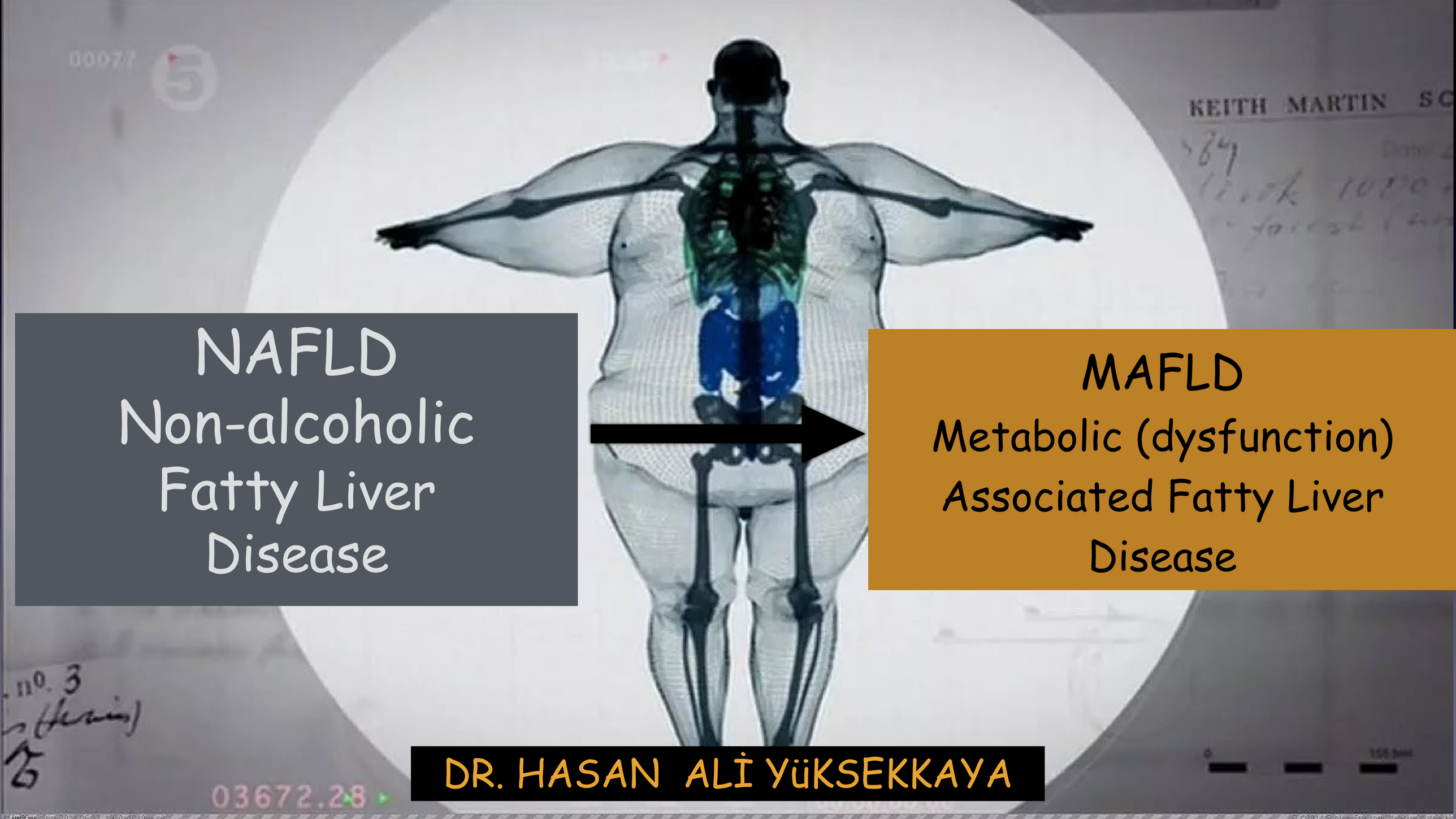
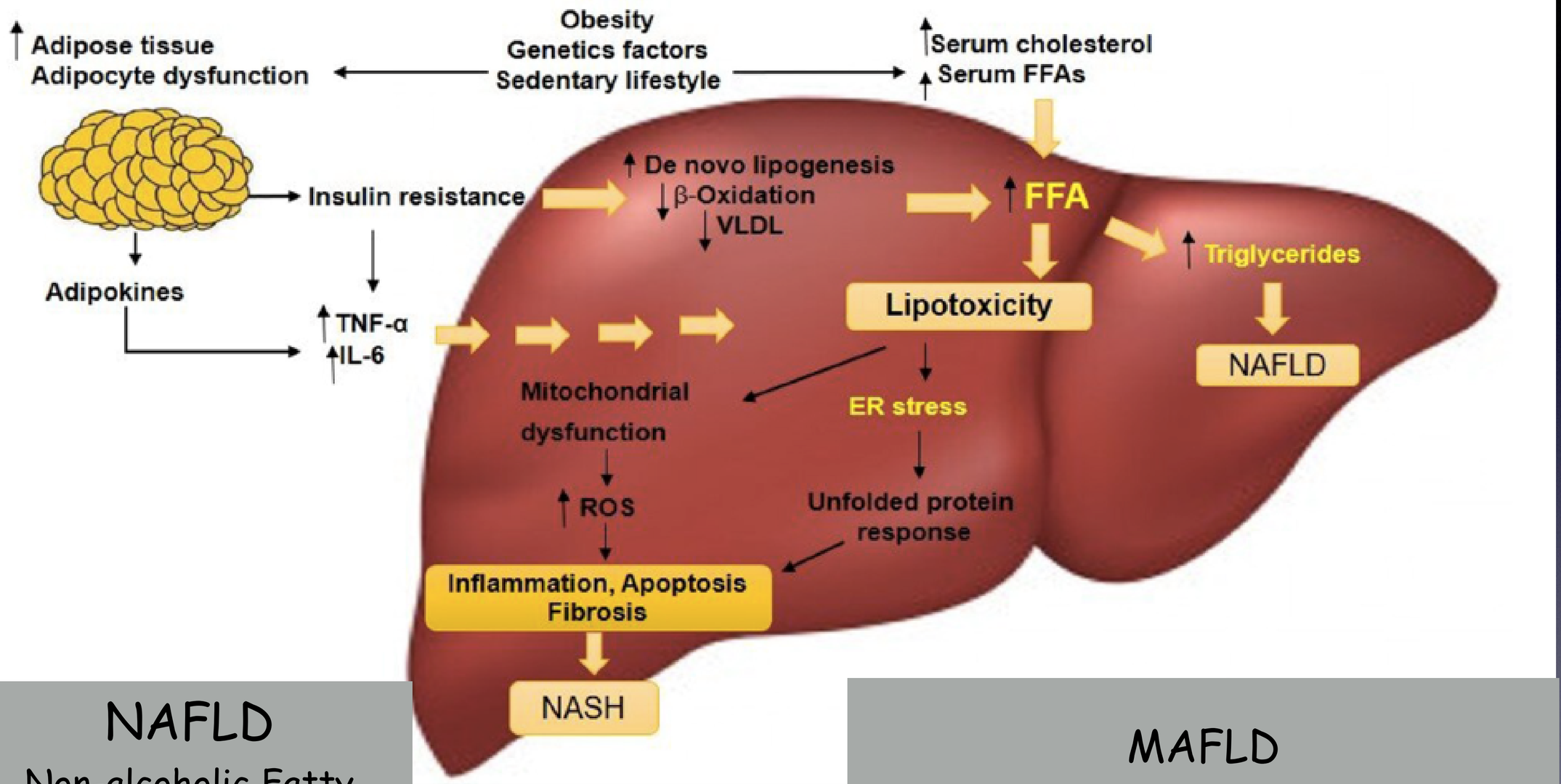

NAFLD
Non-alcoholic
Fatty Liver
Disease
MAFLD
Metabolic (dysfunction)
Associated Fatty Liver
Disease
DR. HASAN ALİ YÜKSEKKAYA

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

Mohammed Eslam[1,2], Jacob George[3], International Consensus

, Gastroenterology 2020 May;158(7):1999-2014.e



NAFLD

Non-alcoholic Fatty Liver disease

MAFLD

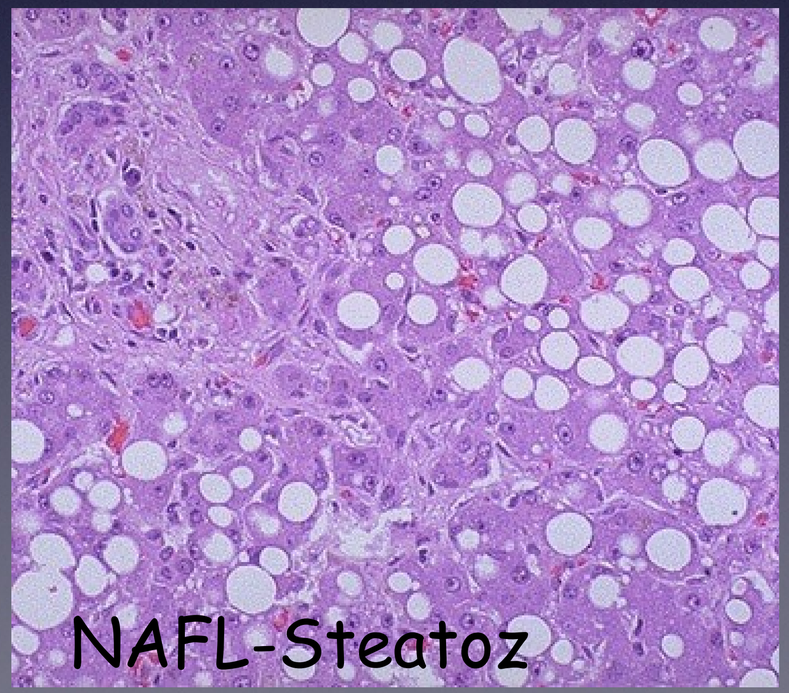
Metabolic (dysfunction) Associated Fatty Liver Disease

MAFLD

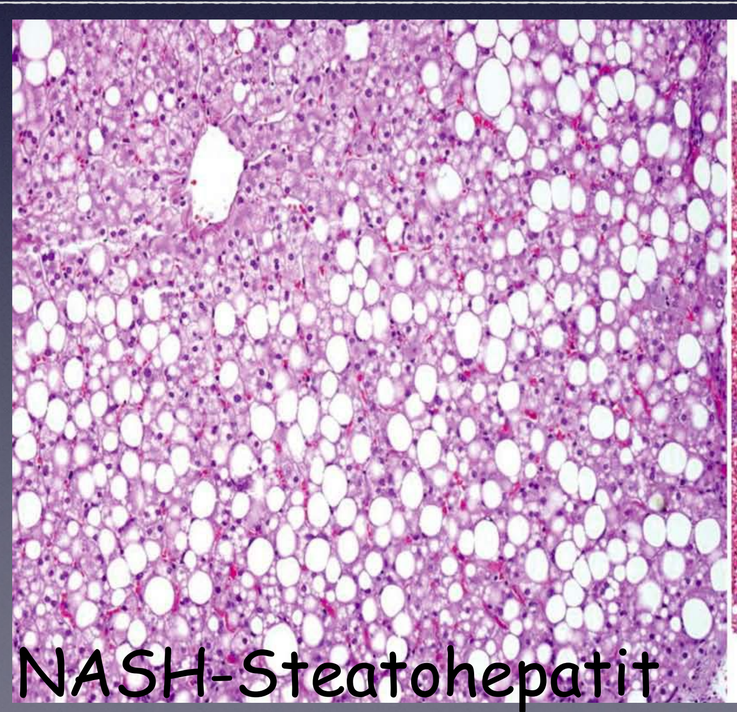
= KC'de yağ birikimi > %5

< 10yaş nadir
Yaplı KC yapan başka hastalık ??

