Diyabetik yağlı karaciğer ve nonalkolik yağlı karaciğer hastalığı farklı mıdır?

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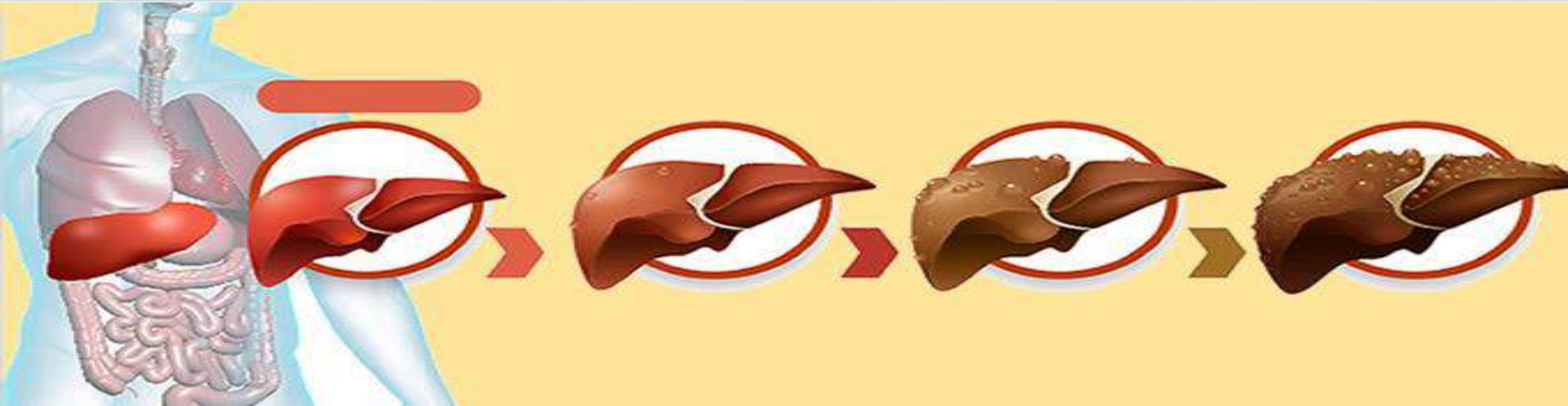
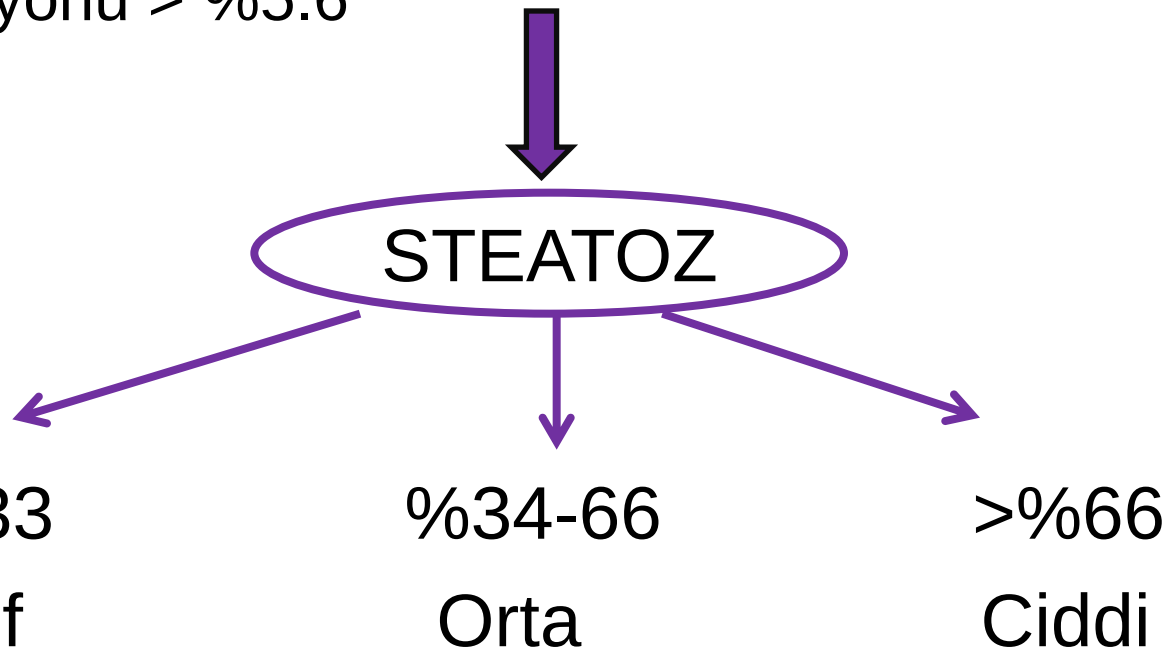
Ankara Yıldırım Beyazıt Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Endokrinoloji ve Metabolizma Hastalıkları



Nonalkolik yağlı karaciğer hastalığı (NAYKH)

- Sekonder yağ birikimine neden olabilecek herhangi bir hastalık olmadan gelişen karaciğer yağlanması

- Karaciğer biyopsi histolojik incelemelerinde yağ içeren hepatositler >%5
- Proton MR spektroskopi (^{1}H-MRS) veya kantitatif yağ/su selektif MR görüntüleme ile proton dansite yağ fraksiyonu > %5.6

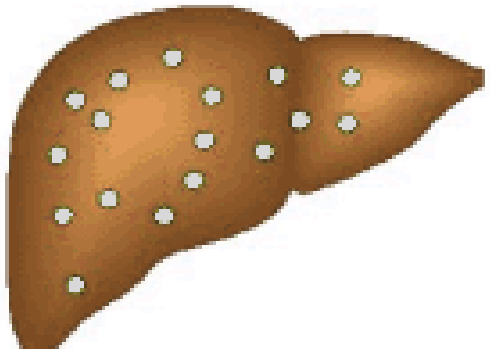


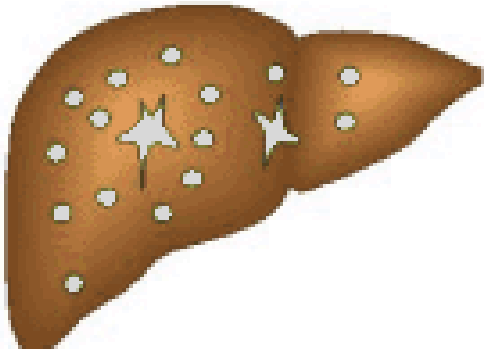
1. Hepatik steatozun görüntüleme veya biyopsi ile gösterilmesi
2. Alkole bağlı yağlı karaciğerin ekarte edilmesi (haftada erkek>21, kadın>14)
3. Yağlı karaciğer yapabilecek diğer nedenlerin ekarte edilmesi

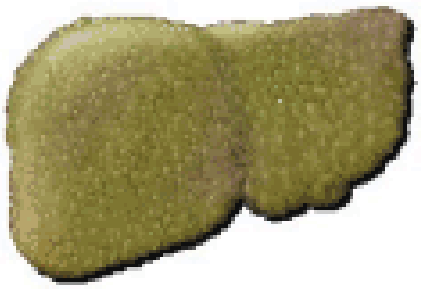
Nonalkolik yağlı karaciğer
NAYK

Nonalkolik steatohepatit
NASH

Siroz







Belirgin inflamasyon olmadan hepatik steatosis

Fazla yağın yanı sıra hepatoselüler hasar ve nekroinflamatuar değişikliklerin histolojik kanıtı

