24, 2004

7. Metabolik Bozukluklar





1. Raised in a GF state,
2. Allowed to acquire a microbiota from birth to adulthood (CONV-R),
3. Raised GF until adulthood and then colonized for 2 weeks with an unfractionated cecal microbiota harvested from CONV-R donors (CONV-D).

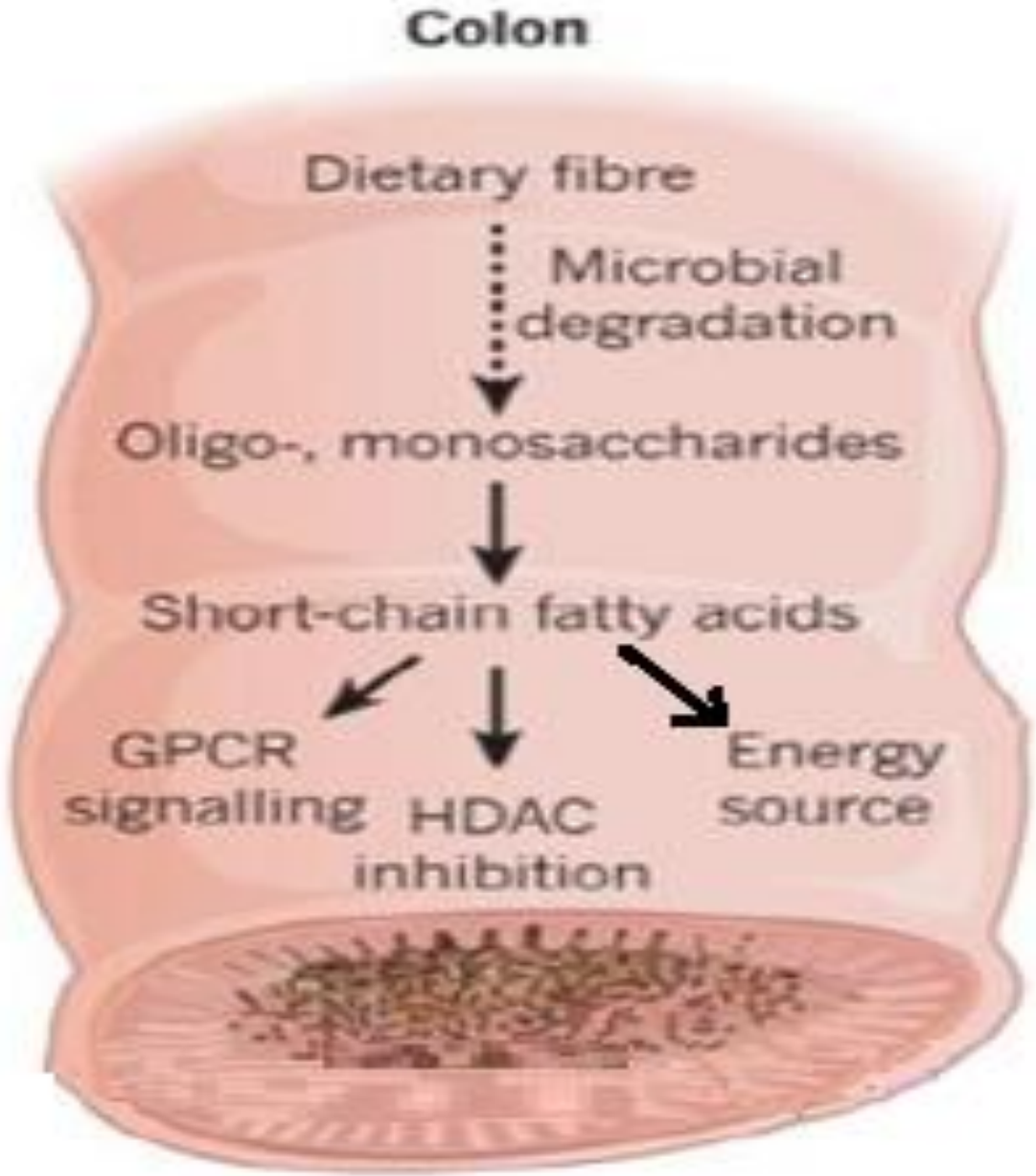
- Analyzed for total body fat content by Dual Energy X-ray Absorptiometry.

Obezite mi mikrobiyomu değiştirir

yoksa mikrobiyom mu obezite riskini

değiştirir?