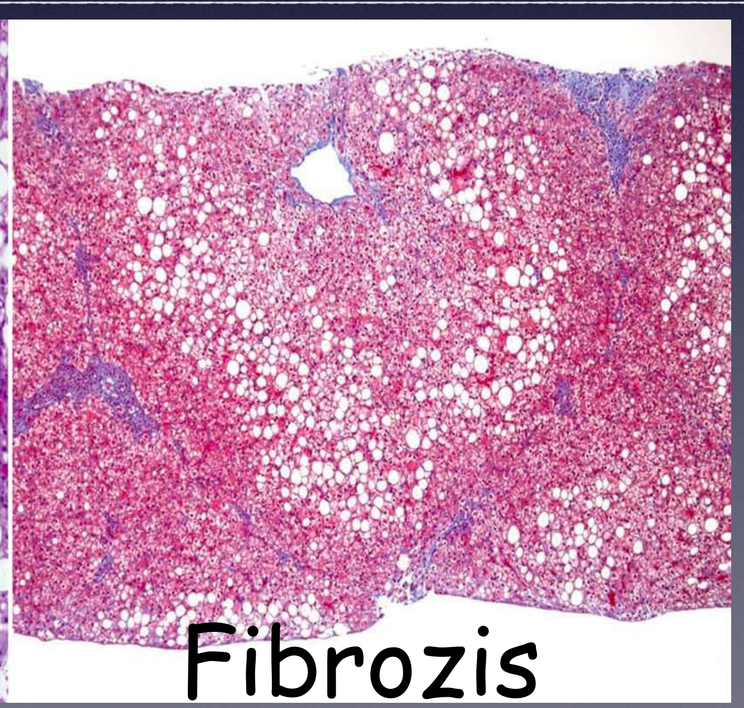
- USG; Yağlanma + + +
- KC yağlanması yapan başka hastalık yok
- Alkol kullanımı yok - minimal



NAFL-Steatoz



NASH-Steatohepatit



Fibrozis

Yağlı KC nedeni hastalık ve ilaçlar

General or systemic	Genetic-metabolic causes	Drugs/chemicals
Anorexia nervosa (± refeeding)	α- and β-oxidation defects	Corticosteroids
Celiac disease	Abeta or hypobetalipoproteinemia	Diltiazem
Diabetes mellitus type 1	Alpha 1 -antitrypsin deficiency	Ecstasy, Cocaine, Solvents
Hepatitis C	Cholesterol ester storage disease/LAL	Estrogens
Hypothalamic–pituitary disorders	Citrin deficiency	Ethanol
Inflammatory bowel disease	Congenital disorders of glycosylation	Methotrexate
Obesity/Metabolic syndrome	Cystic fibrosis/Shwachman syndrome	Nifedipine
Obstructive sleep apnea	Familial hyperlipoproteinemias	Pesticides
Polycystic ovary syndrome	Glycogen storage disease (I , VI and IX)	Prednisolone
Protein calorie malnutrition	Hereditary Fructose Intolerance	Solvents
Rapid weight loss	Lipodystrophy	Valproate
Small intestine bacterial overgrowth	Mitochondrial and peroxisomal defects	Vitamin A
Thyroid disorders	Organic acidosis	Zidovudine and HIV treatments
	Porphyria cutanea tarda	
	Turner syndrome	
	Urea cycle disorders	
	Wilson's disease	

YAĞLI KARACİĞER NEDENİ HASTALIK VE İLAÇLAR

Hastalıklar	İlaçlar
Wilson hastalığı	Kortikosteroid
Anorexia	Valproik asit
Malnutrisyon	Risperidon
Abeta ve hipobetalipoproteinemi	Metotreksat
Tirozinemi	L-asparajinaz
Glikojen depo tip-1,6	TPN
Herediter Früktoz intoleransı	
Kolesterol ester depo hastalığı	
Çölyak hastalığı	
Kistik fibrozis	
AlfA-1 Antitripsin eksikliği	
Galaktozemia	
Hepatit C (genotip-3)	
Mitokondrial hastalıklar (Alper’s, ..)	
Peroksizomal hastalıklar	

MAFLD

- Modern yaşam ve diyet
- Azalmış fiziksel aktivite
- Sosyoekonomik düzey

En önemli risk faktörü: OBEZİTE

Seçili Ülkelerde **Obezite Oranı** 2020

Daha fazlası için bizi takip edin
dogruverii dogruveri dogru_veri

ABD	%40
Şili	%34.4
Meksika	%33.3
Yeni Zelanda	%32.2
Macaristan	%30
Türkiye	**%28.7**
Kanada	%28.1
İngiltere	%26.2
Almanya	%23.6
İsrail	%18.8
Fransa	%17
Norveç	%12
İtalya	%9.8
Kore	%5.5
Japonya	%4.2

Kaynak: OECD

Çocukluk çağı başlayan MAFLD

Erişkinde ağır seyirli

Çocukluk çağı overweight-obezite oranı : %13- 34

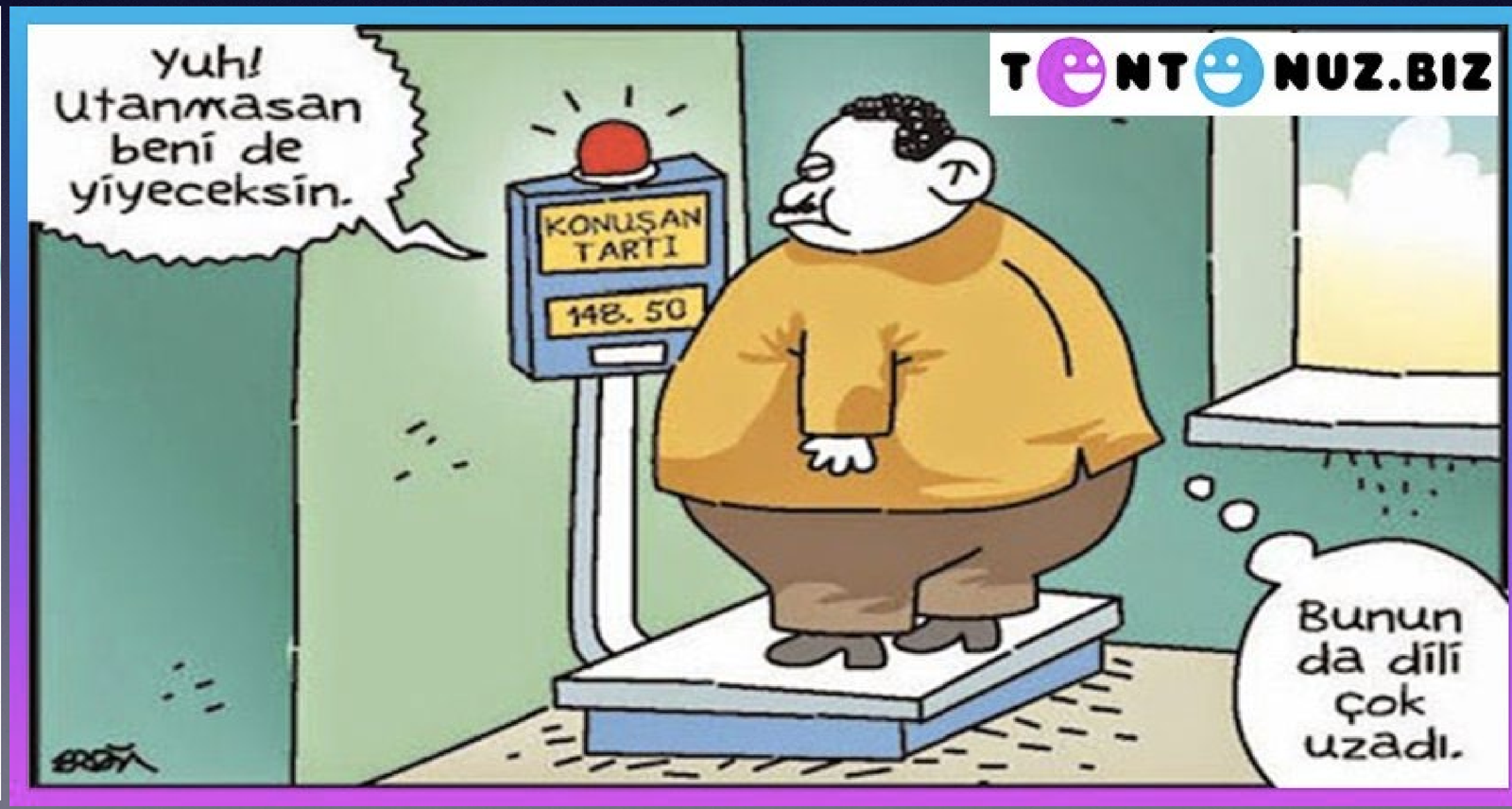
Çocukluk MAFLD prevalansı : %7,6-9,6

Erkek %9, Kızlar: %6

Pediatrik- Erişkin MAFLD

Yaşam tarzı benzerliği

Yağlı ve Besin Değeri Düşük Gıda, Sedanter yaşam, Fiziksel aktivite ↓



Combat the obesity epidemic for a healthier future now and post-COVID-19

DSÖ-2021

Everyone can take action to combat the obesity epidemic by working together to address its many root caus thier lives. By raising awareness and improving we can combat this disease now and post-CO -income countries, in which obesity is rising fastes treated through the adoption of healthy lifestyles. Raising people's awareness of the links between lifestyle and obesity, and COVID-19 complications and obesity, can not only reduce the burden but empower people to make healthy lifestyle choices, such as keeping physically active and choosing healthy food and drinks.

The obesity epidemic

Globally, 800 million people are living with obesity. In WHO's Eastern Mediterranean Region, most countries have experienced a nutrition transition towards unhealthy diets and sedentary lifest les. In the Regio

Almost half
49%
of adults are overweight or obese

Over a quarter
26%
of adolescents are overweight or obese

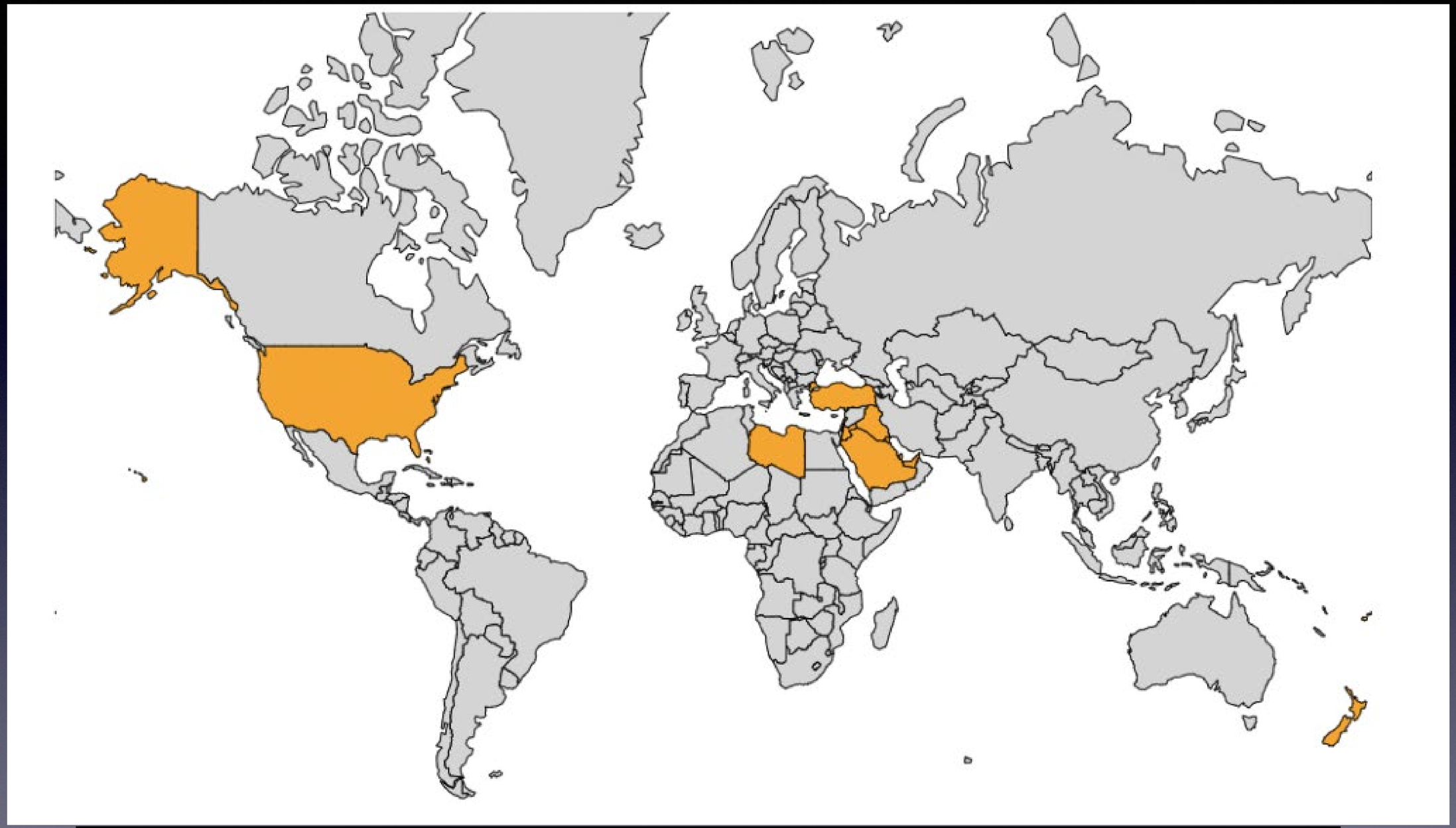
Nearly
6%
of children under 5 are overweight or obese

Noncommunicable diseases are responsible for 62% of all deaths in the Region and unhealthy diet is a major contributor. Most countries in the Region are faced with the double burden of malnutrition, whereby undernutrition and overweight/obesity co-exist within the population. Across the Region, unhealthy dietary practices are prevalent in children, adolescents and adults.