NAYKH

10-20 yılda karaciğer ilişkili mortalite %0-3

Nispeten benign bir durum

NASH

Siroza ilerleme riski 8 yılda %12

20 yıllık takipte karaciğer ilişkili mortalite %17.5

Myers RP. Noninvasive diagnosis of nonalcoholic fatty liver disease. Ann Hepatol 8 [Suppl. 1]: S25–S33, 2009.
Rafiq N, et al. Long-term follow-up of pa-tients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7:234 –238

Sıklık

- Endüstrileşmiş batı toplumları başta olmak üzere tüm dünyada oldukça yaygın - %20-30

HEPATOLOGY, VOL. 64, NO. 1, 2016

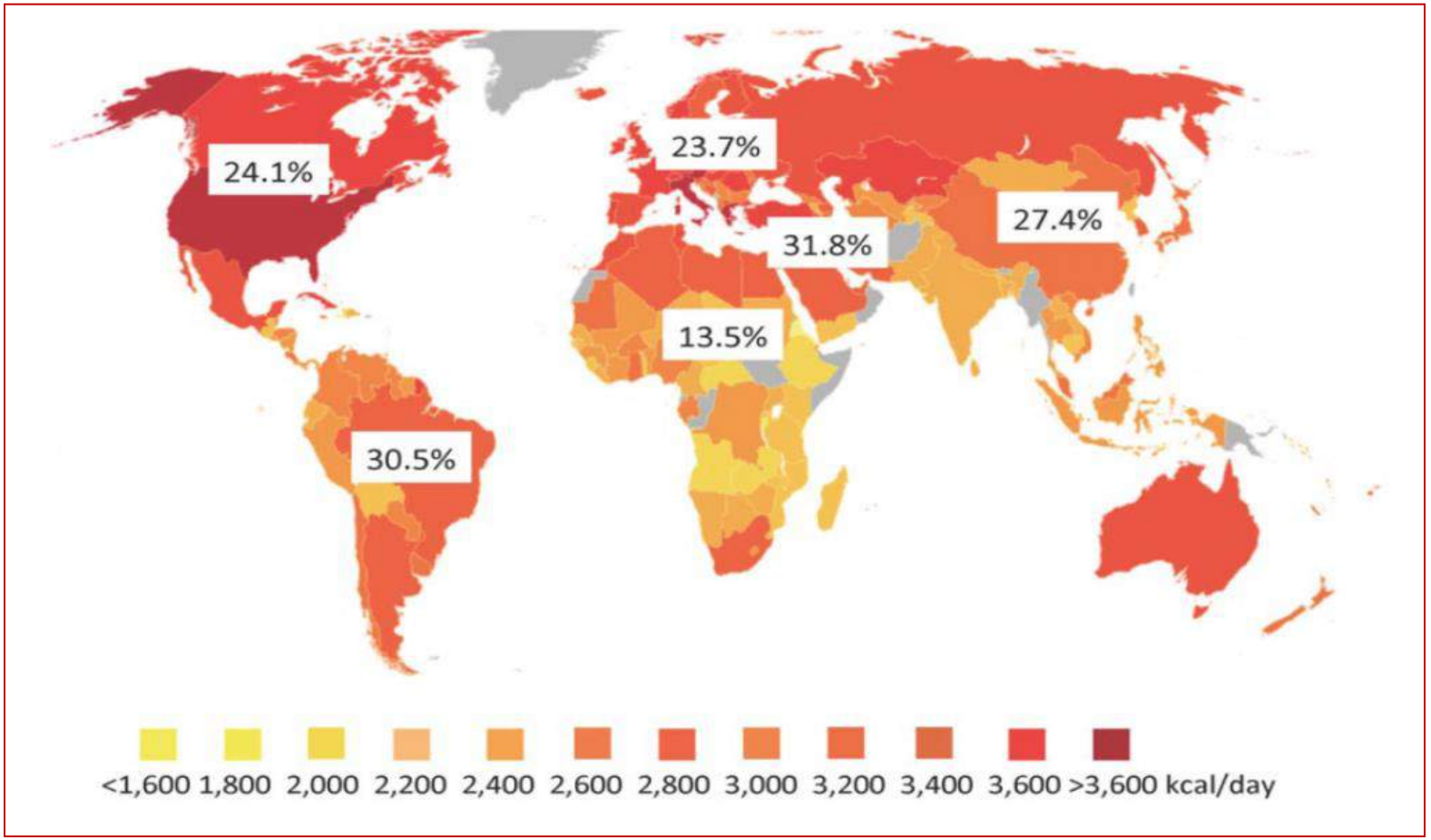
Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes

Zobair M. Younossi,[1,2] Aaron B. Koenig,[2] Dinan Abdelatif,[2] Yousef Fazel,[2] Linda Henry,[3] and Mark Wymer[1,2]

- 22 ülkeden 86 çalışma, 8,515,431 vaka
- NAYKH global prevalans %25.24

Buzzetti E, et al. Metabolism. 2016;65(8):1038-48.
Williams CD, et al. Gastroenterology 2011; 140:124.
Vernon G, et al. Aliment Pharmacol Ther 2011; 34:274.

Sıklık



- En yüksek prevalans Orta Doğu ve Güney Amerika'da, en düşük Afrika'da

Sıklık

- Nondiyabetik nonobez >30 yaş check-up için gelen 768 kişide NAYKH %23.4
  - Normal kilolularda %16.1
  - Fazla kilolularda %34.4

- Obezitede ve tip 2 diyabette >%70

Day CP. Clin Med 11: 176-178, 2011.
Leite NC,Liver Int 2009; 29: 113-119
Stefan N, Häring HU. Diabetes 2011;60:2011
Targher G, et al. Diabetes Care 30: 1212–1218, 2007
Kim HJ et al. Arch Intern Med.2004;164(19):2169-75.