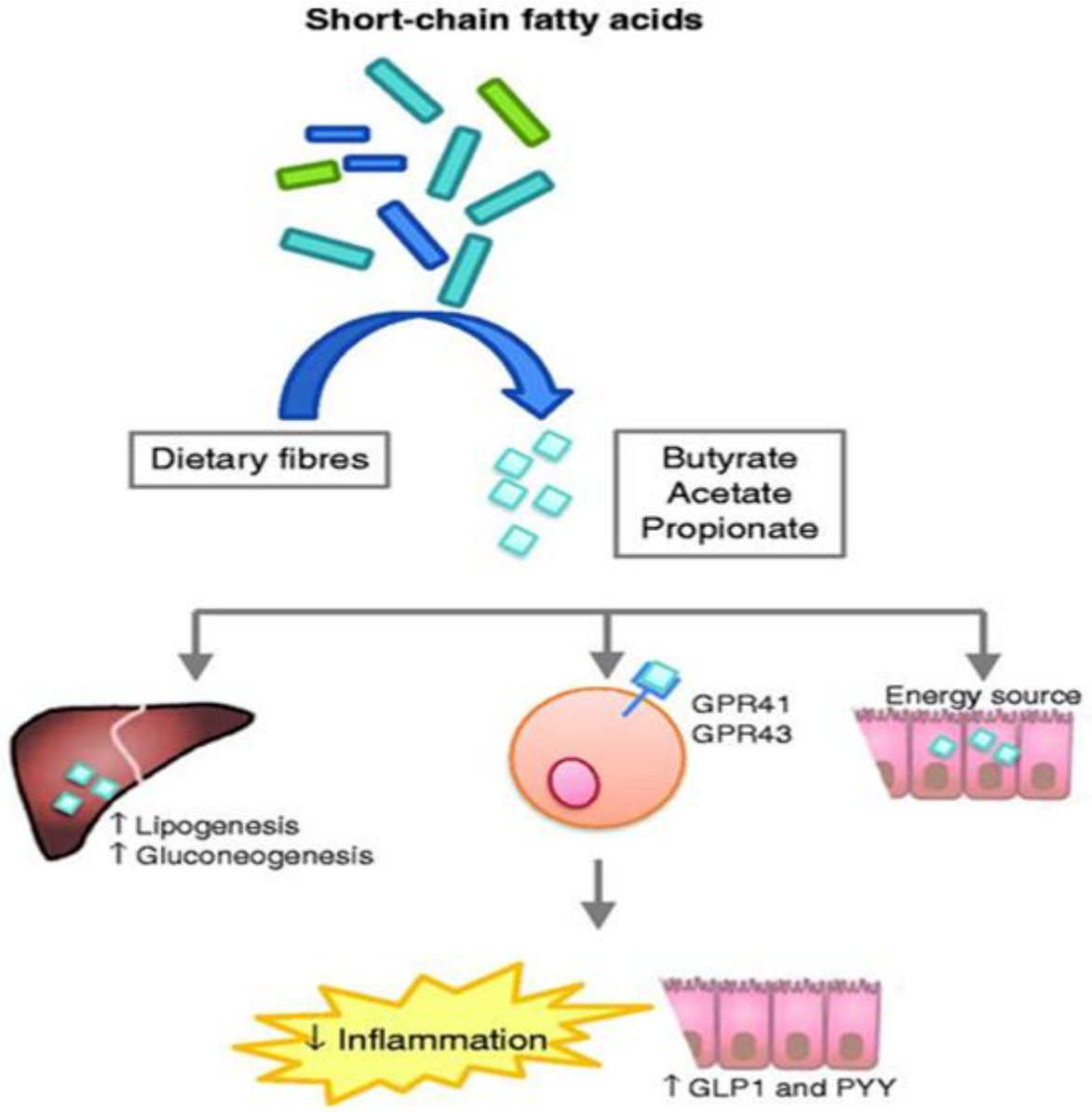
7. Metabolik Bozukluklar



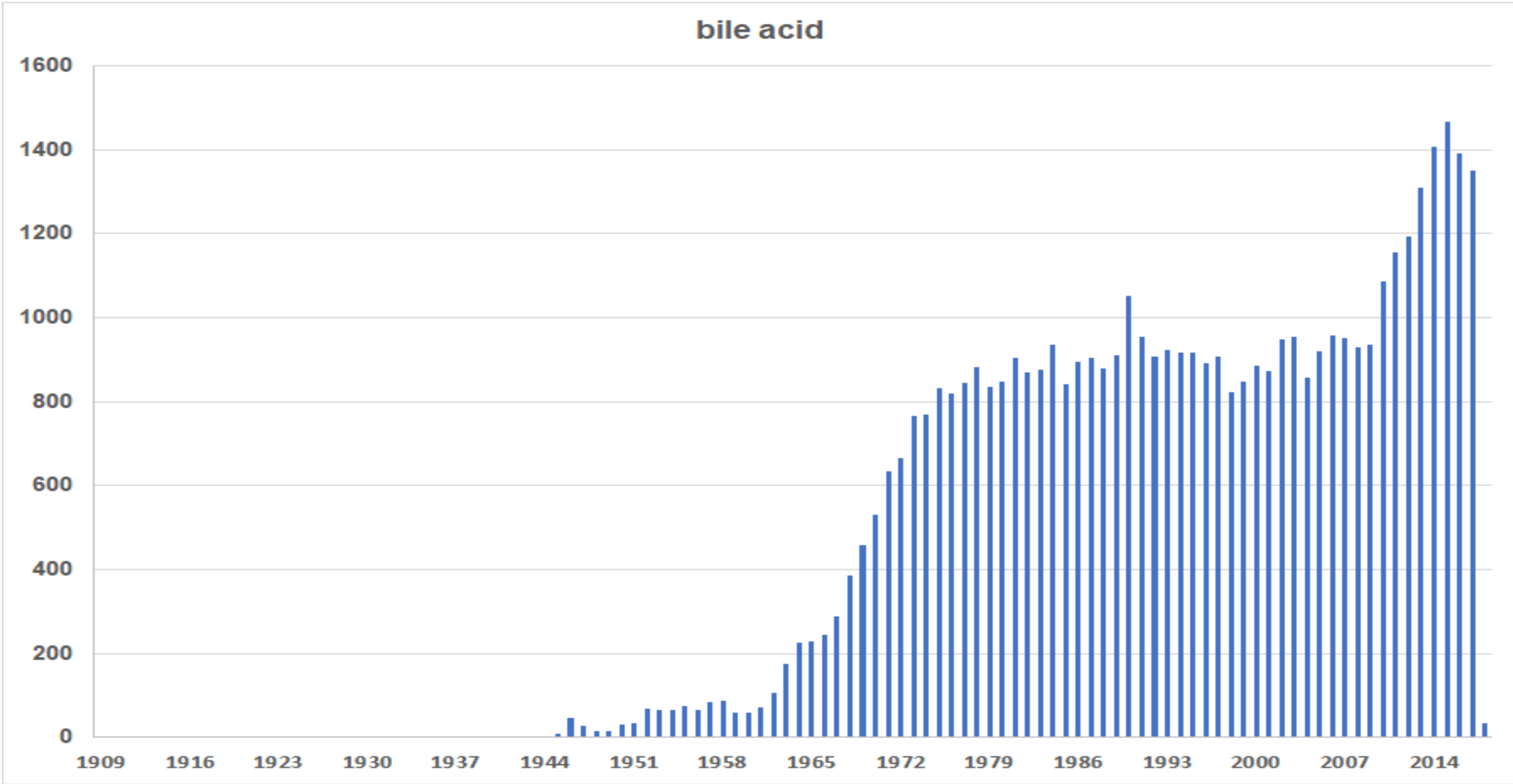
- **Selüloz**
- **Ksilan**
- **Enzime dirençli nişasta**
- **İnülin**