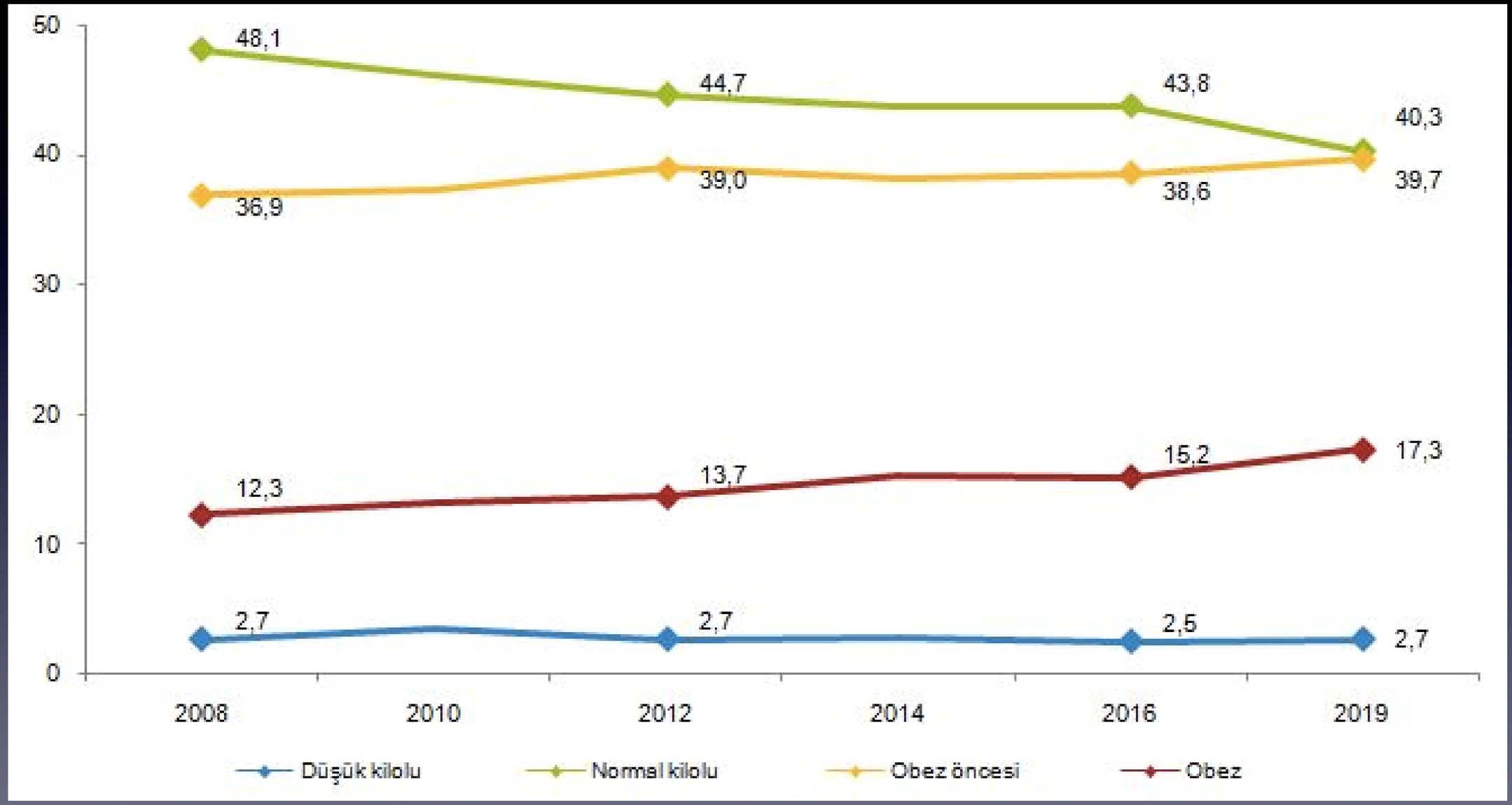
People living with obesity are twice as likely to be hospitalized if tested positive for COVID-19. In children, obesity has nearly doubled every 10 years. By 2030, it will rise to 60%, affecting 250 million children. The medical consequences of obesity are high and will cost over US $ 1 trillion by 2025. To treat this disease effectively and halt its rise, we need effective health care and wider cross-sectoral support.