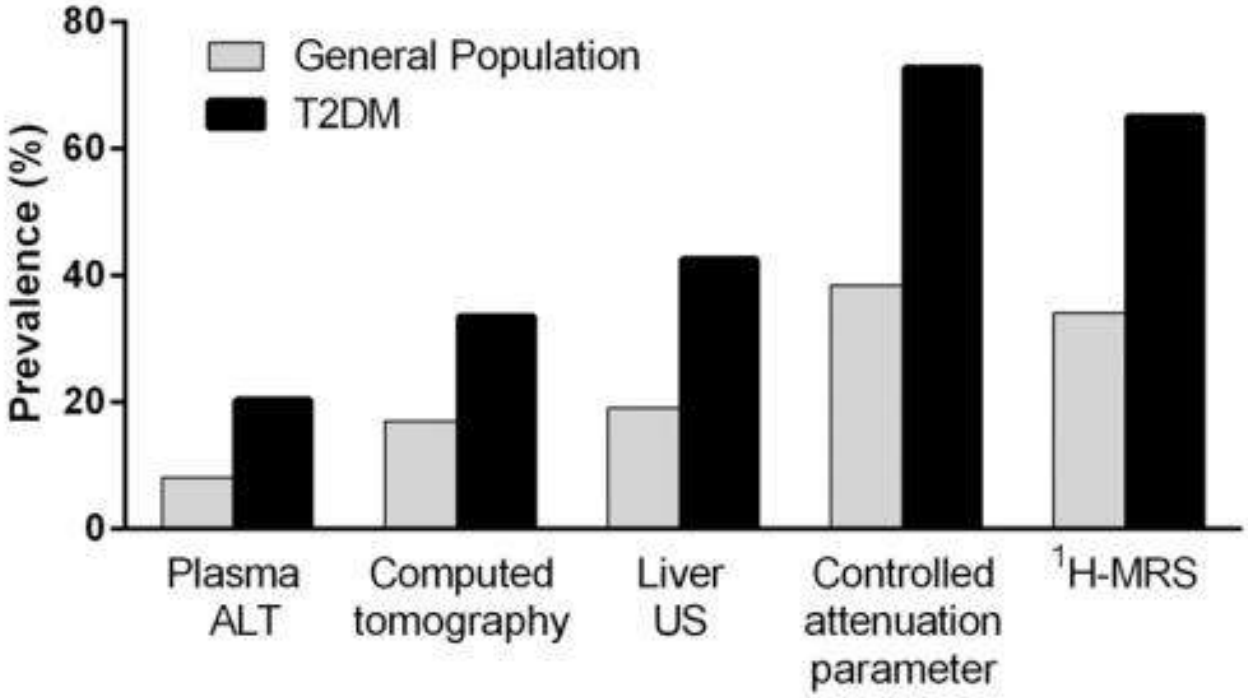
Diabetes Care Volume 40, March 2017 419

Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action

Fernando Bril[1] and Kenneth Cusi[1,2]

Diabetes Care 2017;40:419–430 | DOI: 10.2337/dc16-1787

Farklı tanısal yöntemlerle NAYKH prevalansı



Risk faktörleri

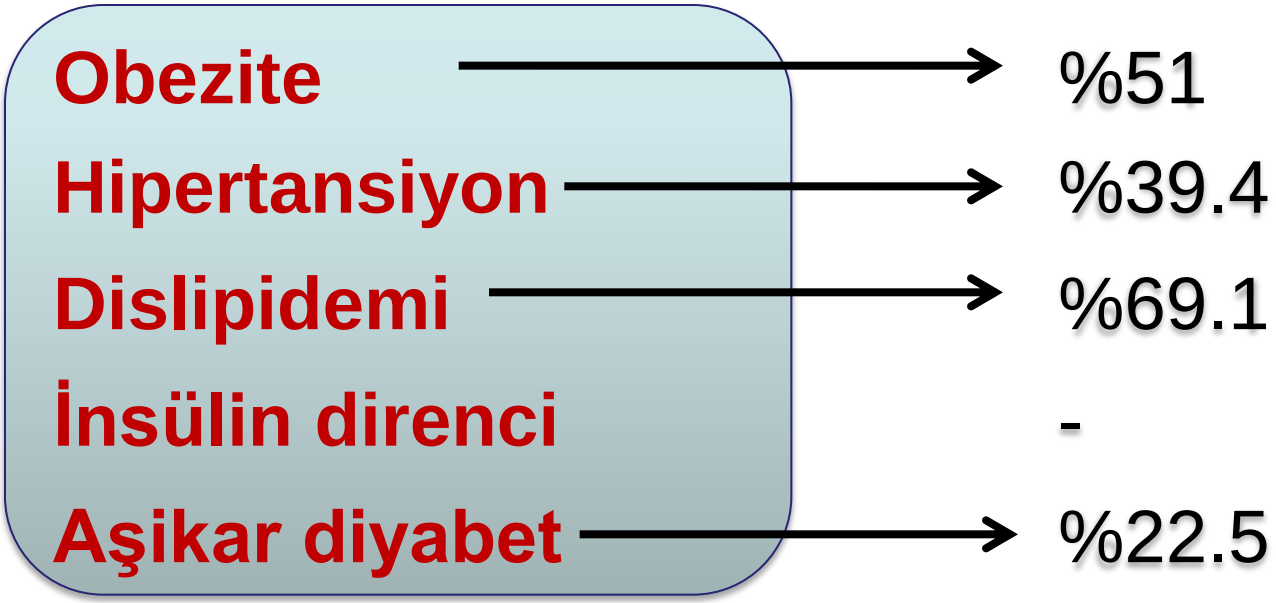
- Sağlıksız yaşam şekli
- Yüksek kalorili diet,
- Aşırı yağlı beslenme
- Rafine karbonhidrat
- Şekerle tatlandırılmış içecekler
- Yüksek fruktoz alımı
- Batı tarzı beslenme
- Sedanter yaşam

- PCOS
- Hipotiroidi
- OSA
- Hipopituitarizm
- Hipogonadizm
- Pankreatoduodenal rezeksiyon

Chalasani N, et al. Hepaology, 2012;55(6):2005-2023

Risk faktörleri

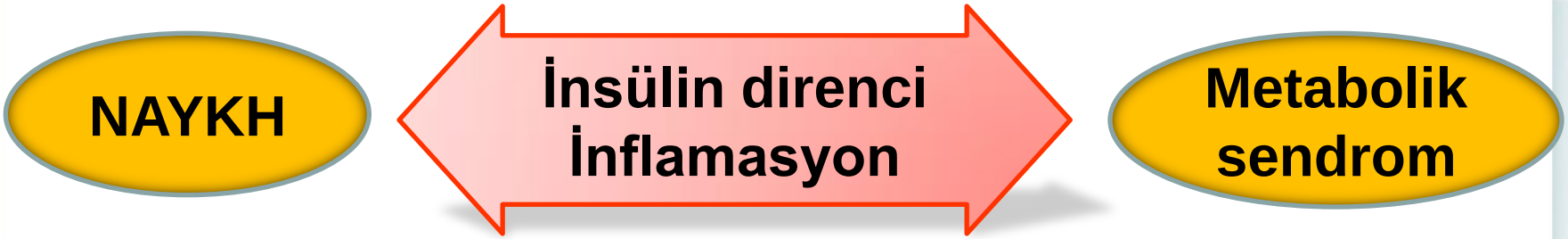
- NAYKH olanların çoğunluğunda metabolik sendromun bir veya birden fazla komponenti var



Chalasani N, et al. Hepaology, 2012;55(6):2005-2023
Younossi ZM, et al. Hepatology 2016;64(1):73-84

Risk faktörleri

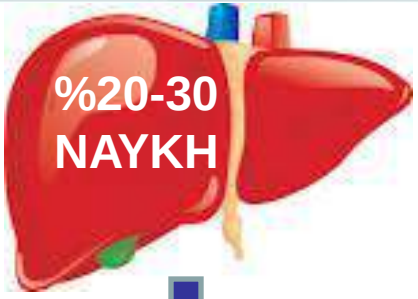
- Metabolik sendrom bileşenlerinin sayısı arttıkça yağlı karaciğer görülme riski ve ciddiyeti arttığı kabul edilmekte