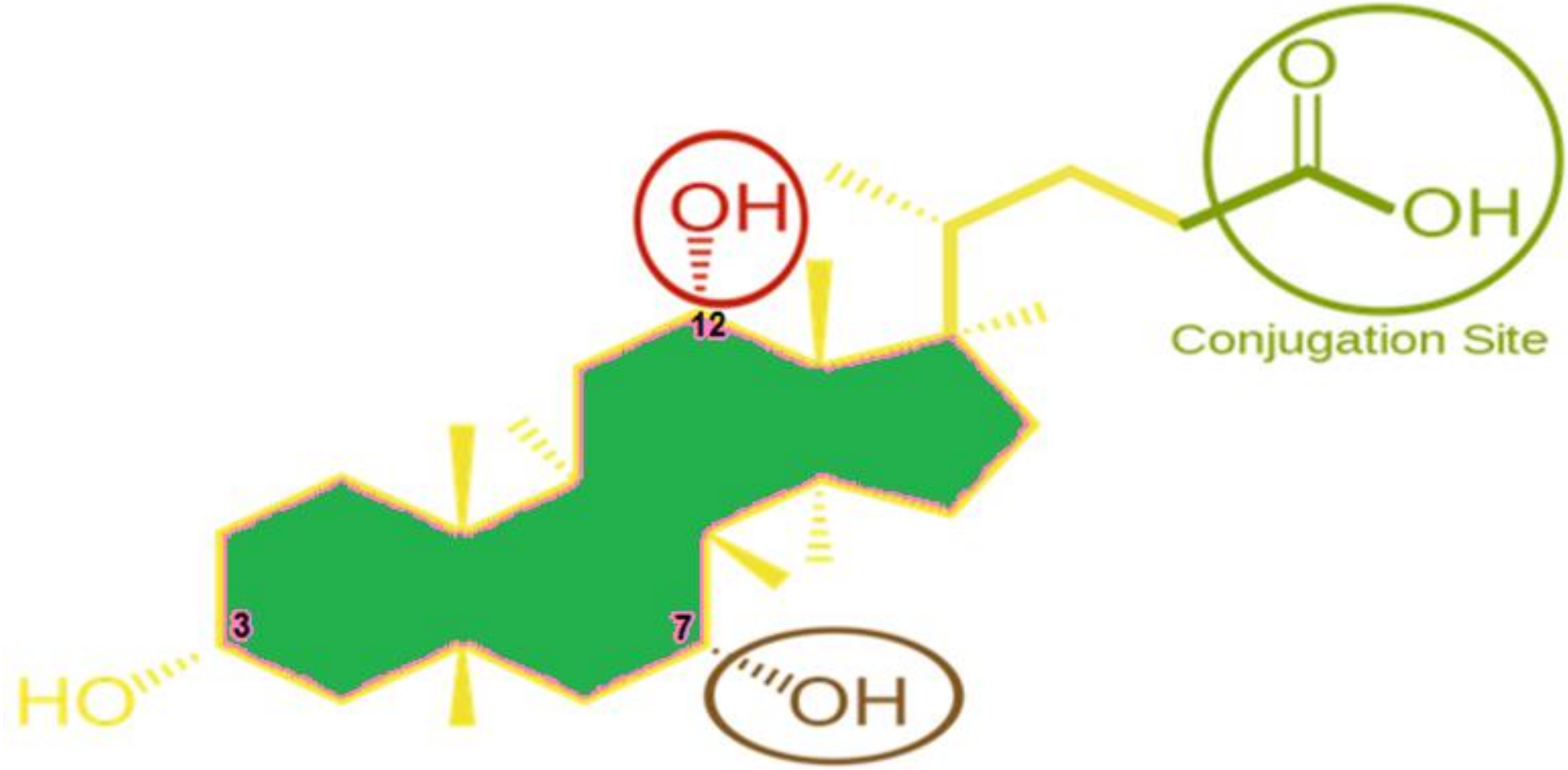
7. Metabolik Bozukluklar

- Mukus üretimini ve tight junction fonksiyonunu artırıp LPS gibi **endotoksinlerin kolon lümeninden dolaşıma geçmesini azaltırlar**.
- Adezyon moleküllerini, kemokin üretimini, monosit, makrofaj ve nötrofillerin toplanmasını inhibe edip **anti-inflamatuvar** etki gösterirler.
- GLP-1 salınımını stimüle ederek **insulin hassasiyetine** katkıda bulunabilirler.
- **Anoreksigenik** adipokin ekspresyonunu artırabilirler.
- Lipogenez ve glukoneogenezde kullanılmak üzere karaciğere **enerji sağlarlar.**