Overweight - Obez
adelosan oranı 2030'da %60

Her 10 yılda 2 kat artış
250 milyon Obez çocuk

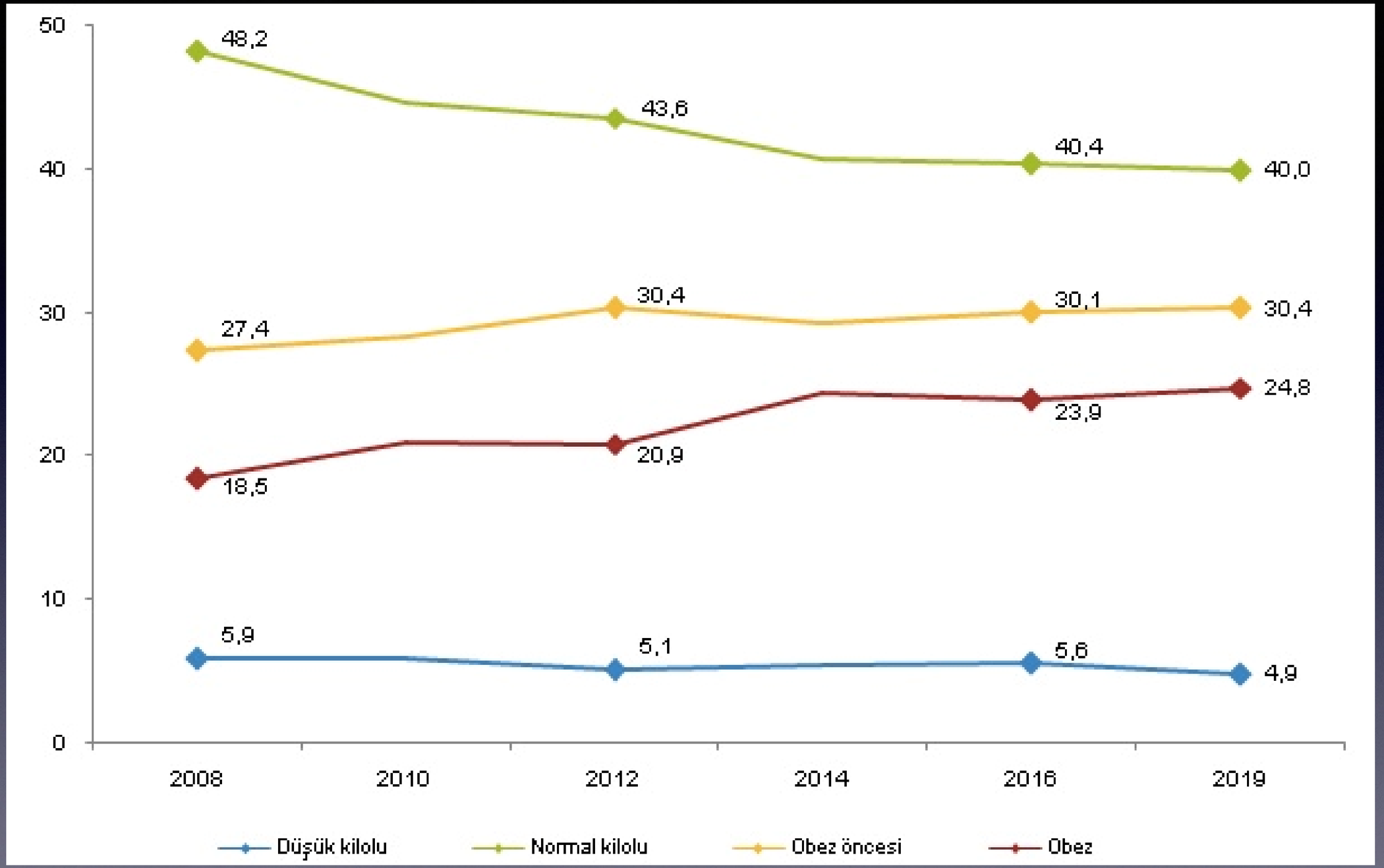


Dünya obezite oranı 2018 – 2019 DSÖ verileri



Erkeklerin vücut kitle indeksi dağılımı (%), 2008-2019 >15 yaş

Kaynak: TÜİK

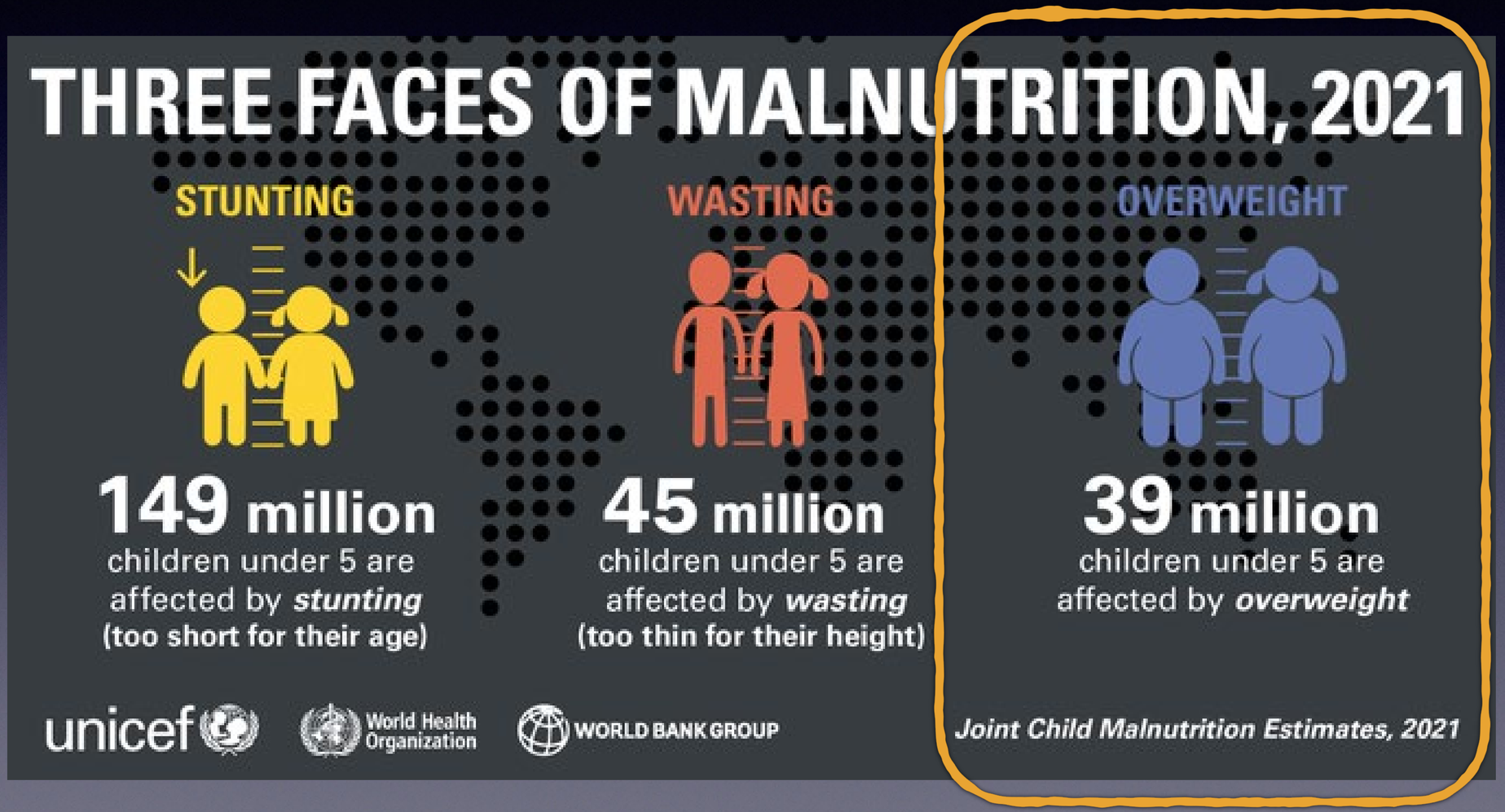


Kadınların vücut kitle indeksi dağılımı (%), 2008-2019 **15 yaş>**

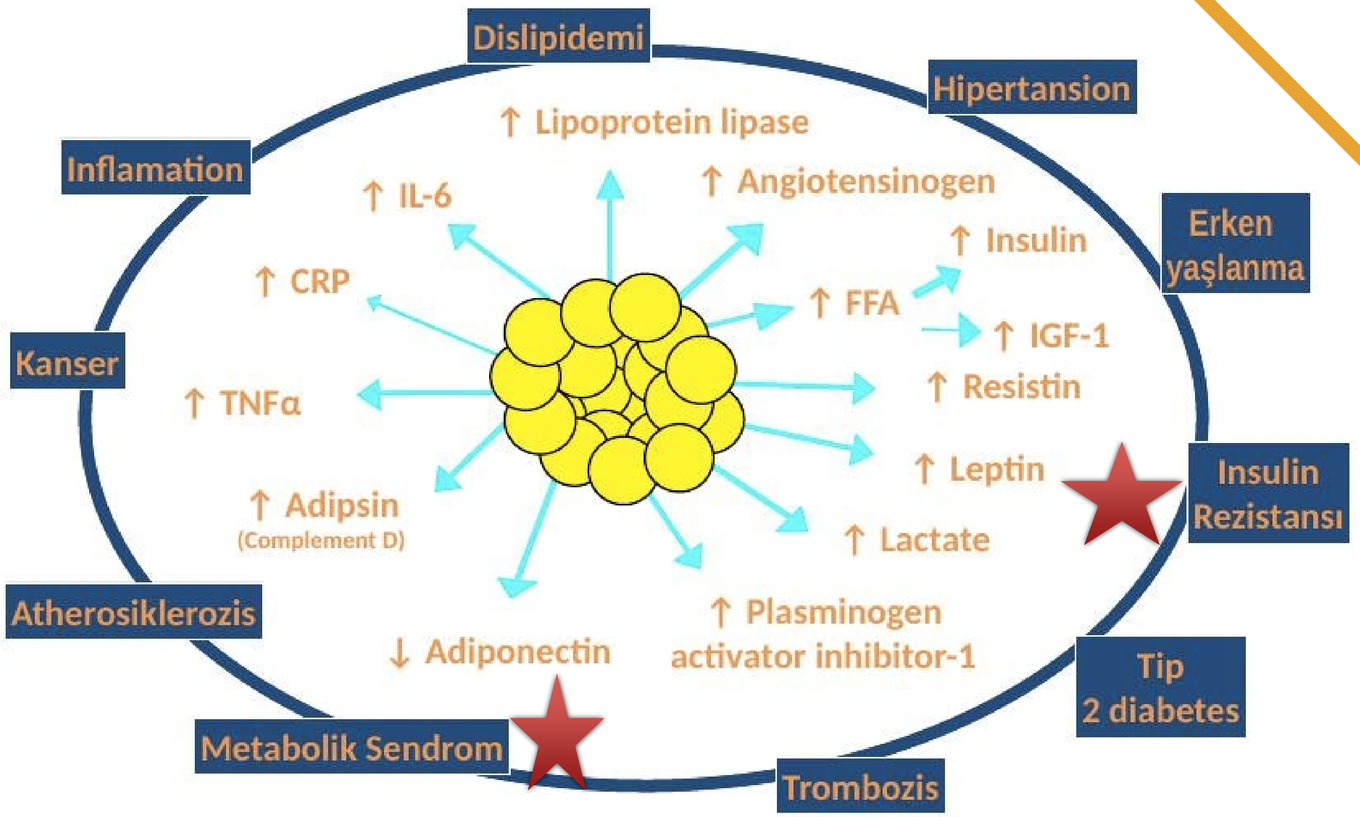
Kaynak: TÜİK

MAFLD

%7'si Obez olmayan çocuklar



Visseral Yağ Dokusu aşırı artış



Adipoz doku disfonksiyonu

Yüksek Leptin

Obezitenin tetiklediği leptin yüksekliği NAFLD alevlenmesi nedeni

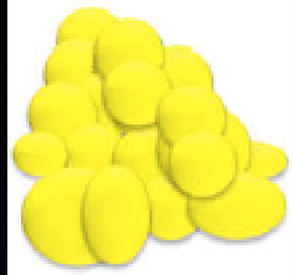
Düşük Adiponektin

Hepatik
insülin direnci
Lipid yükünde artış

Adiponektin

PPAR-alfa-**aracılı**
insülin duyarlılığını artırarak NAFLD iyileştirici

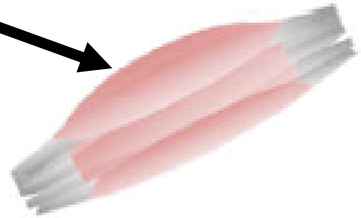
Adipoz doku



- Proinflammatory cytokines ↑ (TNF-α, IL-6 etc.)
- Lipolysis ↑
- FFA release ↑
- Leptin ↑
- Adiponectin ↓

İnsulin direnci

İskelet Kası



- Intramyocellular lipids ↑
- Glucose uptake ↓
- Sarcopenia

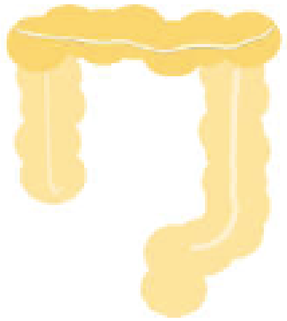
Genetik faktörler

- *PNPLA3*
- *TM6SF2*
- *MBOAT7*

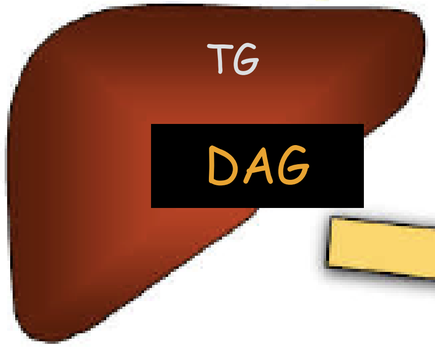
İnsulin direnci

DNL

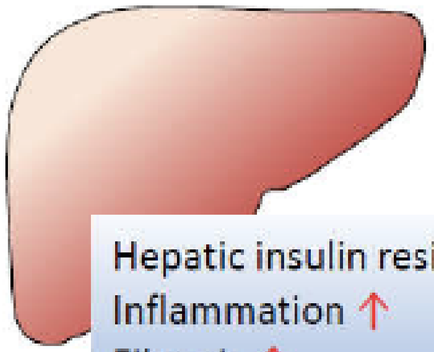
Bağırsak



KARACİĞER



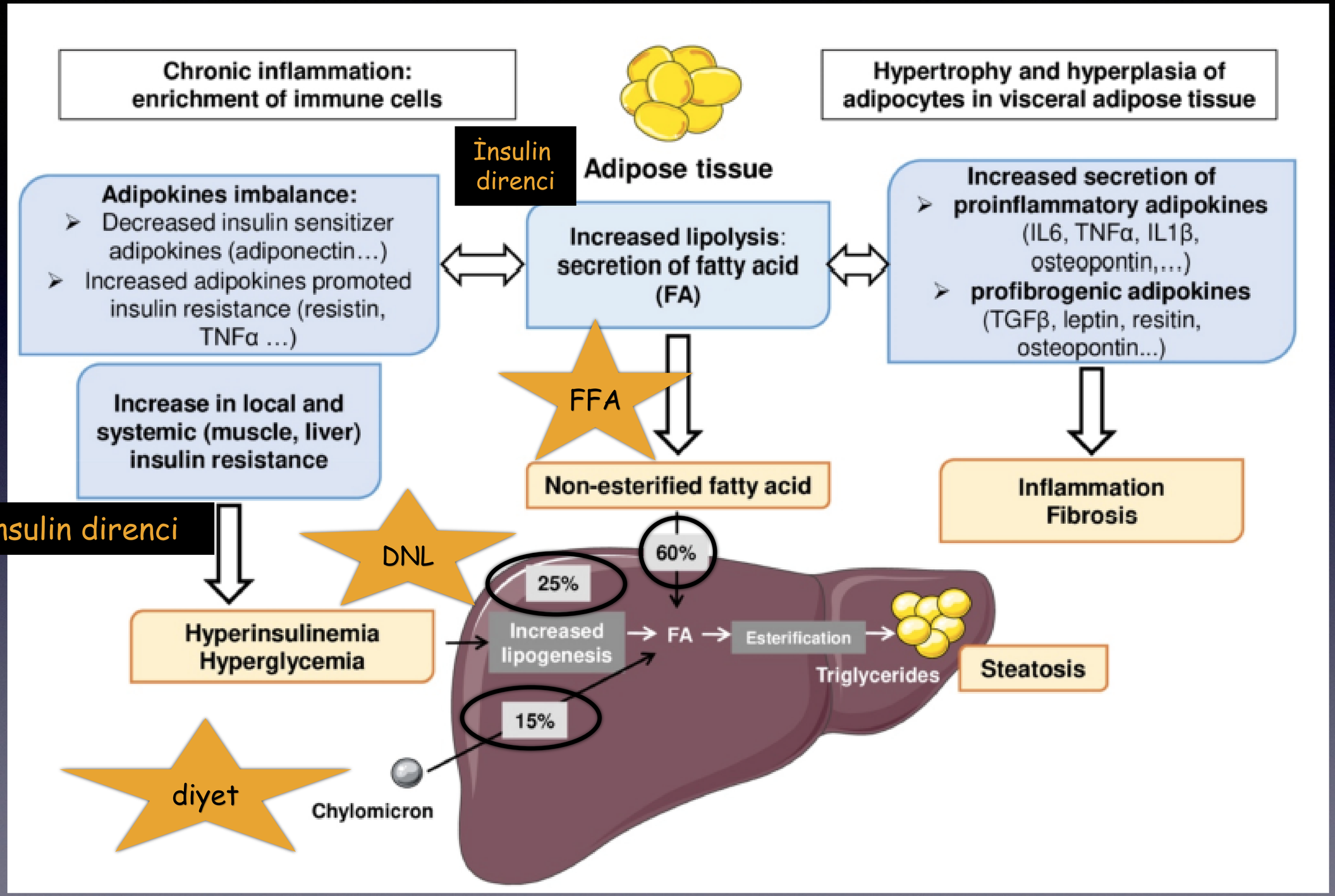
Yağlı KC



- Dysbiosis
- Endotoxin ↑
- Gut permeability ↑
- Small intestinal-bacterial overgrowth ↑
- Endogenous ethanol ↑

- Lipogenesis ↑ (SREBP1c, ChREBP etc.)
- FFA oxidation ↑, then ↓ (relatively)
- FFA uptake via CD36 ↑
- VLDL-TG secretion ↑, then ↓ (relatively)

- Hepatic insulin resistance ↑
- Inflammation ↑
- Fibrosis ↑
- Carcinogenesis ↑


Chronic inflammation: enrichment of immune cells
Hypertrophy and hyperplasia of adipocytes in visceral adipose tissue
İnsulin direnci
Adipose tissue
Adipokines imbalance:
Decreased insulin sensitizer adipokines (adiponectin…)
Increased adipokines promoted insulin resistance (resistin, TNFα …)
Increased lipolysis: secretion of fatty acid (FA)
Increased secretion of
proinflammatory adipokines (IL6, TNFα, IL1β, osteopontin,…)
profibrogenic adipokines (TGFβ, leptin, resitin, osteopontin...)
FFA
Increase in local and systemic (muscle, liver) insulin resistance
Non-esterified fatty acid
Inflammation
Fibrosis
İnsulin direnci
DNL
60%
25%
Hyperinsulinemia
Hyperglycemia
Increased lipogenesis
FA
Esterification
Triglycerides
Steatosis
15%
diyet
Chylomicron

Genetik faktörler

SNP: Single Nucleotide polymorphism

İKİZLER

Table 1. Major single nucleotide polymorphisms identified in pediatric MAFLD. Single nucleotide polymorphisms (SNP) related to variants in *PNPLA3*, *TM6SF2*, *GCKR* and *IFNL4* and have a moderate impact on the risk of MAFLD because these depend on multifactorial interactions, and their impact on the pediatric MAFLD risk is currently not well defined.