Bu risk faktörlerinin hiçbiri de görülmeyebilir

Klinik

- Genellikle rastlantısal
  - Rutin biyokimyada transaminaz yüksekliği
  - Fizik muayenede hepatomegali
- NASH varlığında
  - Halsizlik, yorgunluk
  - Tanımlanamayan sağ üst kadran ağrısı
  - Nadiren spider anjiomlar, asit veya splenomegali



İyileşme %18-30

Stabil %34-50

%5-10

NASH %2-3

Stabil %50-70

Progresyon %25-37

%9-25

NASH SİROZ

%40-62

NAYK-HCC %0-0.5

NASH-HCC %0-2.8

HCC Komplikasyonlar KC yetm

%30-40

KC ilişkili mortalite

Klinik

NAYKH (NAYK/NASH)

Artmış mortalite

En sık neden kardiyovasküler hastalık

NASH

Artmış karaciğer ilişkili mortalite

Laboratuar

- Hafif veya orta derecede transaminaz yüksekliği

- Normal transaminaz değerleri NAYKH'nı ekarte ettirmez

- Transaminaz yükseklikleri hepatik inflamasyon ve fibrosis derecesi ile korele değil

Mofrad P, Hepatology 2003; 37:1286.
Noguchi H,. Acta Paediatr Jpn 1995; 37:621.
Charatcharoenwitthaya P. Dig Dis Sci 2012; 57:1925.

Görüntüleme

- ✓ Ultrasonografi: Ucuz ve noninvazif
  - Sensitivite %60-94, spesifite %84-95
  - Abdominal obezite ve KC yağ içeriği< %20 ise ↓
- ✓ Bilgisayarlı tomografi
- ✓ Manyetik rezonans görüntüleme

Tanıyı destekleyebilir ancak karakteristik bulguların olmaması NAYKH tanısını dışlamaz

Williams KH, et al.Endocr Rev. 2013;34(1):84-129.

Tanı

- Altın standart → **KARACİĞER BİYOPSİSİ**
- Birçok hastaya yapılmıyor

Tanı

- Steatoz için
  - Sitokeratin-18 fragmanları (hepatosit apoptoz belirteci)
  - Transient elastografi
  - Fatty liver index (FLI)
  - The SteatoTest®
  - NAFLD liver fat score
- Fibrosis için:
  - NFS (NAYKH fibrosis skor)
  - Fibrosis 4 calculator
  - Enhanced Liver fibrosis
  - FibroTest®

Bhatt HB, HepatoBiliary Surg Nutr 2015;4(2):101-108

Tanı

Hiçbir klinik, laboratuar veya görüntüleme histolojik aktiviteyi değerlendirmekte biyopsinin yerini alamaz ve NAYK ile NASH ayrımını yapamaz

Tarama

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

AASLD PRACTICE GUIDELINE

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACG,[1] Zobair Younossi, MD, FACG,[2] Joel E. Lavine, MD, PhD,[3] Anna Mae Diehl, MD,[4] Elizabeth M. Brunt, MD,[5] Kenneth Cusi, MD,[6] Michael Charlton, MD,[7] and Arun J. Sanyal, MD[8]

Recommendation

5. Screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost-effectiveness of screening. (Strength – 1, Evidence -B)

Diyabet obezite gibi risk faktörü olanlarda dahi rutin tarama önerilmemekte

Tarama

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

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

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

Patients with IR and/or metabolic risk factors (i.e. obesity or metabolic syndrome [MetS]) should undergo diagnostic procedures for the diagnosis of NAFLD, which relies onthe demonstration of excessive liver fat (**A1**)

İnsülin direnci veya metabolik risk faktörü olanlarda (obezite veya metabolik sendrom) NAYKH için tanısal değerlendirme (karaciğer enzimler ve/veya US) yapılmalı

Tarama

In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (**A2**)

Tip 2 diyabetli hastalarda karaciğer enzimlerinden bağımsız olarak NAYKH varlığı araştırılmalı

Tarama

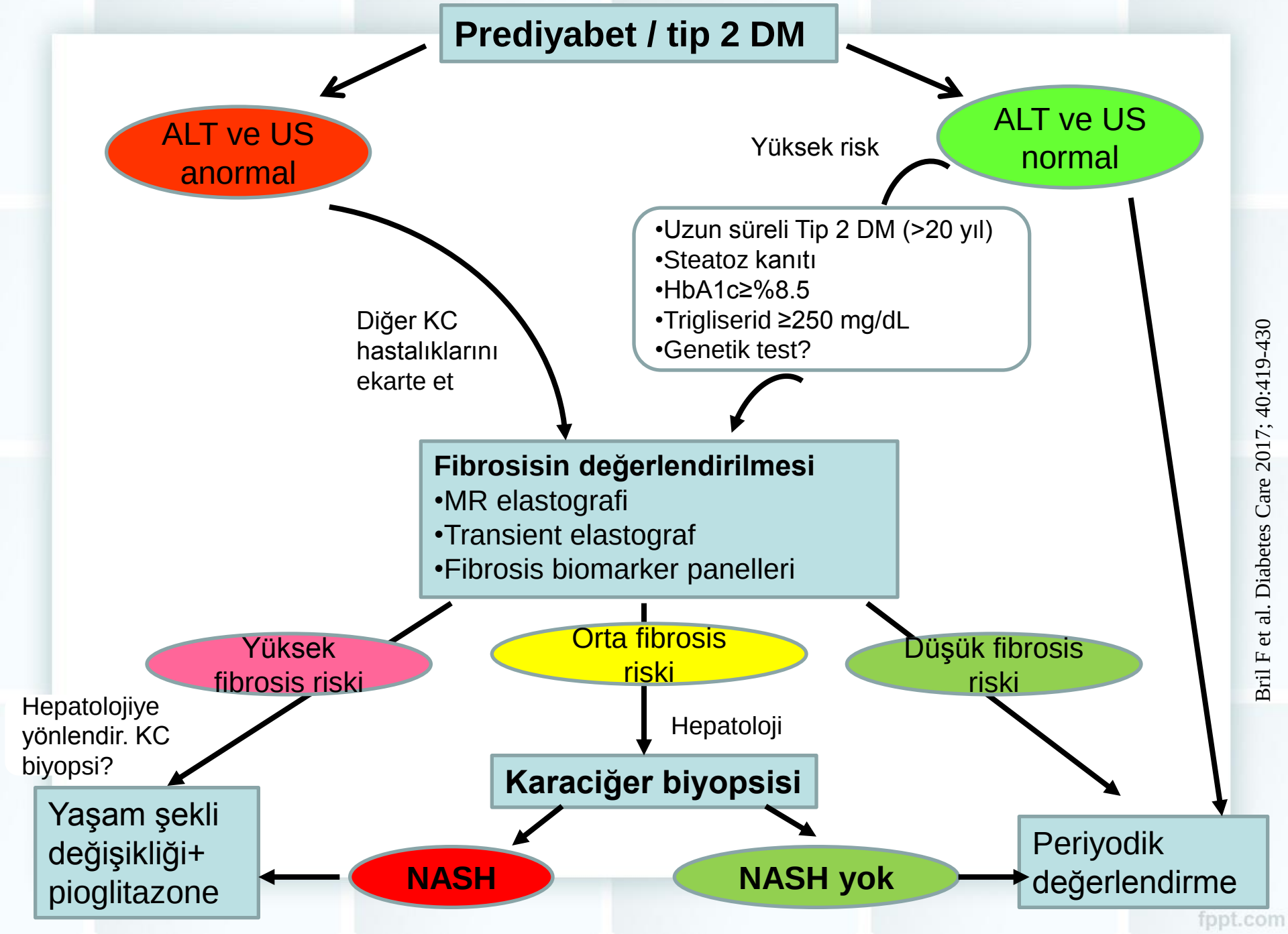
All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All