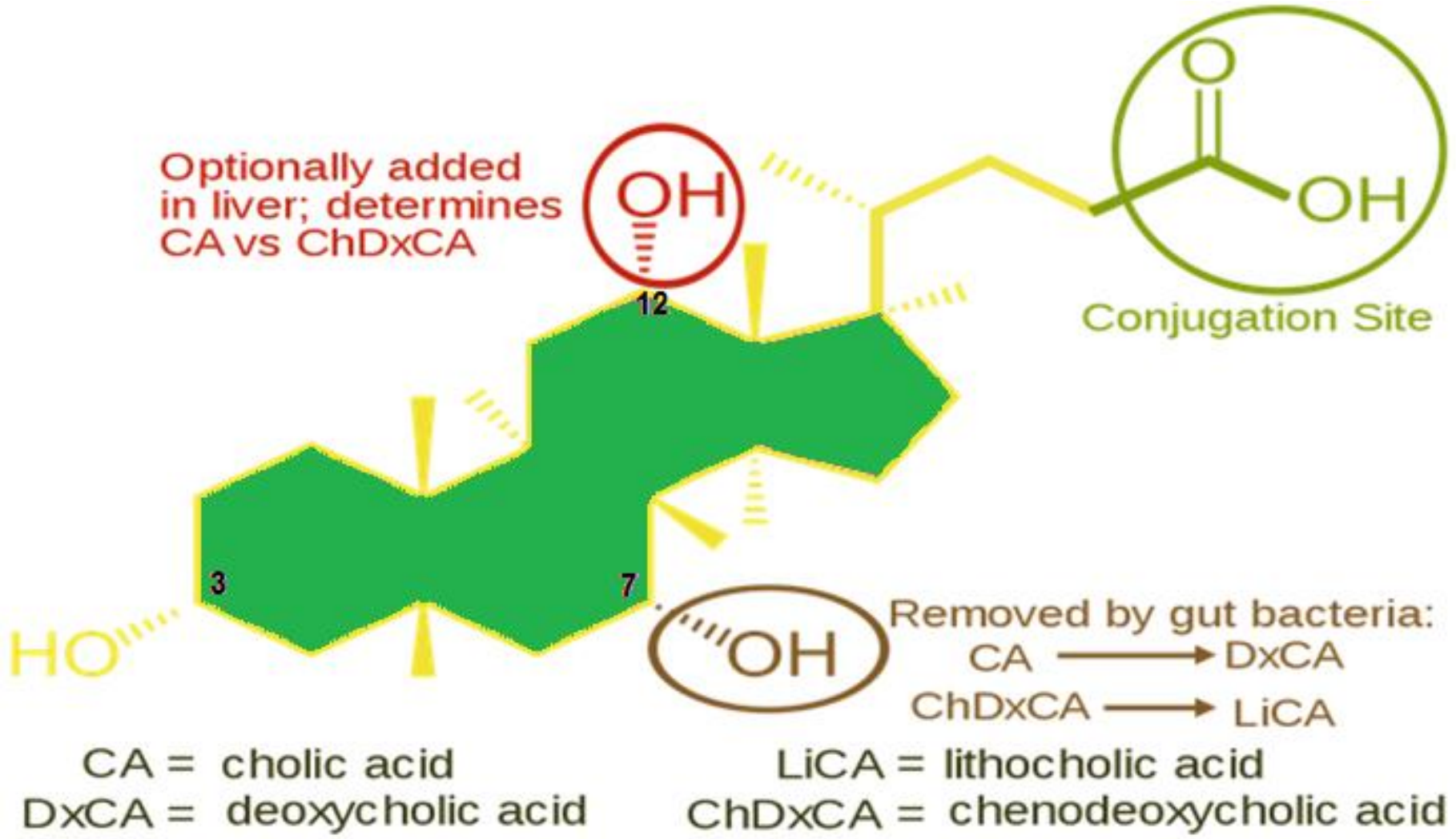


Kristine H Allin et al. Eur J Endocrinol 2015;172:R167-R177


bile acid
1600
1400
1200
1000
800
600
400
200
0
1909
1916
1923
1930
1937
1944
1951
1958
1965
1972
1979
1986
1993
2000
2007
2014



- **Safra asitleri**; yapılarındaki steran halkasında bir veya daha fazla hidroksil grubu ve beş karbonlu yan zincirlerinde bir karboksil grubu bulunan 24 karbonlu steroidlerdir.
- Safra asitlerinin glisin veya taurine ile konjugasyonu sonucu konjuge safra asitleri (**safra tuzları**) oluşur.



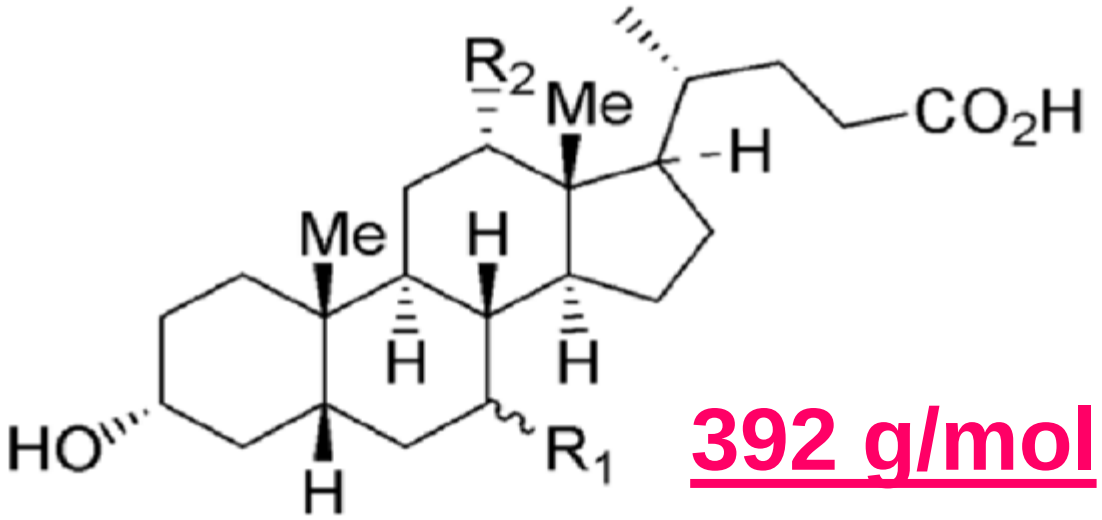
Primer Safra asitleri

- Kolik asit (3,7,12-Trihidroksi Kolanik Asit)
- Kenodeoksi kolik asit (3,7-Dihidroksi Kolanik Asit)

Sekonder Safra asitleri

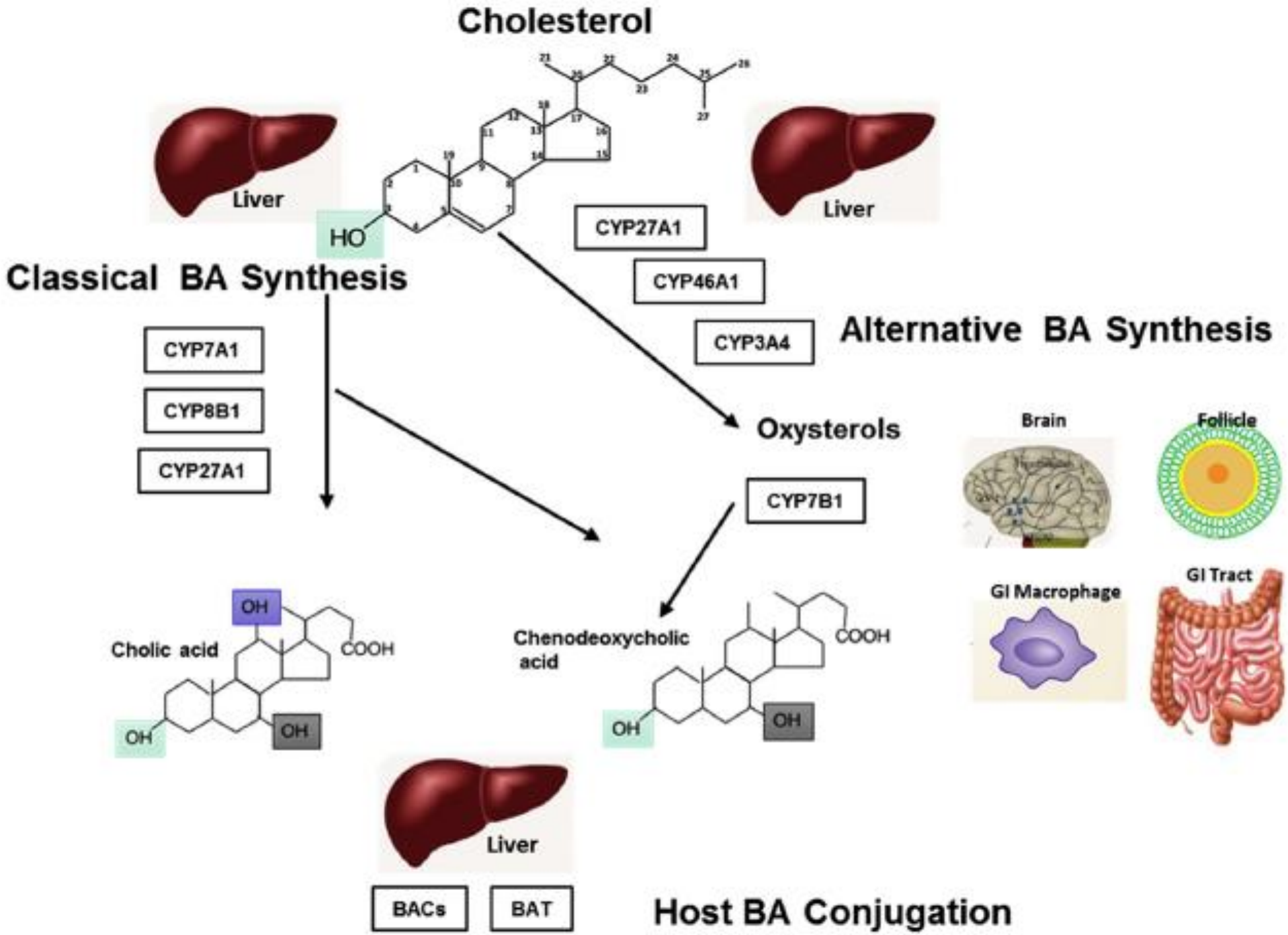
- Deoksi kolik asit (3,12-Dihidroksi Kolanik Asit)
- Litokolik asit (3-Hidroksi Kolanik Asit)