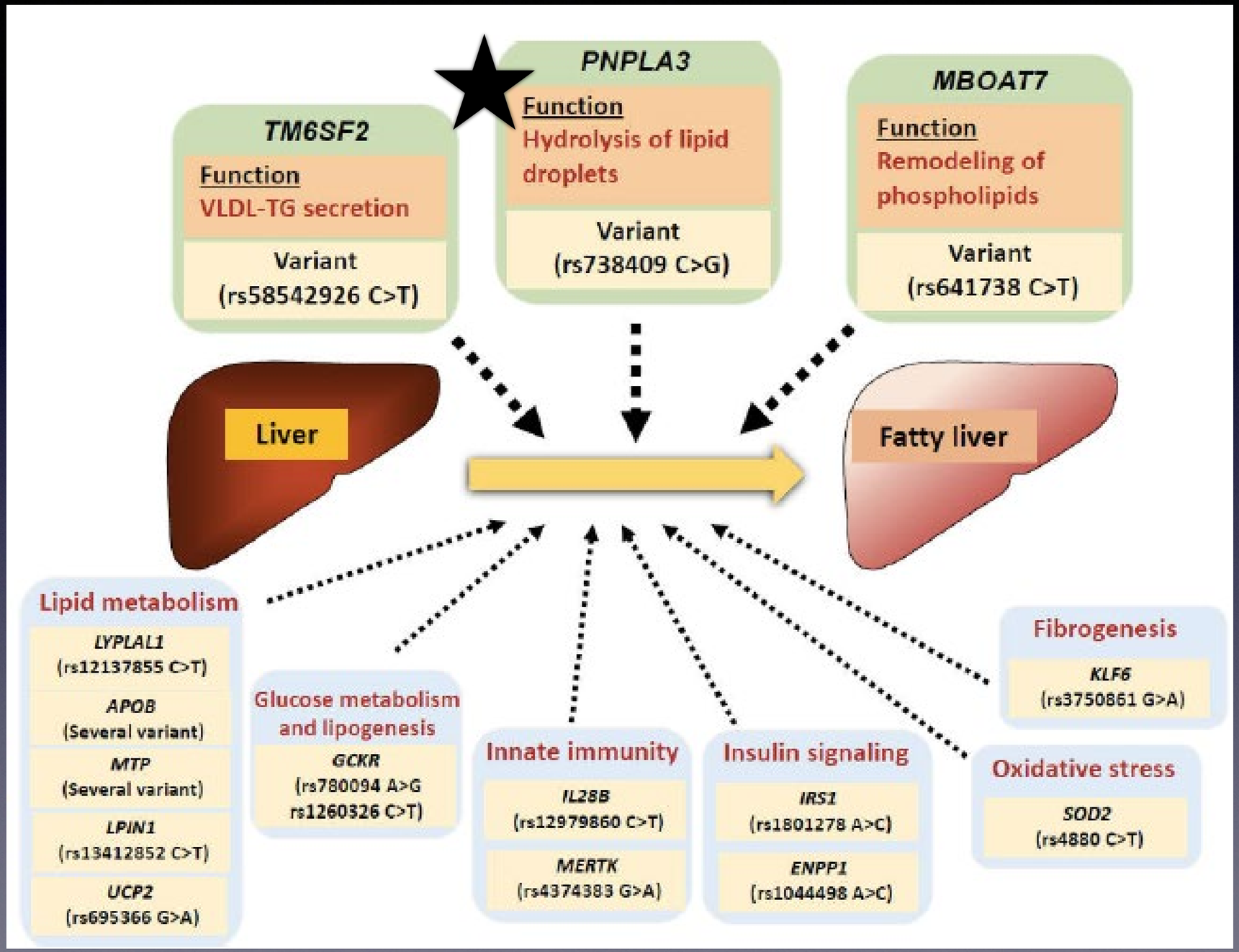
Gene	Variant	Function	Clinical Form	Reference
PNPLA3	I148M	Lipid droplets remodeling	NAFL with the risk of progressive steatosis	[33]
TM6SF2	E167K	Impact VLDL-mediated lipid secretion leading to fat accumulation in liver	NAFL	[32]
GCKR	rs1260326	Inhibition of glucokinase enzymatic activity and modulation of hepatic lipogenesis	NAFL	[32]
IFNL4	rs368234815 δG	Increase fat accumulation	NAFL	[16]

NAFLD kalıtım %35-60

Ailede sirotik NAFLD (+) 12 kat yüksek progresif hastalık

İnsülin sinyal yolağı genleri; IRS1 ve ENPP1… reseptör genleri

Genetik faktörler



Genetik Varyasyonlar

TABLE 2 | Genetic variations associated with pediatric MAFLD.

Gene	Variant						Phenotype	References
PNPLA3	rs738409 C>G	22q13.31	Mexican	1,037	Lipid droplets remodeling	Ile148Met	↑MAFLD, Fibrosis	(41)
			Taiwanese	520				(42)
			Hispanic	327				(43)
			Caucasian	149				(44)
TM6SF2	rs58542926 C>T	19p13.11	Italian	1,010	Modulate hepatic VLDL secretion	Glu167Lys	↑MAFLD, Fibrosis	(45)
			402 Caucasians 266 African Americans 289 Hispanics	957				(46)
			Taiwanese	831				(47)
*GCKR**	rs780094 C>T	2p23	Taiwanese	797	Modulate hepatic lipogenesis	Intronic variant	↑MAFLD, Fibrosis	(48)
	rs1260326 C>T		181 Caucasians 139 African Americans 135 Hispanics	455		Leu446Pro		(49)
*MBOAT7***	rs641738 C>T	19q12.42	Italian	1,002	Remodeling of phosphatidylinositol	Glu17Val	↑MAFLD, Fibrosis	(50)
			Caucasian	467				(51)
			Taiwanese	831			No effect	(47)
	rs626283 G>C		Caucasian	860		Intron variant	↑MAFLD	(52)
HSD17B13	rs72						ibrosis	(53)
IRGM	rs10							(54)
								(55)
MTTP	rs23						ibrosis	(56)
LPIN1	rs13						ibrosis	(57)
IRS-1	rs18							(58)
ENPP1	rs10						↑MAFLD, Fibrosis	(58)
			German	70				(59)
GPR120	rs116454156 G>A	10q23.33	Italian	581	Modulate inflammation response	Arg270His	↑MAFLD	(60)
UGT1A1	rs4148323 G>A	2q37.1	Taiwanese	234	Increase bilirubin with anti-oxidant activity	Gly71Arg	↓MAFLD	(61)
PPARGC1A	rs8192678 G>A	4p15.1	Taiwanese	781	Regulate cellular energy metabolism	Gly487Ser	↑MAFLD	(62)
HO-1	(GT)n repeat	22q12	Taiwanese	101	Anti-oxidative stress	Promoter activity	↑MAFLD	(63)
CNR2	rs35761398 A>G	1p36.11	Italian	118	Modulate inflammation response	Gln63Arg	↑MAFLD	(64)
KLB	rs17618244 G>A	4p14	Italian	249	Upregulate lipotoxic and proinflammatory genes	Arg728Gln	↑MAFLD	(65)
KLF6	rs3750861 G>A	10p15.2	Italian	152	Regulate hepatic stellate cell activation and fibrogenesis,	IVS1-27A	↓Fibrosis	(66)
FDFT1	rs2645424 A>G	8p23.1	87 Caucasians 61 African Americans 81 Hispanics	229	Modulate intrahepatic cholesterol biosynthesis	Intronic variant	↑MAFLD	(67)

Rutin genetik analiz önerilmiyor

Uzakdoğu Asya toplumları için önemli ??

EPİGENETİK

- DNA Dizisi değişmeden gen aktarımı
- Çevresel ve Genetik etkileşim aktarımı

  (DNA -Metilasyonu-Hepatosit MicroRNA de-regülasyonu)

  - Yaşam şekli ile geri döndürülebilir

- HAMİLELİK ÖNCESİ (BM>30 ise ciddi)
- Hamile Obez Anne

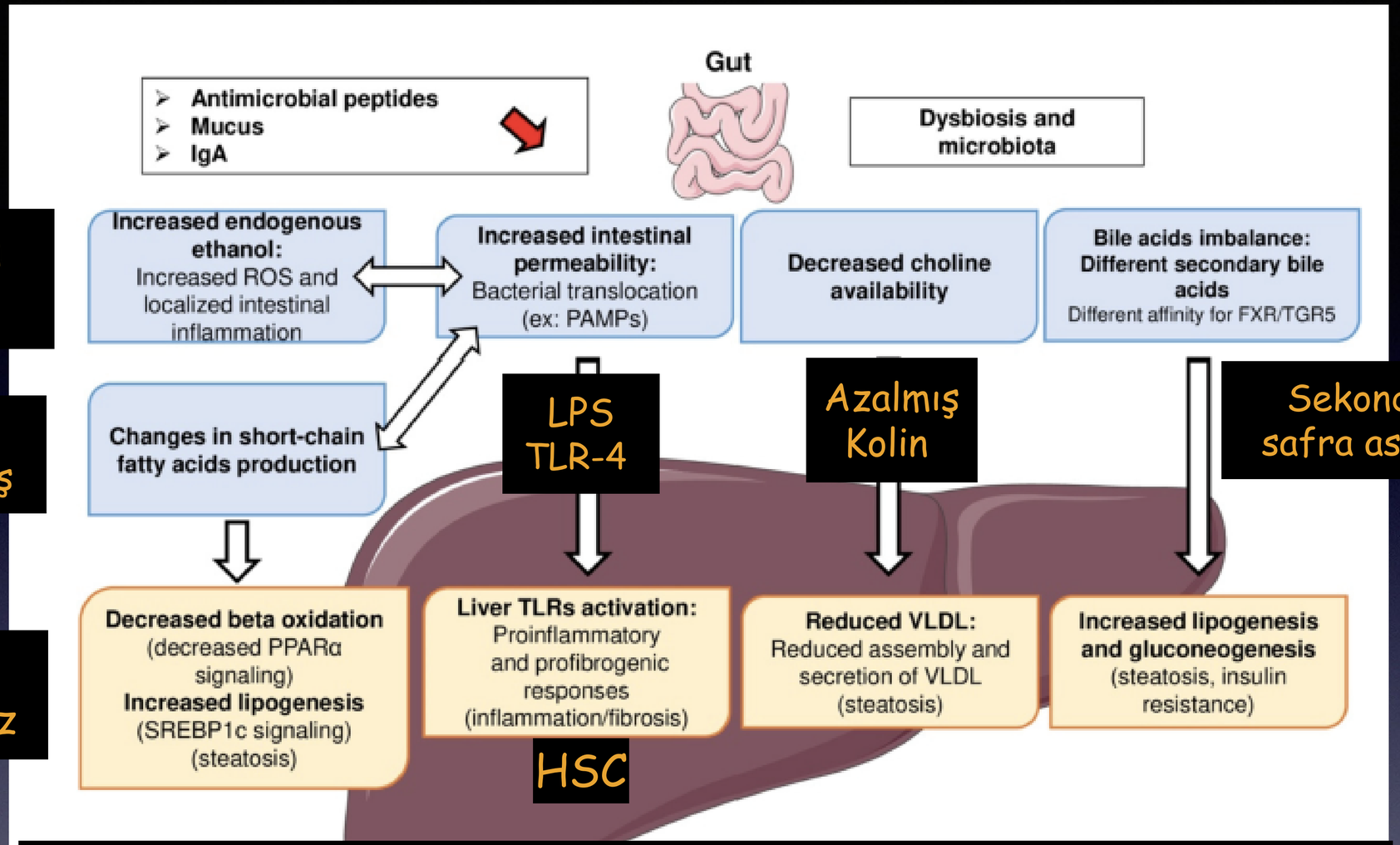
- Gestasyonel DM
- Hipertansiyon
- Pre-eklampsi- SGA

- Paternal obezite Sperm oksidatif stres artışı ve DNA metilasyona yatkınlık

Endojen Etanol

Kısa Zincirli yağ asidi artış

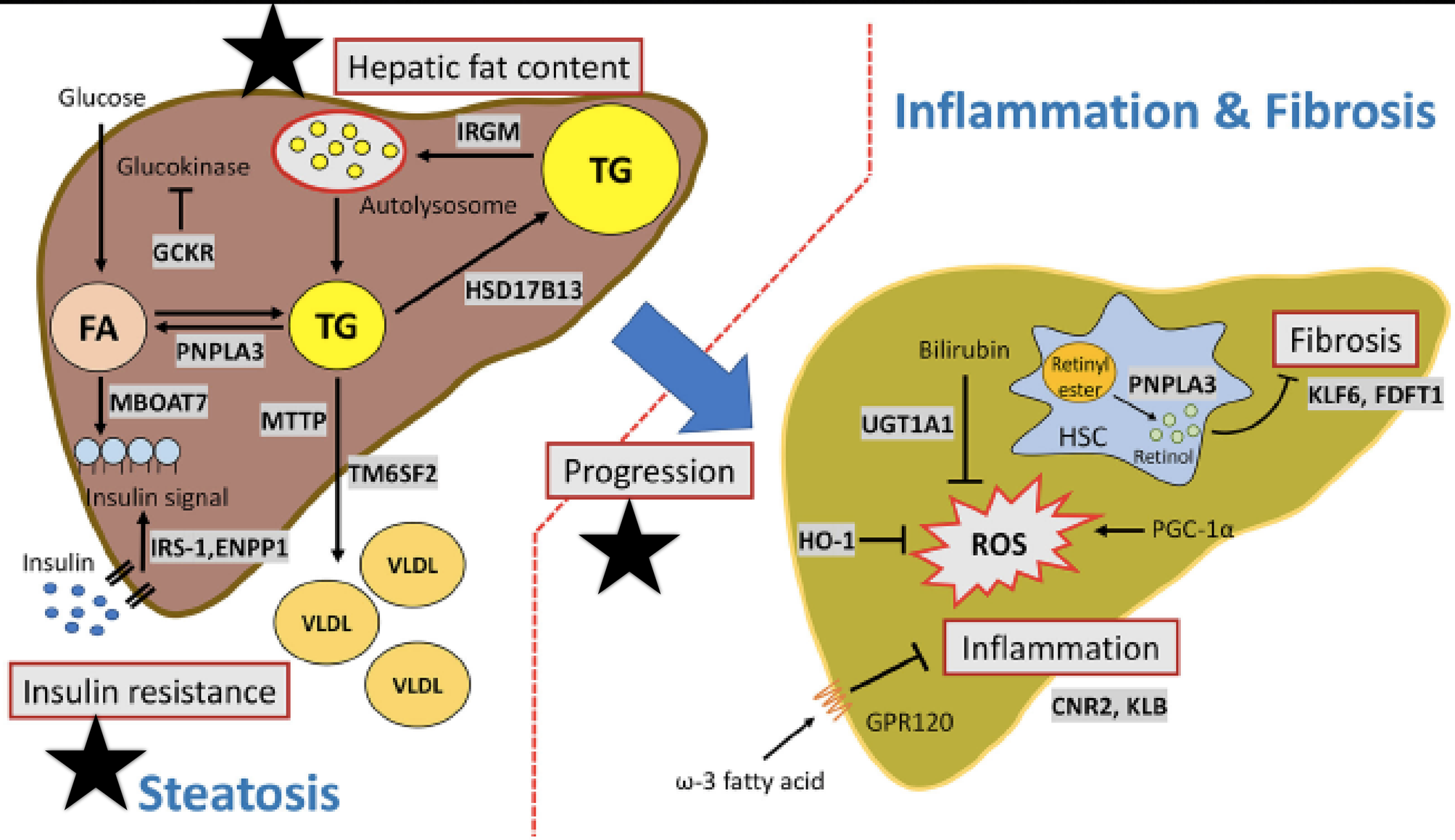
Artmış lipogenez



Spesifik Microbiota Değişikliği ???