In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (**A1**) and if available by the standardized 75 g OGTT in high-risk groups (**B1**)

NAYKH olanlarda da

- Metabolik sendrom özellikleri

- Diyabet (APG, random PG, HbA1c, OGTT) taranmalıdır



Bril F et al. Diabetes Care 2017; 40:419-430

Metabolik sendrom, insülin direnci ve DM'de NAYKH daha SIK

- İnsulin direnci ve diyabet, NAYKH ve NASH için en sık ve en önemli risk faktörleri
- Obez ve diyabeti olmayan NASH hastalarında dahi insülin direnci olduğu gösterilmiş

Kim HJ, et al. Arch Intern Med. 2004;164(19):2169-75
Chitturi S, et al. Hepatology,. 2002;35,373-379

Metabolik sendrom, insülin direnci ve DM'de NAYKH daha CİDDİ

- NAYKH ciddiyeti için belirteç
- Metabolik sendrom → X 3 NASH ve ilerlemiş hepatik fibroz
- Tip 2 diyabet → *Daha ciddi NASH
  *Fibrosis ile ilişkili
  *Fibrosise ilerlemenin bir belirteci
  *Siroz riski ↑

Marchesini G, et al. Hepatology 37: 917–923, 2003.

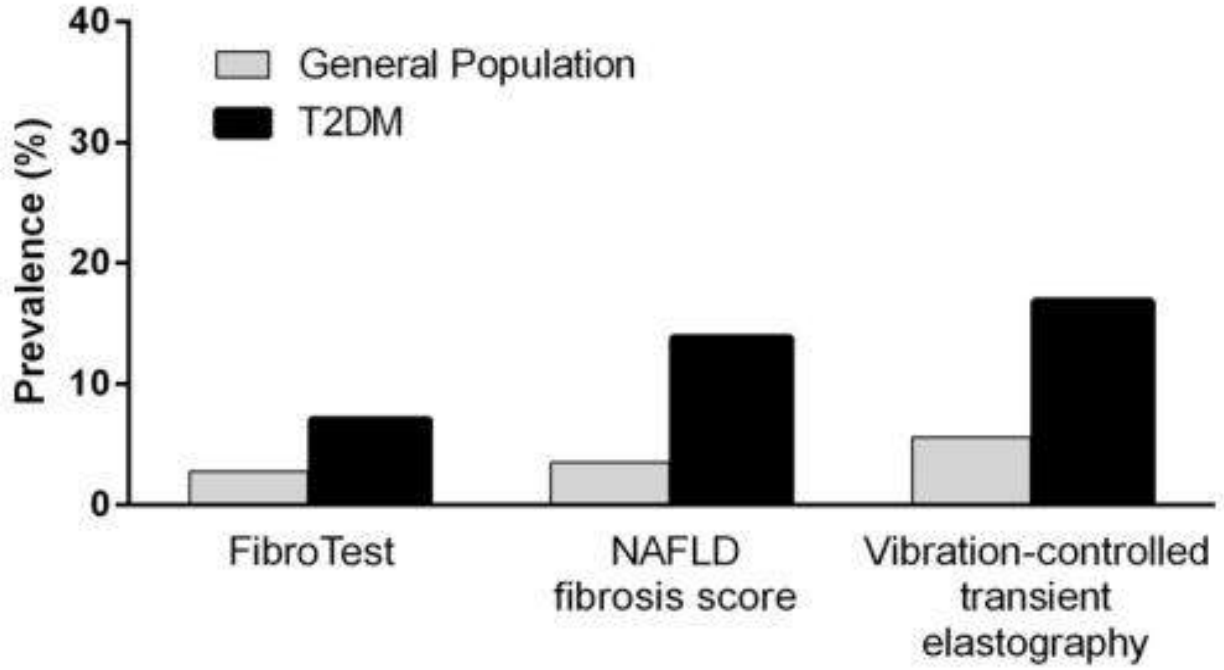
Diabetes Care Volume 40, March 2017 419

Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action

Fernando Bril[1] and Kenneth Cusi[1,2]

Diabetes Care 2017;40:419–430 | DOI: 10.2337/dc16-1787

İlerlemiş fibrosis prevalansı



Prediyabette NAYKH daha sık, daha ciddi

Diabetes and Nonalcoholic Fatty Liver Disease: A Pathogenic Duo

Endocrine Reviews, February 2013, 34(1):84–129

K. H. Williams, N. A. Shackel, M. D. Gorrell, S. V. McLennan, and S. M. Twigg

TABLE 1. Summary of relative strength of associations of NAFLD and its subtypes with predi diabetes based on human studies

NAFLD pathological subcategory	Type 1 diabetes[c]	Prediabetes[c] (IFG, IGT)	Type 2 diabetes
Simple steatosis	+	++	++
NASH with high NAS[a]	+/−	++	++
NASH with substantial fibrosis (F2-F3)	+/−	++	+++
Cirrhosis due to NAFLD (includes F4)[b]	+/−	+++	++++

- Histolojik olarak kanıtlanmış NAYKH olan 432 hasta

Tip 2 diyabet orta derece fibrosisden ciddi fibrosise ilerleme için bağımsız bir risk faktörü

- NAYKH nedeniyle biyopsi yapılan 458 hasta

Diyabet varlığı NASH ve ciddi fibrosis için bağımsız prediktör

Hossain N, et al Clin Gastroenterol Hepatol 2009;7:1224 –1229
Fracanzani A, et al. Hepatology 2008; 48:792–798

BBA Clinical 3 (2015) 141–145

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Clinical spectrum of non-alcoholic fatty liver disease in diabetic and non-diabetic patients☆

George Boon-Bee Goh [a], Mangesh R. Pagadala [a], Jaividhya Dasarathy [c], Aynur Unalp-Arida [f], Ruth Sargent [a], Carol Hawkins [b], Achuthan Sourianarayanane [a], Amer Khiyami [b], Lisa Yerian [d], Rish K. Pai [d], Srinivasan Dasarathy [a,e], Arthur J. McCullough [a,e,*]

Comparison of liver histology between DM and non-DM patients.