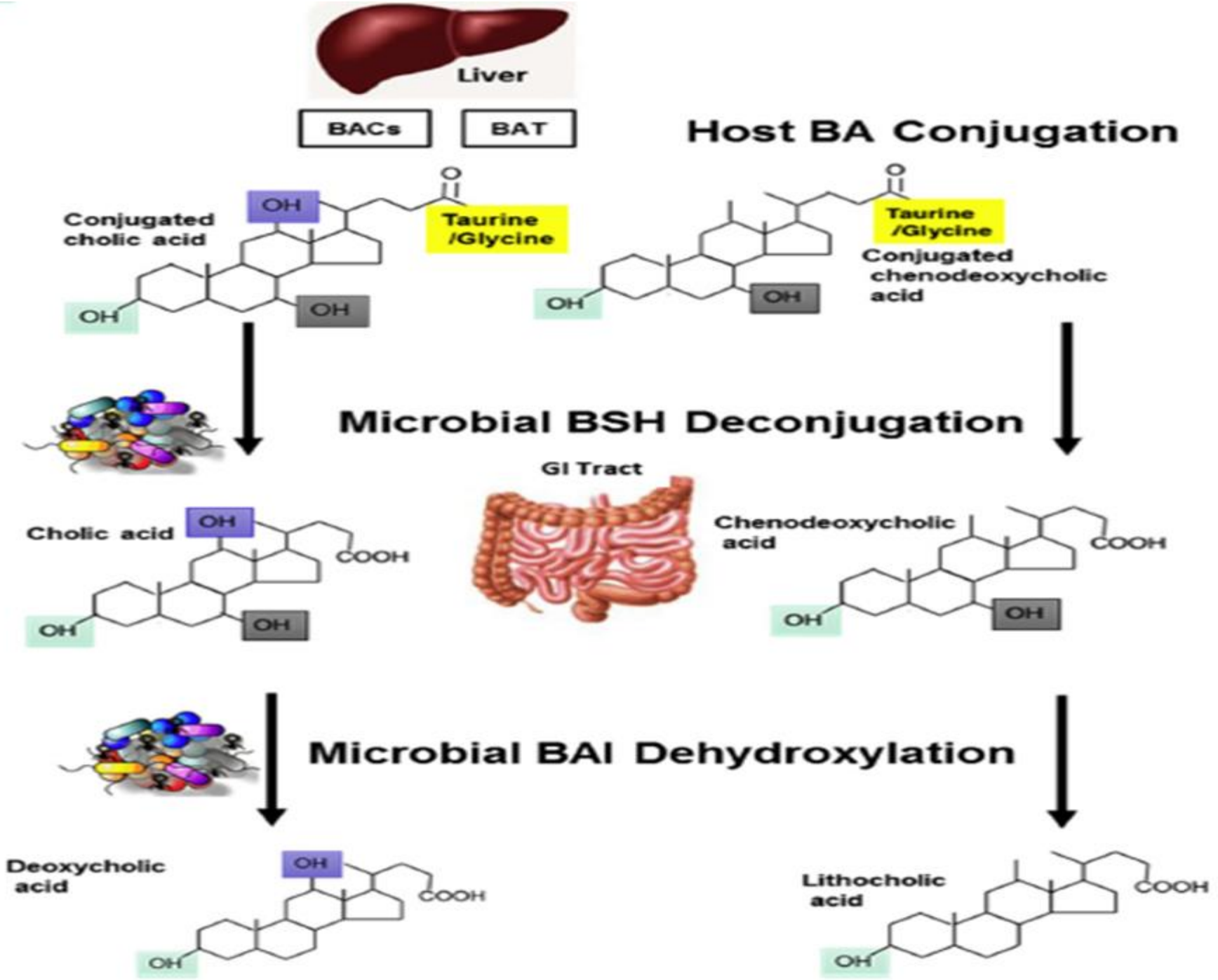
İZOMERİK SAFRA ASİTLERİ



392 g/mol

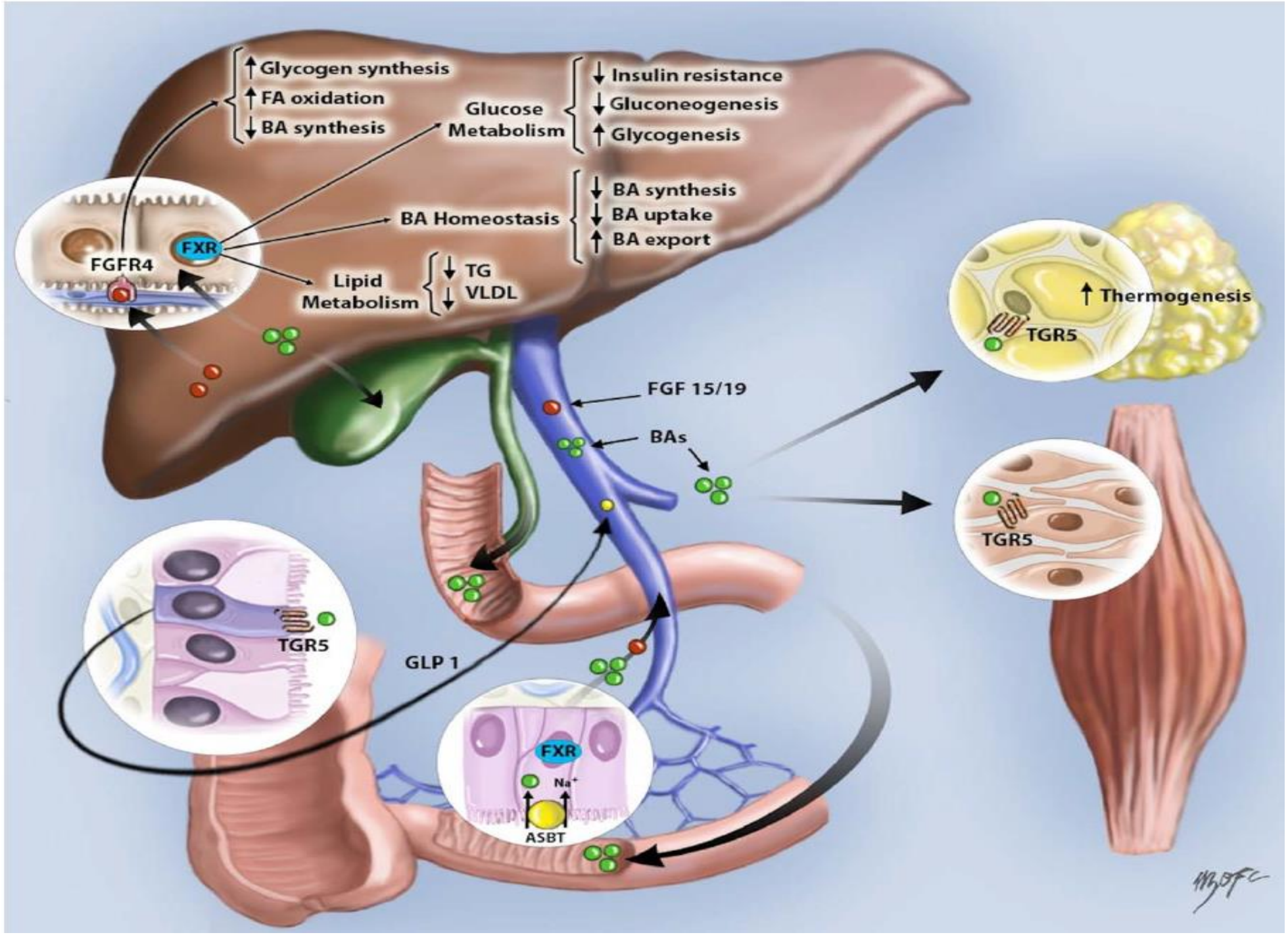
	R_1	R_2
CA	α–OH	OH
CDCA	α–OH	H
DCA	H	OH
LCA	H	H
UDCA	β–OH	H


Cholesterol
Liver
HO
Liver
Classical BA Synthesis
CYP27A1
CYP46A1
CYP3A4
Alternative BA Synthesis
CYP7A1
CYP8B1
CYP27A1
Oxysterols
CYP7B1
Brain
Follicle
GI Macrophage
GI Tract
OH
Cholic acid
COOH
OH
OH
Chenodeoxycholic acid
COOH
OH
OH
Liver
BACs
BAT
Host BA Conjugation

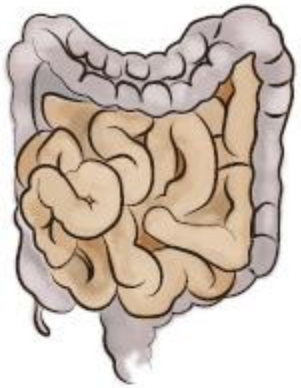


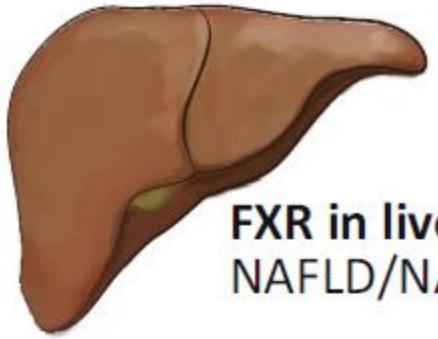
- Aşırı safra asidi birikimi hepatotoksik olduğu için safra asidi havuzunun büyüklüğü ve metabolizması çok sıkı kontrol altındadır.

- Safra asitleri glukoz, lipid ve enerji dengesini kontrol eden signal molekülüdür.


Glycogen synthesis
FA oxidation
BA synthesis