7 yaş; Overweight çocuklar
staph.aureus oranı yüksek, bifidobakter oranı düşük

MAFLD lı Çocuklarda
Provitella, Proteobakteri ve Escherichia

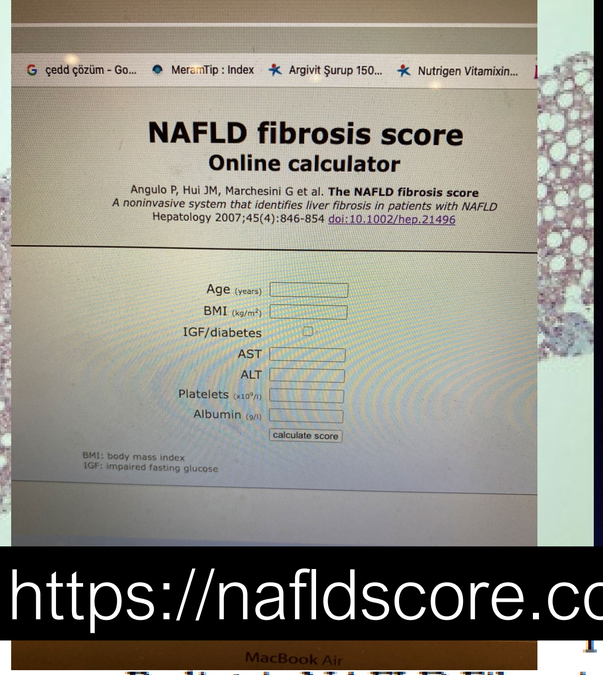


Genetik Polimorfizmler,
Antioksidan Mekanizmalar
Hepatik Stellat hücre aktivasyonu

Non-invaziv testler

Table 1 Non-invasive diagnostic tests of non-alcoholic fatty liver disease

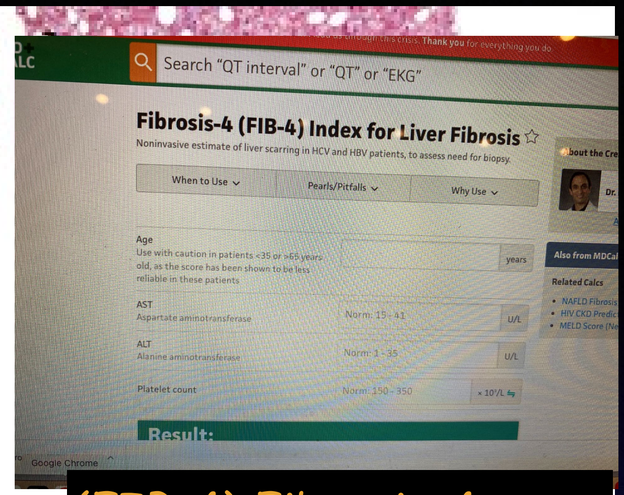
Hepatic fibrosis scores	Advanced biochemical markers	Newly proposed markers
AST/ALT ratio	Cytokeratin 18 fragment levels (CK-18)	Serum potassium
Platelet ratio index (APRI)	Extracellular matrix turnover biomarkers:	Soluble Fas and Fas Ligand (sFasL)
Fibrosis (FIB)-4 index	Enhanced liver fibrosis (ELF) test	Plasma catepsin D (CatD)
NAFLD Fibrosis score (NFS)	Amino-terminal propeptide III procollagen (PIIINP)	Circulating zonulin
Pediatric NAFLD fibrosis score	Hyaluronic acid (HA)	Adipokines (*e.g.*, chemerin)
		Serum Uric Acid (UA)
		Vitamin D
		Proteomics signature
		Metabolomic signature



https://nafldscore.com/

- Çocuklarda fibrozis güvenilir belirteç??
- AST/ALT >1
- Hyaluronik asit, TIMP-1

  Amino-terminal Propeptit -3



(FIB-4) Fibrosis-4

brosis test proposed in children. AST to platelet ratio index (APRI); fibrosis-4 (FIB-4) index; Pediatric NAFLD Fibrosis Index (PNFI); Pediatric NAFLD Fibrosis Score (PNFS). TG, triglyceride; WC, waist circumference.

Indexes Scores	Clinical and Biological Data								
	Age	BMI	WC (cm)	Fasted TG	ALT	AST	Platelet Count (10^9/L)	Albumin (g/dL)	Reference
APRI					X	X	X		[57]
FIB-4	X				X	X	X		[57]
PNFI	X		X	X					[58]
PNFS	X	X			X	X	X	X	[53]

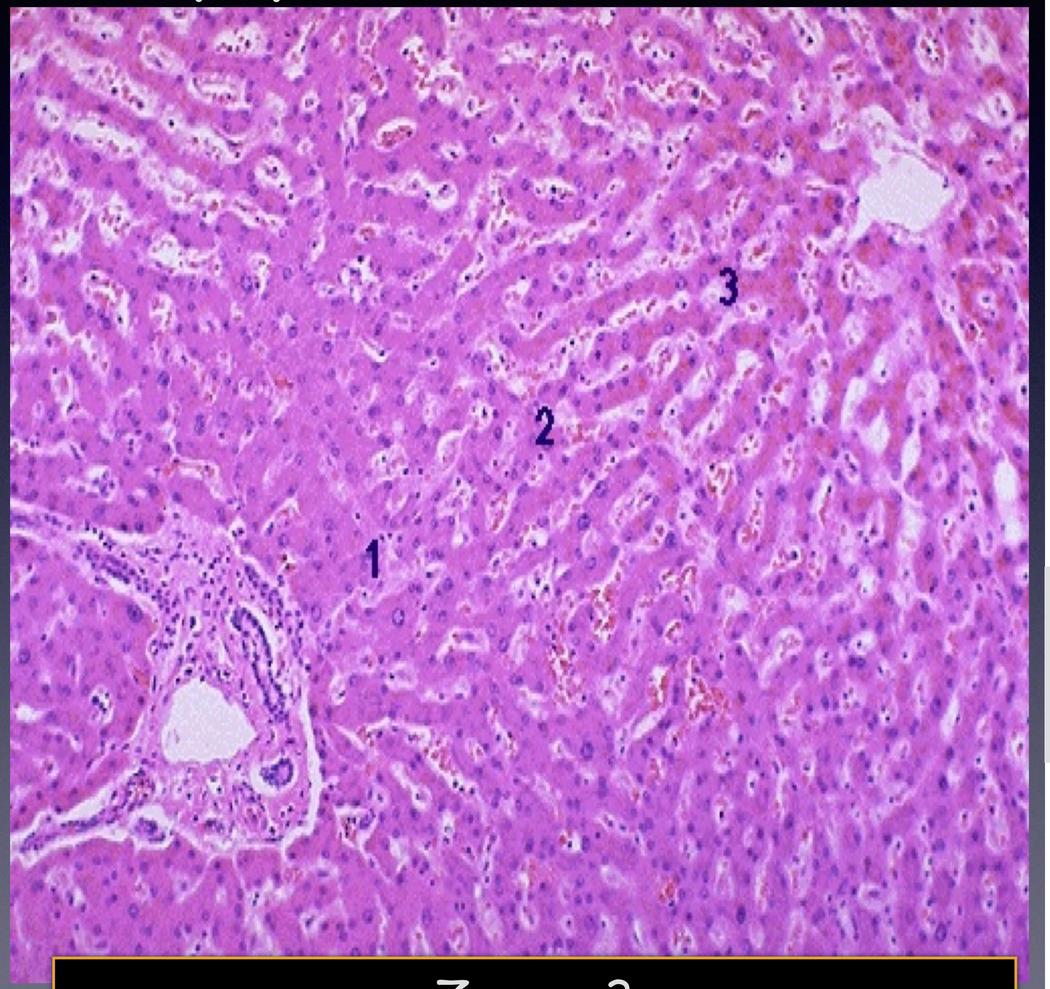
Pediatrik NAFLD Fibrozis Skoru (PNFS)

Görüntüleme Yöntemleri

- Abdominal USG
- Kontrollü zayıflatma parametreli (CAP)-USG, yağlanma derecesi
- Vibration-controlled transient elastography (VCTE) : KC sertliği- fibrozis evresi
- BT
- MRI
- MR spektroskopi -proton (yağ doku dansitesinde)