Histology feature	Presence of DM		p value*
	Yes (n = 238)	No (n = 263)	
Grade of steatosis			0.500
0	5 (2.1%)	6 (2.3%)	
1	85 (36.0%)	81 (30.9%)	
2	79 (33.5%)	104 (39.7%)	
3	67 (28.4%)	71 (27.1%)	
Lobular inflammation			0.017
0	8 (3.4%)	28 (10.7%)	
1	104 (44.1%)	113 (43.1%)	
2	111 (47.0%)	109 (41.6%)	
3	13 (5.5%)	12 (4.6%)	
Ballooning			<0.001
0	39 (16.6%)	70 (26.7%)	
1	98 (41.7%)	129 (49.2%)	
2	98 (41.7%)	63 (24.0%)	
NAFLD activity score			0.200
NAS < 5	108 (46.0%)	136 (51.7%)	
NAS ≥ 5	127 (54.0%)	127 (48.3%)	
Median NAS (interquartile range)	5 (3)	4 (3)	0.022
Stage of fibrosis			<0.001
0	40 (16.8%)	98 (37.3%)	
1	55 (23.1%)	79 (30.0%)	
2	47 (19.7%)	41 (15.6%)	
3	47 (19.7%)	30 (11.4%)	
4	49 (20.6%)	15 (5.7%)	

- ✓ **NAYKH'nda klinik spektrum eşlik eden diyabet olup olmamasına göre farklı**
- ✓ **Diyabetli hastalarda NAYKH daha agresif**

İnsülin direnci NAYKH patogenezinde çok önemli

NAYKH varlığı metabolik sendrom ve ileride tip 2 diyabet gelişimi için önemli bir prediktör

Williams KH, et al.Endocr Rev. 2013;34(1):84-129.
Sung KC, etal. J Clin Endocrinol Metab 2011; 96:1093–1097

NAYKH'da metabolik sendrom ve DM

- 20 yıllık takipte sadece NAYKH olanlarda sağlıklı gruba oranla daha fazla metabolik sendrom geliştiği saptanmış

NAYKH

- Tip 2 diyabet prevalansı X 2-5
- Artmış mikro ve makrovasküler komplikasyonlar

Luukkonen PK, et al. J Hepatol 2016;64(5):1167-75
Armstrong MJ, et al. Hepatology 2014;59:1174–1197.
Williams KH, et al.Endocr Rev. 2013;34(1):84-129.
Lonardo A, et al Dig Liver Dis 2015;47(3):181-90).

NAYKH’da metabolik sendrom

- NAYKH metabolik sendrom gelişimi için bir risk faktörü

Retrospektif	
Hui AY, 2005	17 Chinese patients who had liver biopsy at least 3 years before and accepted to undergo a second liver biopsy
Friis-Liby I, 2004	Of 102 biopsy-proven NAFLD patients, 80 (77% males; median age 46) were re-evaluated
Sung KC,2014	Cohort of 11,448 Korean people without hypertension (health check-up). FL status (absent or present) assessed by US
Prospektif	
Lee DH, 2003	4,844 black and white men and women aged 18-30 years (CARDIA study)
Nakanishi N, 2004	Occupational cohort of 2,957 MS-free and 3,260 non-diabetic Japanese men aged 35-59 years who did not have any medications for hepatitis, ALT > 3 times ULN, or CVD history at baseline (health check-up)
Hanley AJG, 2005	633 African-American, Hispanic and non-Hispanic white subjects aged 40–69 from the Insulin Resistance Atherosclerosis Study, free of MS at baseline
André P, 2007	Cohort of 1,656 men and 1,889 women MS-free at baseline, according to the International Diabetes Federation definition.
Lee DS, 2007	3,451 participants in the Framingham Study cohort (mean age 44 years, 52% women)
Adams LA, 2009	358 subjects, 68% male, mean age 59.9 (109 with and 249 without NAFLD diagnosed by raised ALT (>40 IU/l) after exclusion of other causes)
Jo SK, 2009	Korean cohort of 15,250 men (mean age 38 years) and 6,280 women (mean age 41 years) (health check-up)
Ryu S, 2010	Cohort of 9,148 MS-free healthy male workers (health check-up)
Xu Y, 2011	5,404 subjects (aged ≥ 40) from two urban communities in Shanghai (cross sectional study); a MS-free subgroup (n= 681) was included in the longitudinal study
Onat A, 2012	Cohort of 1,667 adults from general Turkish population (age 52 ±11 years)
Liu CF, 2012	Metanalysis of 9 prospective cohort studies involving 47,499 participants and 5,009 cases of MS
Chun H, 2013	Cohort of 13,435 Korean healthy adult men (mean age 42.0 ± 6.6 years) with normal BP (health check-up)
Ryoo JH, 2013	A MS-free cohort of 11,926 (out of 46,874) Korean men were classified in 3-group according to US-NAFLD status (normal, mild, moderate to severe) (health check-up)
Suh YJ, 2013	Cohort of 18,510 initially non-obese (health check-up)
Cicero AF,2013	Subsample of 824 pharmacologically untreated subjects from the Brisighella Heart Study (male, 401; female, 423) without MS, T2D, alcohol abuse, or known liver diseases.
Ryoo JH, 2014	Cohort of 22,931 healthy Korean men without baseline IR (HOMA-IR < 2.7) (health check-up)

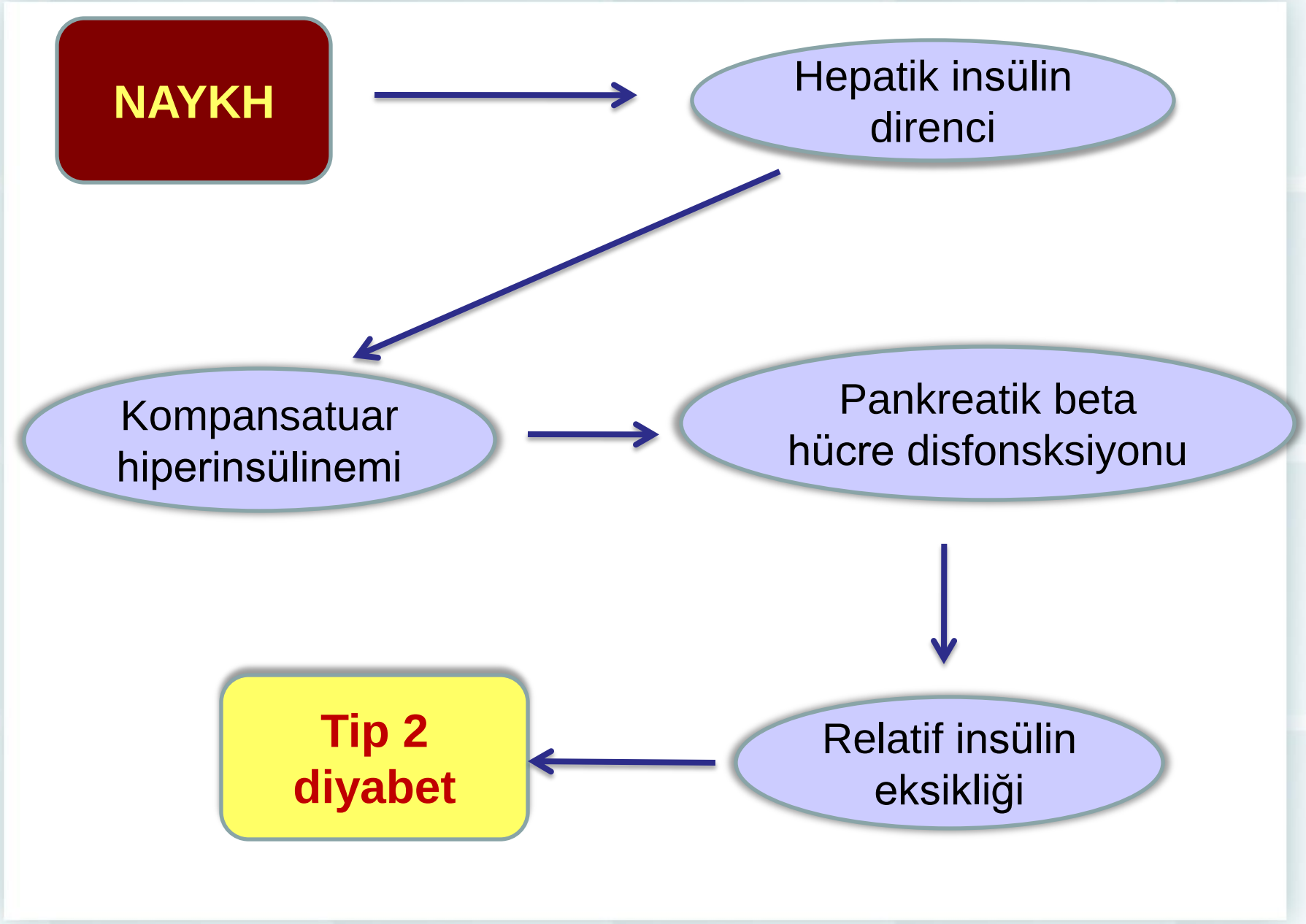
Lonardo A et al Dig Liver Dis. 2015 Mar;47(3):181-90.