Glucose Metabolism
Insulin resistance
Gluconeogenesis
Glycogenesis
BA Homeostasis
BA synthesis
BA uptake
BA export
Lipid Metabolism
TG
VLDL
FXR
FGFR4
FGF 15/19
BAs
Thermogenesis
TGR5
TGR5
TGR5
GLP 1
FXR
Na+
ASBT

TGR5 in L-cells ↑ **GLP-1**
FXR in L-cells ↓ **GLP-1**





FXR in liver
NAFLD/NASH

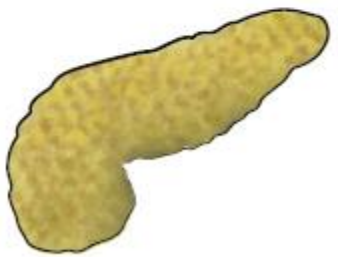
TGR5 in BAT
Insulin sensitivity ↑
Energy expenditure ↑

(T/G)CA
(T/G)CDCA
Tα/βMCA
In mice

Microbial modifications of bile acids in the gut

FXR in WAT
Lipid storage

LCA
DCA
ωMCA
MDCA
UDCA
HDCA
HCA



TGR5 in muscle
Insulin sensitivity ↑
Energy expenditure ↑

TGR5 in α-cells and FXR in β-cells of pancreas
GLP-1 and insulin secretion

Molinaro A. Trends in Endocrinology & Metabolism. 2017

Lancet. 2015 March 14; 385(9972): 956–965. doi:10.1016/S0140-6736(14)61933-4.