Histo-patoloji

Biyopsi-Altın Standart



Zone - 3
ilaç metabolizması merkezi

Erişkinler

Tip-1

Yağlanma ve
balon dejenerasyonu
Perisinuzoidal
fibrozis

Yağlanma
portal İnflamasyon
portal fibrozis

Tip-2
Pediatrik

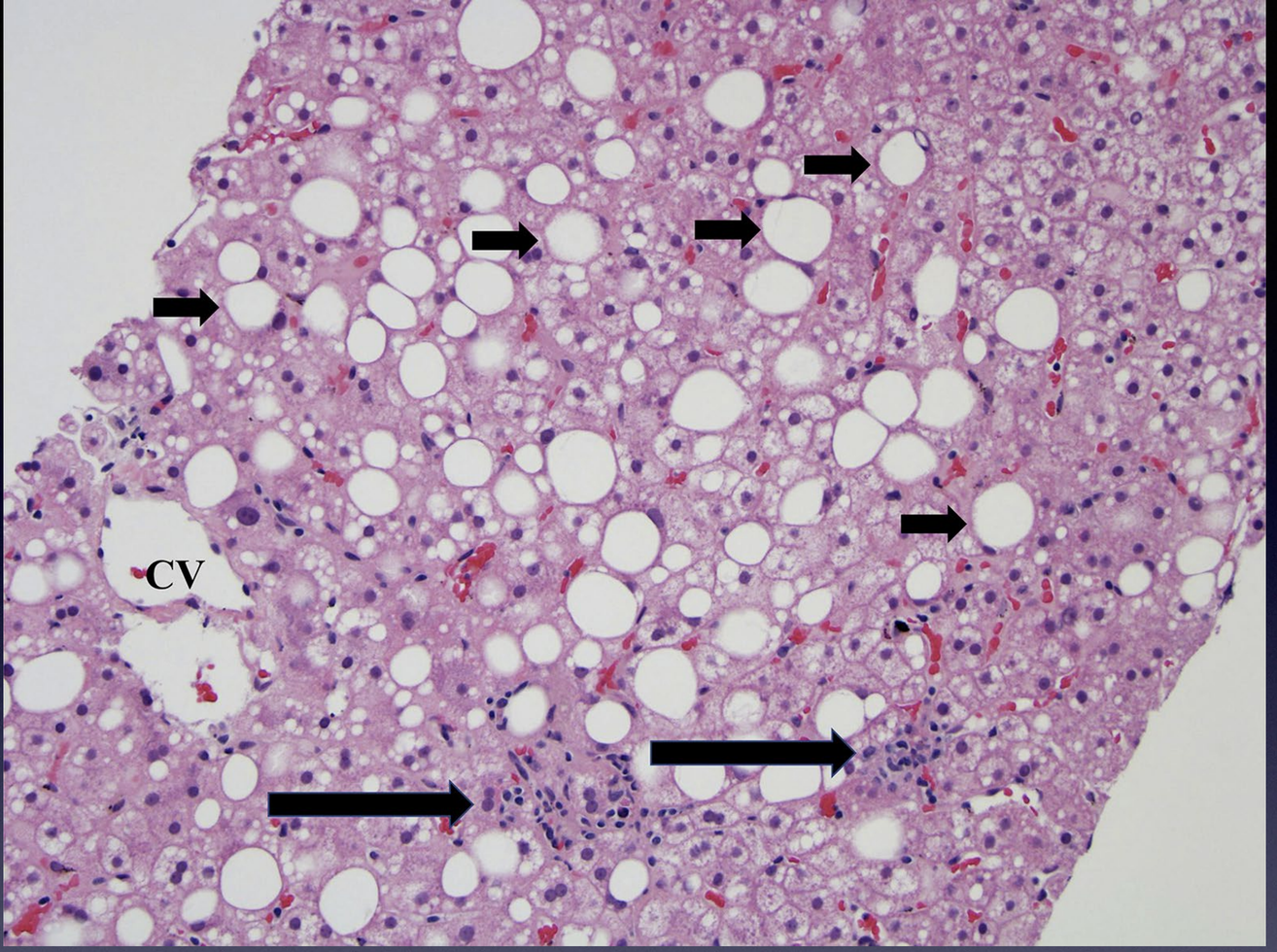
Risk faktörleri

Obezite
insulin direnci
Tip-2 DM
Dislipidemi
Uyku apnesi
Aile öyküsü

Metabolic Fatty Liver Disease in Children: A Growing Public Health Problem

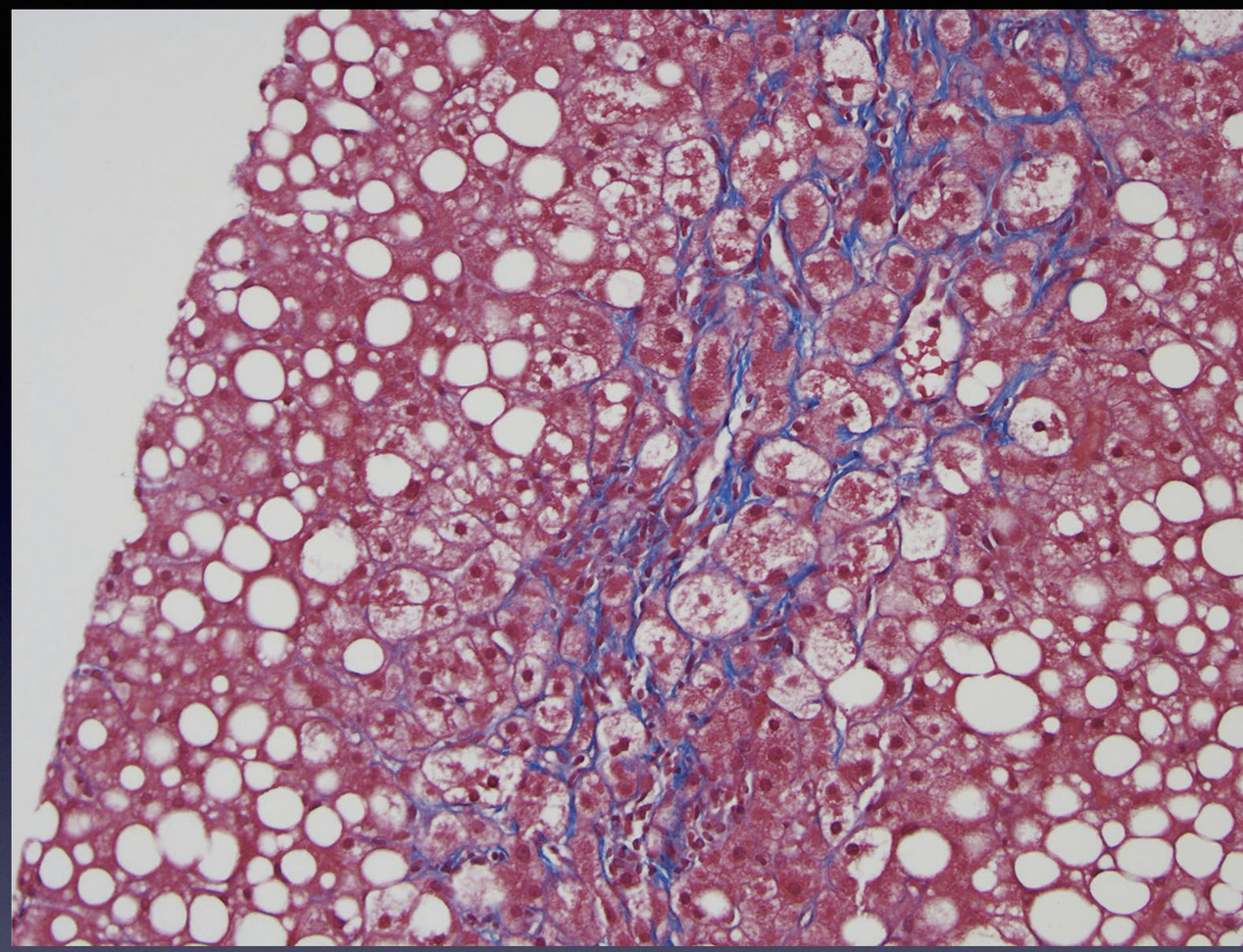
Biomedicines **2021**, *9*, 1915.

Sébastien Le Garf [1]

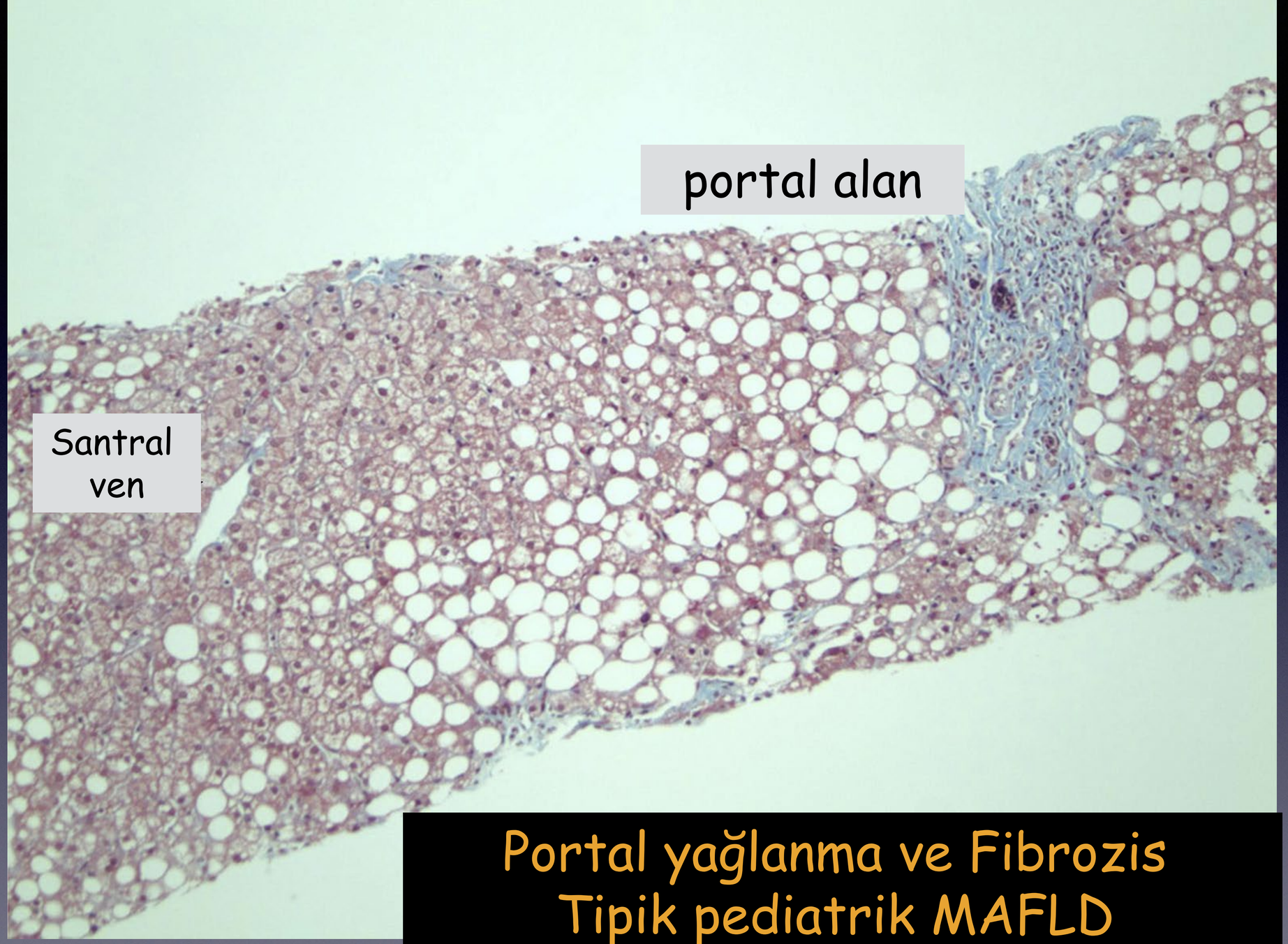


Santral ven çevresi
hepatositlerde balonlaşma

Perifere itilmiş Nukleus ve İnflamasyon



Santral ven çevresi fibrozis
(chicken Wire görünümü)
(Erişkin için tipik)



Portal yağlanma ve Fibrozis
Tipik pediatrik MAFLD

Klinik Özellik	Pediatrik	Erişkin
Prevalans	%7,6 (toplumda) %34 (obezlerde)	%24 %45-70 (obezlerde)
Histo-patoloji ✦ Steatoz ✦ İnflamasyon ✦ Balonlaşma ✦ Fibrozis	Zon-1 Portal alan Nadir Periportal	Zone-3 Lobuler Yaygın Perisantral
Siroz	%1-2	%5-10
Prognoz	Net Veri ???	Fibrozis Evresi

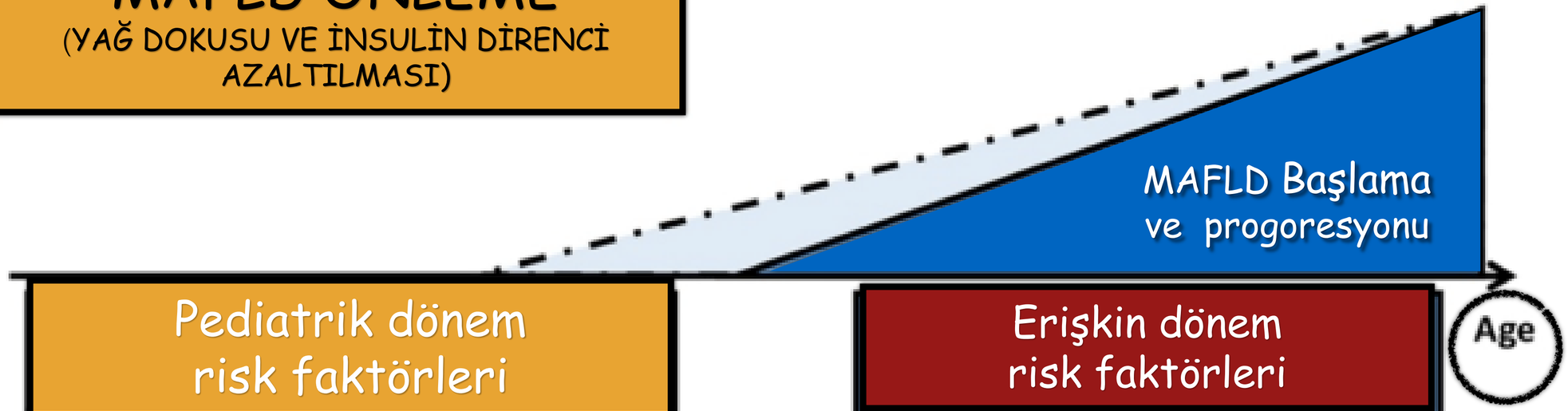
overlap
Patolojik
bulgular

Prognoz

Genel popülasyona göre yüksek mortalite

- Kardiyovasküler
- Kanser (HCC, diğer kanserler
- Siroz

MAFLD ÖNLEME
(YAĞ DOKUSU VE İNSULİN DİRENCİ AZALTILMASI)