NAYKH’da tip 2 DM

- NAYKH tip 2 diyabet gelişimi için risk faktörü

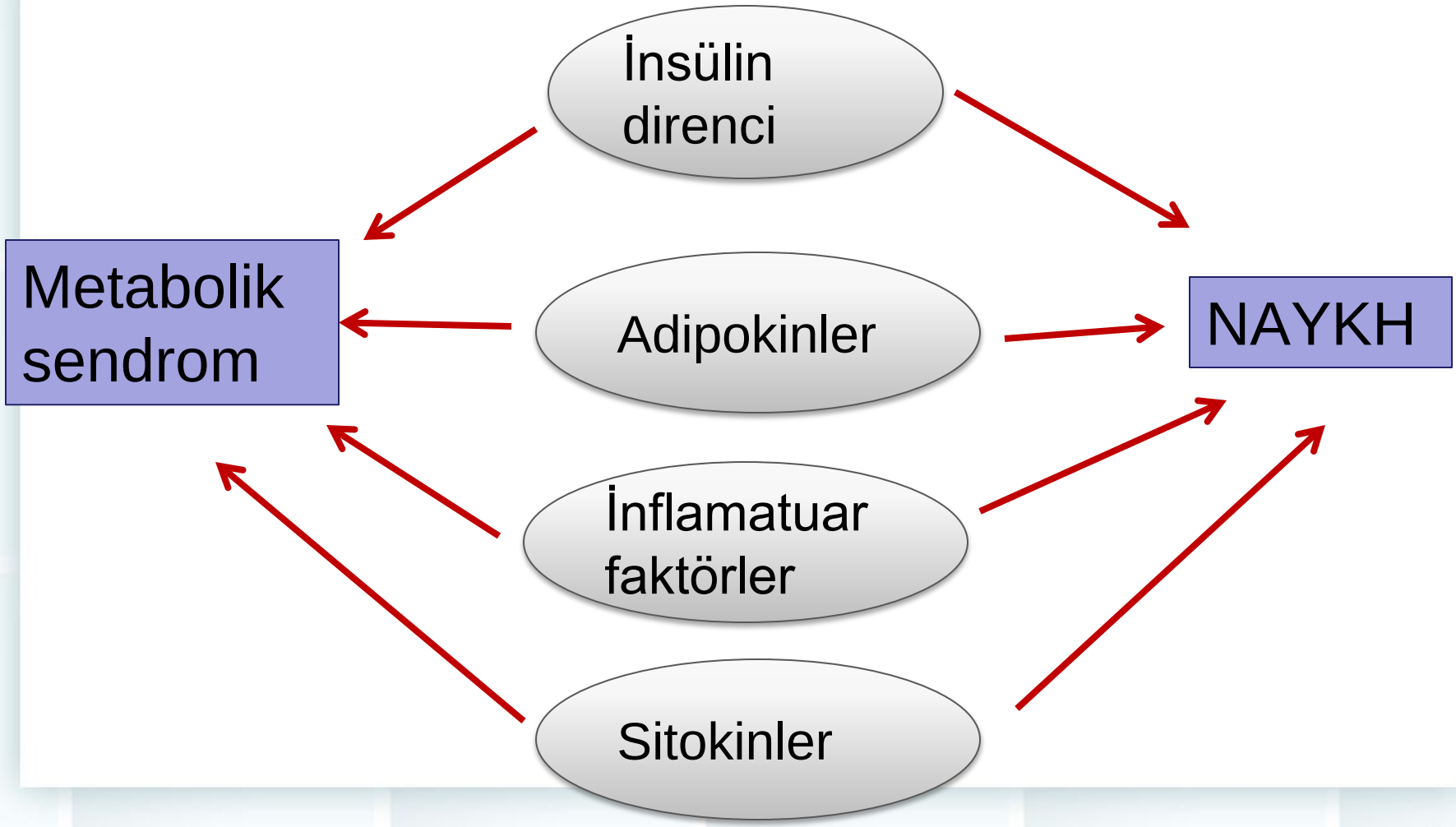
Retrospektif	
Ekstedt M,2006	129 Swedish NAFLD pts. with raised liver enzymes; baseline T2D status unknown (hospital-based)
Kim CH, 2008	5,372 South Korean people aged 20–79 years without T2D (health check-up)
Arase Y, 2009	6,003 NAFLD patients (mean age 48.8 years, 88.3% males)
Yamada T, 2010	12,375 non-diabetic Japanese people (mean age 49.2 ± 10.5) (health check-up)
Sung KC, 2011	11,091 South Korean people without T2D (health check-up)
Bae JC, 2011	7,849 South Korean people aged ≥20 (mean 44.5 years) without T2D (health check-up)
Sung KC, 2012	12,853 South Korean people without T2D (health check-up)
Chon CW, 2012	1,558 Korean males without components of MS - ATP III criteria (health check-up)
Choi J, 2013	7,849 Korean people without T2D (health check-up)
Sung KC, 2013	Occupational cohort of 13,218 Korean subjects without T2D (health check-up)
Imamura Y, 2013	Cross sectional study: 11,235 subjects (61% males); longitudinal study: 5,318 subjects without T2D
Jung CH, 2013 (	7860 T2D-free Asian subjects (65.6% men; age 48.6 years) (health check-up)
Prospektif	
Vozarova B, 2002	451 nondiabetic Pima Indians (aged 30 ± 6 years; 67% males); prospective analysis on 370 with NGT
Lee DH, 2003	4,088 T2D-free healthy male workers aged 25-55 years (health check-up)
Okamoto M, 2003	Cohort of 840 Japanese volunteers (health check-up)
Nannipieri M, 2005	Cohort of 1,441 men and women from a population-based T2D survey
Fan JG, 2007	1,146 Chinese people (health check-up)
Shibata M, 2007	3,189 Japanese male workers ≥40 years old (health check-up)
Monami M, 2008	2,617 Italian community people T2D and CVD-free (FIBAR study)
Goessling W, 2008	2,2812 subjects (mean age 44; 56% women) from the Framingham Offspring Heart Study
Fraser A, 2009	4,286 women 60-79 years old (BWHHS) plus meta-analysis of 21 prospective studies with NAFLD assessed by US (3 studies) or ALT, GGT
Balkau B, 2010	3,811 non-diabetic subjects (aged 30-65; 51.2% women) (DESIR study)
Park SK, 2013	25,232 Korean men without T2D (health check-up)
Chang Y, 2013	38,291 Korean subjects without T2D aged 30-59 years (health check-up)
Kasturiratne A, 2013	2,276 subjects free of T2D, aged 35-64 years (Ragama Health Study, Sri Lanka)
Zelber-Sagi S, 2013	141 volunteers (mean age 49 ± 10) no pre-D T2D / T2D (subsample of the Israeli National Health Survey)

Lonardo A et al Dig Liver Dis. 2015 Mar;47(3):181-90).