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

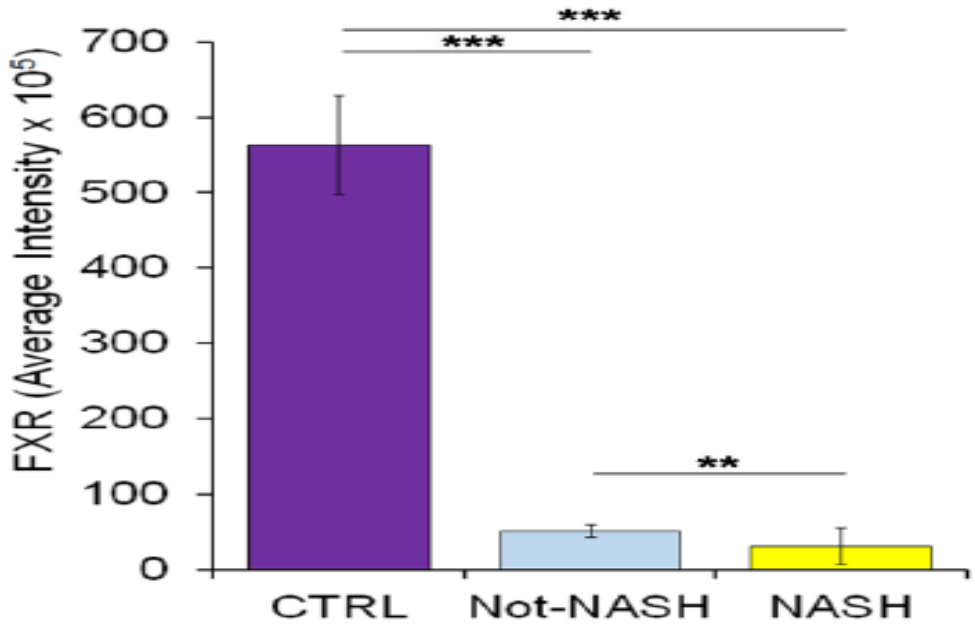
Table 2

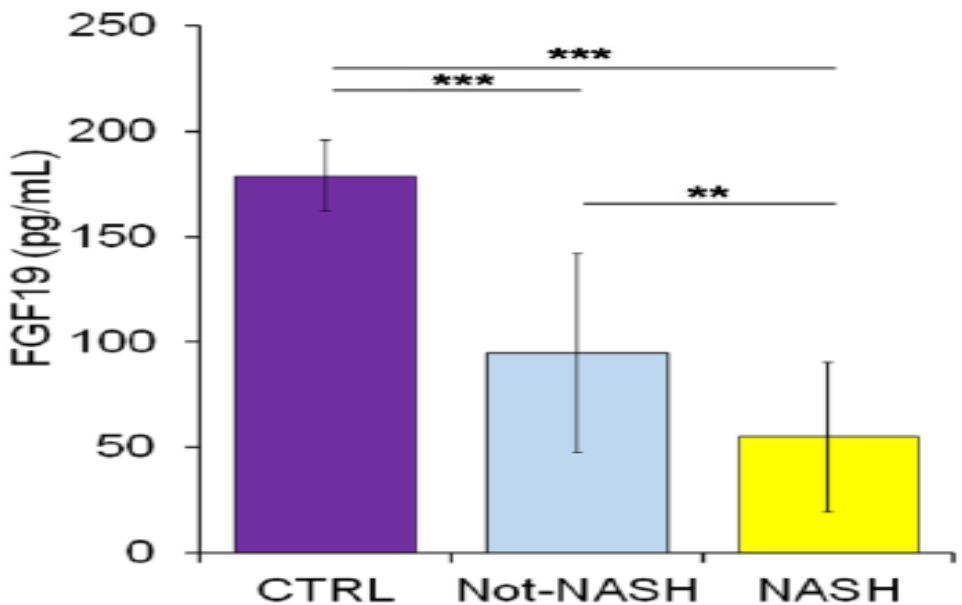
Changes in histological features of the liver after 72 weeks of treatment