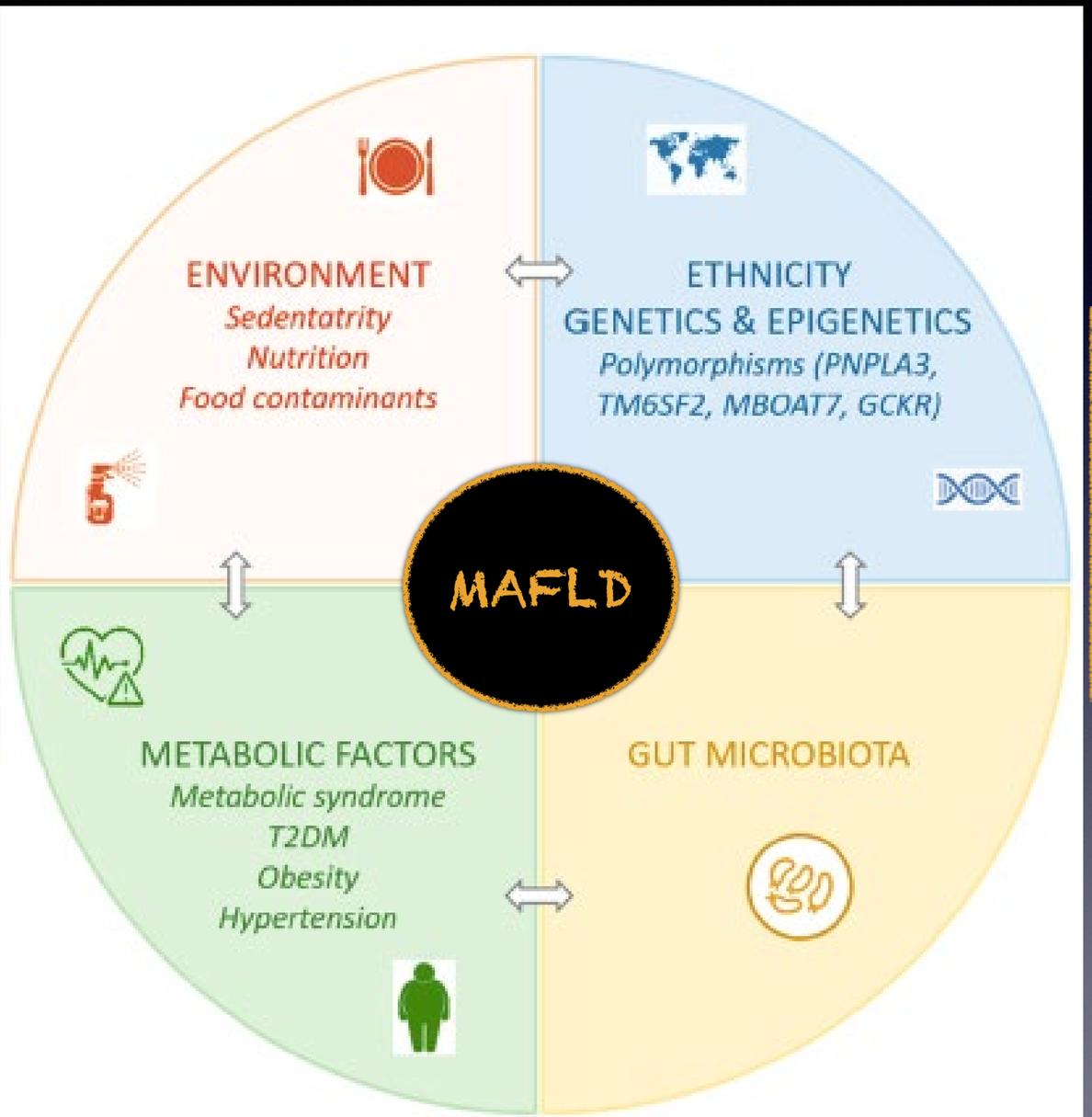
Pediatrik dönem risk faktörleri

- SGA
- İnsulin yüksekliği
- >BMI
- Erkek cinsiyet
- Etnik yapı (latin..)
- Genetik (PNPLA3,TM6SF2)

Erişkin dönem risk faktörleri

- Tip-2 DM
- Metabolik sendrom
- Obezite
- Hipertansiyon
- Disbiyozis
- Erkek cinsiyet
- Etnik yapı (latin)
- Genetik (PNPLA3,TM6SF2)

MAFLD - Tedavi



- Sistemik bozukluğun KC yansıması
- Karaciğere özgü bir tedavi ??...
- Metabolik bozukluk düzeltilmeli

Tedavi

Ebeveynler çocukların rol modelidir…

NASPGHAN

- Şekerli içeceklerden kaçınılması,
- Sağlıklı ve dengeli besin tüketilmesi
- Orta ve yüksek yoğunluklu günlük egzersiz
- Günde iki saatten DAHA AZ EKRAN süresi

- YAŞAM TARZI MODİFİKASYONU

SEFERBERLİK
Tüm aile fertleri

- Beslenme Düzenlemesi

EAT
unsaturated fats:
fish, avocado, nuts, and use sunflower, canola and olive oil

DON'T EAT
industrially-produced trans fats:
fast food, snack food,

foods and drinks with high amounts of sugars:
sugary snacks, candies, oriental sweets, and

Eat at least 5 portions of fruits and vegetables a day

At least 400g

- Yaşına uygun 500-1500 kcal azaltılmış diyet
- Haftada 500-1500g kilo kaybı hedeflenmelidir.

Limit salt to less than 5g per day

Equivalent to approximately 1 teaspoon

Use iodized salt

Egzersiz programı

- Haftada 5 gün, 30 dakika orta düzeyde
- Haftada 3 gün, ≥20 dakika, ağır yoğunlukta

Tedavi - ilaçlar

- Vitamin-E : 2*400
- Omega-3 : 250-500mg
- Slimarin : 2*160mg
- Metformin : 2*500mg- 2000mg??
- Statinler

…

…henüz rutin onaylanmış ilaç yok.

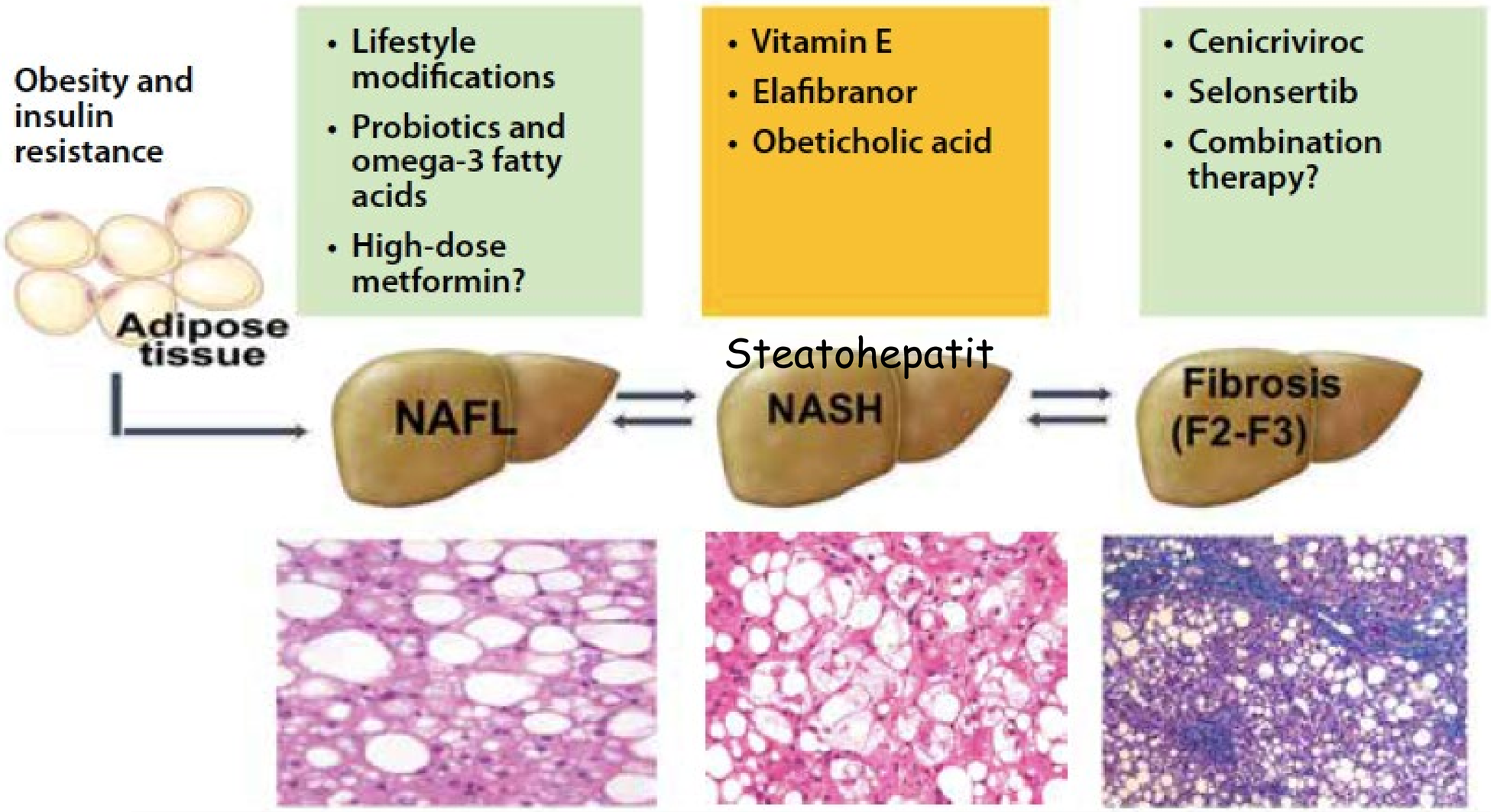
İlaca Yaslanma

Hasta + Aile

Pioglitazon : Mesane CA

Vitamin -E : Prostat CA, Hemorajik inme ???

Erişkin İlaç Çalışmaları



Hastalığın ağırlığına göre tedavi seçeneği..

MAFLD
FAZ-3 Çalışmaları- Erişkin

Etken Madde	Kısaltma	Çalışma İsmi	Firma İsmi	Etki Mekanizması
Obetikolik asit	OCA (Ocaliva)	REGENERATE	INTERCEPT	FXR agonist
Elafibranor	GFT-505	GOLDEN-505 RESOLVE-IT	GENFIT	PPAR-α/δ agonisti
Cenicriviroc	CVC	AURORA	ALLERGAN	CCR2/CCR5 İnhibitörü
Selonsertib	SEL GS-4997	STELLAR 3 STELLAR 4	GILEAD	ASK1 İnhibitörü
Aramchol		ARMOR	GALMED	SCD1 İnhibitörü
Semaglutide		ESSENCE	NOVO NORDISK	GLP-1 reseptör agonisti
Resmetirom	MGL-3196	MAESTRO-NASH	MADRIGAL	THR-β agonisti
Belapectin	GR-MD-02	NAVIGATE	GALECTIN THERA PEUTICS	Galectin-3 inhibitörü

pediatrik MAFLD YÖNETİMİ

Kimler Taranma

Testler

Biyopsi

Non - İnvaziv testler

Tedavi

Table. Summary of the NASPGHAN and AASLD Guidelines on the Diagnosis and Management of Pediatric NAFLD

AASLD

NASPGHAN

	AASLD	NASPGHAN (2017)
Screening for NAFLD	No recommendation regarding screening in overweight and obese children due to paucity of evidence rutin Q	• Screen with ALT levels using sex-specific upper limits of normal in all obese children and in overweight children with other risk factors starting at the age of 9-11 years. • Recommends against using routine ultrasound due to low sensitivity
Diagnosis/Workup	• Rule out other causes of chronic liver diseases. • Additional consideration to be given to monogenic causes of chronic liver disease such as inborn errors of fatty acid metabolism, peroxisomal disorders, and lysosomal storage disorders in very young or nonoverweight children	• Exclude alternative etiologies for elevated ALT levels and/or hepatic steatosis. • Investigate the presence of coexisting chronic liver diseases.
Liver Biopsy	Consider: OİH-otoantikor hepatotoksik ilaç başlama? spesifik ilaç başlama to starting pharmacotherapy for NASH.	• Consider for the assessment of NAFLD in children who have an increased risk of NASH and/or advanced fibrosis, such as patients with higher ALT levels (>80 U/L), splenomegaly, and AST/ALT >1. • Known clinical risk factors for NASH and advanced fibrosis include panhypopituitarism and type 2 diabetes.
Noninvasive Tests to Diagnose NASH and Stage Fibrosis	Further val… noninvasiv… Validasyon gerekir …ore …nic.	
Treatment	• Intensive lifestyle modifications should be the first-line treatment. • Metformin (500 mg twice daily) should not be prescribed as a NASH-specific therapy. • Vitamin E may be used to treat pediatric NASH, but the risks and benefits should be discussed Rutin Metformin Q Seçilmiş vaka VİT E	• Lifestyle modifications to improve diet and increase physical activity are recommended as first-line treatments. • Avoid sugar-sweetened beverages. • Increase moderate- to high-intensity physical activity and limit screen time activities to <2 hours … • No curren… supplemen… …t NAFLD because n… …nefit the majority … Rutin ilaç Q

9-11 yaş
USG - ALT

Diğer KC hastalığı veya Ko-insidans

AST/ALT > 1
Splenomegali
bilinen risk faktörleri
/ panhipopituitarizm

Kendim ne öğrendim…

10 yaş altında

MAFLD azlığı

- Pubertal hormon değişikliği
- İnsulin sinyal yolağı geçici bozulması
- Anormal yağ dağılımı olması

Teşekkürler