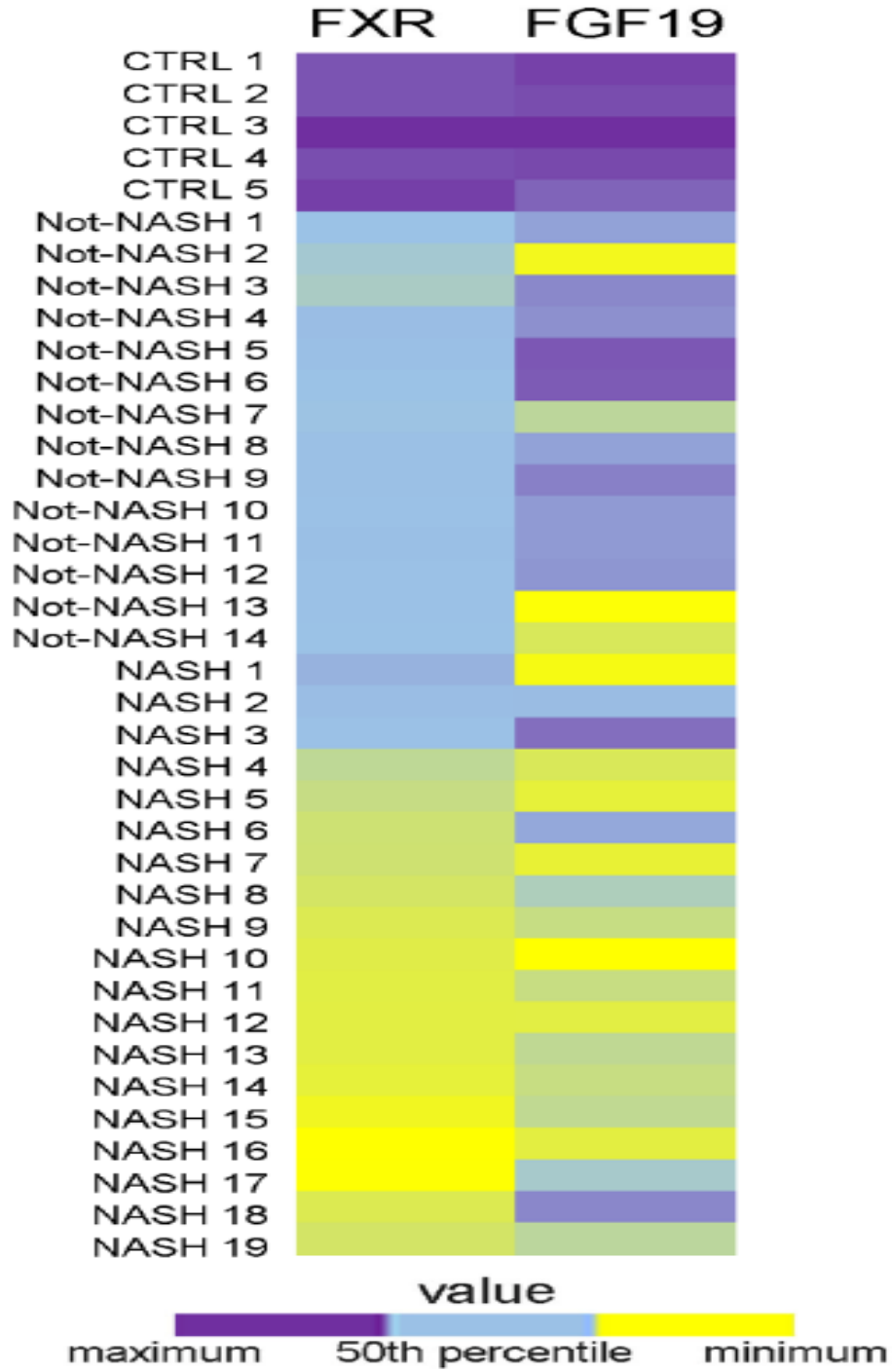
25mg/gün

	Obeticholic acid	Placebo	Relative risks or mean changes from baseline* (95% CI) (obeticholic acid *vs* placebo)	p value*
Primary outcome†				
Number of patients at risk‡	110	109		
Patients with improvement	50 (45%)	23 (21%)	1·9 (1·3 to 2·8)	0·0002
Changes from baseline in histological features				
Fibrosis				
Patients with improvement	36 (35%)	19 (19%)	1·8 (1·1 to 2·7)	0·004
Total NAFLD activity score				
Change in score	−1·7 (1·8)	−0·7 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Hepatocellular ballooning				
Patients with improvement	47 (46%)	30 (31%)	1·5 (1·0 to 2·1)	0·03
Change in score	−0·5 (0·9)	−0·2 (0·9)	−0·2 (−0·5 to 0·0)	0·03
Steatosis				
Patients with improvement	62 (61%)	37 (38%)	1·7 (1·2 to 2·3)	0·001
Change in score	−0·8 (1·0)	−0·4 (0·8)	−0·4 (−0·6 to −0·2)	0·0004
Lobular inflammation				
Patients with improvement	54 (53%)	34 (35%)	1·6 (1·1 to 2·2)	0·006
Change in score	−0·5 (0·8)	−0·2 (0·9)	−0·3 (−0·5 to −0·1)	0·0006

Data are n (%) or mean (SD).





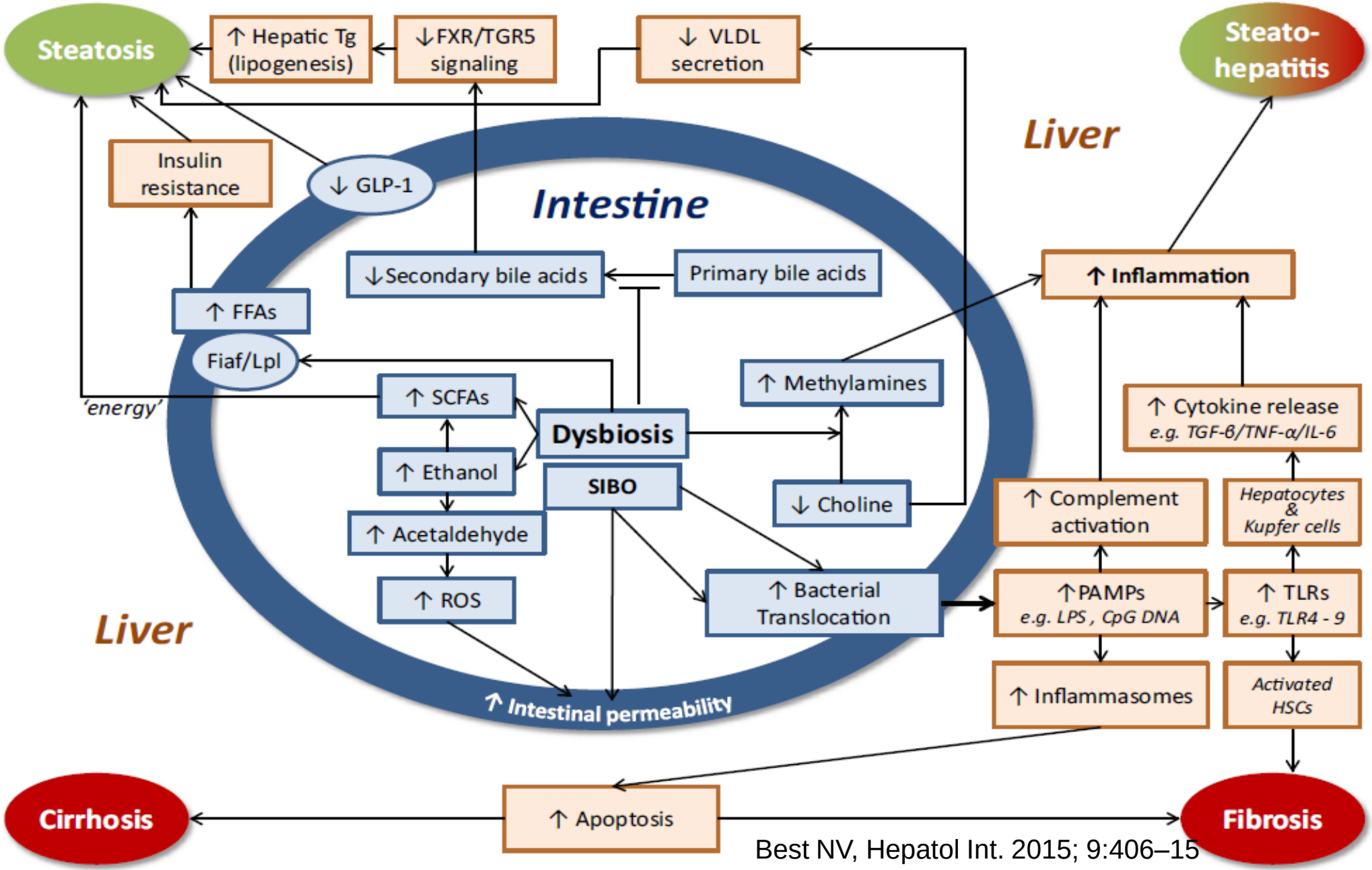


Nobili V. Liver Int, 2017

GELECEKTE NELER BEKLENİYOR?

- Multiomiks (metabolomiks, metagenomiks, metatranskriptiomiks) yaklaşımlar
- Fekal mikrobiyom transplantasyonu
- Safra asidi reseptör agonist ve antogonistleri ile tedavi

ÖZET



Best NV, Hepatol Int. 2015; 9:406–15

SABRINIZ İÇİN TEŞEKKÜR EDERİM