Williams KH, et al.Endocr Rev 2013;34(1):84-129.

NAYKH'da metabolik sendrom ve DM



Yağlı karaciğer varlığı insulin direncinin çok erken gelişen bir göstergesi olabilir mi?

NAYKH - metabolik sendrom, tip 2 DM

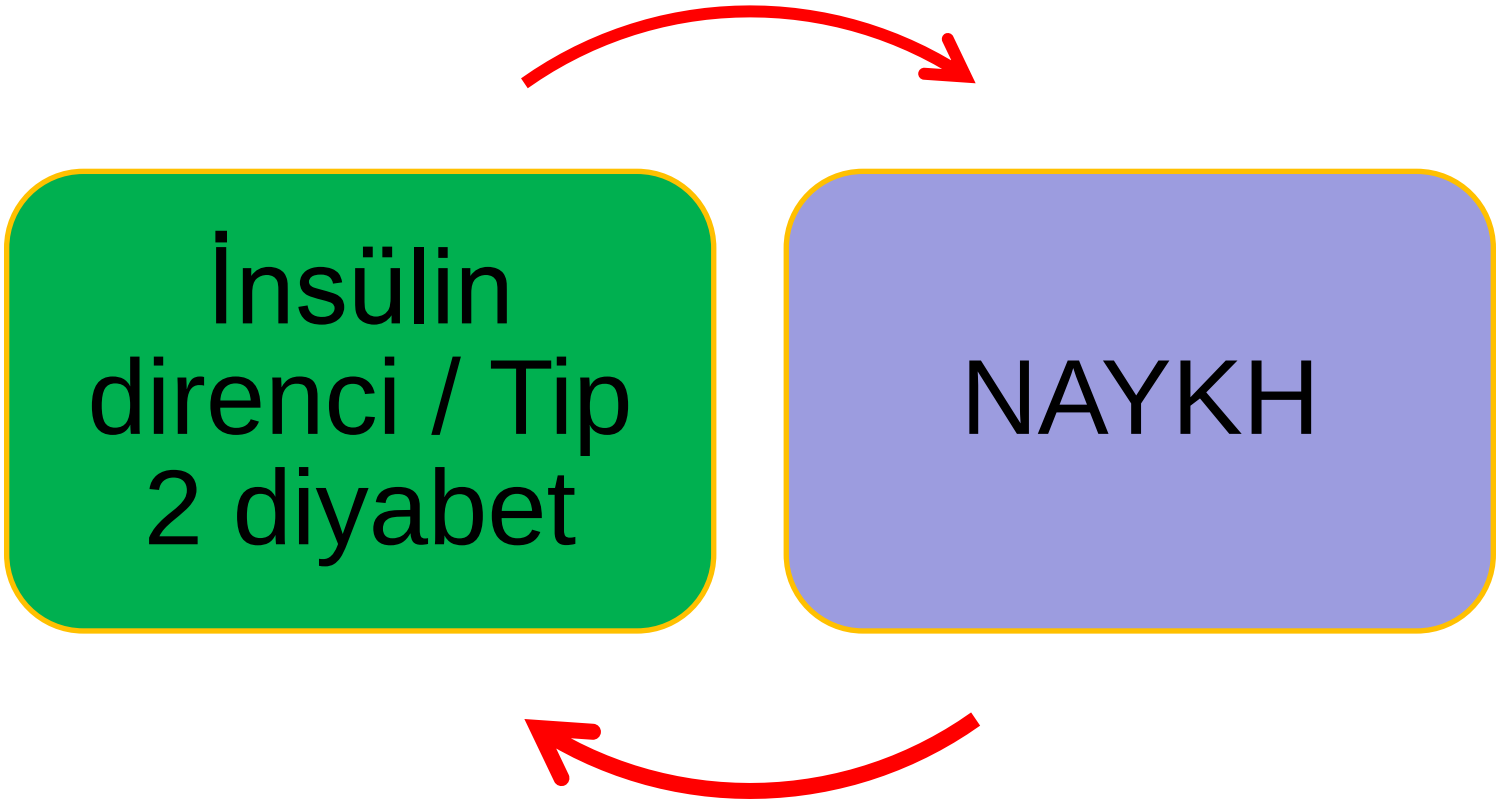
- 1999'dan itibaren bazı araştırmacılar NAYKH'nın **metabolik sendromun hepatik bulgusu** olarak kabul edilebileceğini öne sürmüş

- ✓ İnsülin direnci/DM
- ✓ Obezite- bel çevresi- bel kalça oranı
- ✓ Hipertansiyon
- ✓ Dislipidemi

+ **NAYKH**

Musso G, et al Diabetes Care. 2008 Mar;31(3):562-8
Leite NC, et al. Liver Int. 2009;29:113-9.
Lonardo A. et al Dig Liver Dis. 2015 Mar;47(3):181-90).

- ✓ **NAYKH metabolik sendrom öncülüdür ve henüz metabolik sendrom kriterleri taşımayan hastalarda tek başına erken dönemde saptanabilir**



NAYKH - metabolik sendrom, tip 2 DM

- NAYKH ve metabolik sendrom ilişkisini gösteren kesitsel çalışmalarda hangi durumun daha önce başladığını saptamak mümkün değil

Metabolik sendromun NAYKH üzerindeki etkisi?

NAYKH'nın metabolik sendroma etkisi?

METABOLİK SENDROM, İNSÜLİN DİRENCİ ve DİYABETTE NAYKH DAHA SIK

DİYABETİ OLMAYANLARDA DA NAYKH OLABİLİR

Diyabeti olmayanlarda da NAYKH olabilir

BBA Clinical 3 (2015) 141–145

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Clinical spectrum of non-alcoholic fatty liver disease in diabetic and non-diabetic patients☆

George Boon-Bee Goh [a], Mangesh R. Pagadala [a], Jaividhya Dasarathy [c], Aynur Unalp-Arida [f], Ruth Sargent [a], Carol Hawkins [b], Achuthan Sourianarayanane [a], Amer Khiyami [b], Lisa Yerian [d], Rish K. Pai [d], Srinivasan Dasarathy [a,e], Arthur J. McCullough [a,e,*]

- 503 hastanın 264'ü nondiyabetik
- Nondiyabetik NAYKH'da
  - %64 NASH, %17 ciddi fibrosis

- Fibrogenezde insülin direnci dışında başka faktörler rol oynuyor olabilir

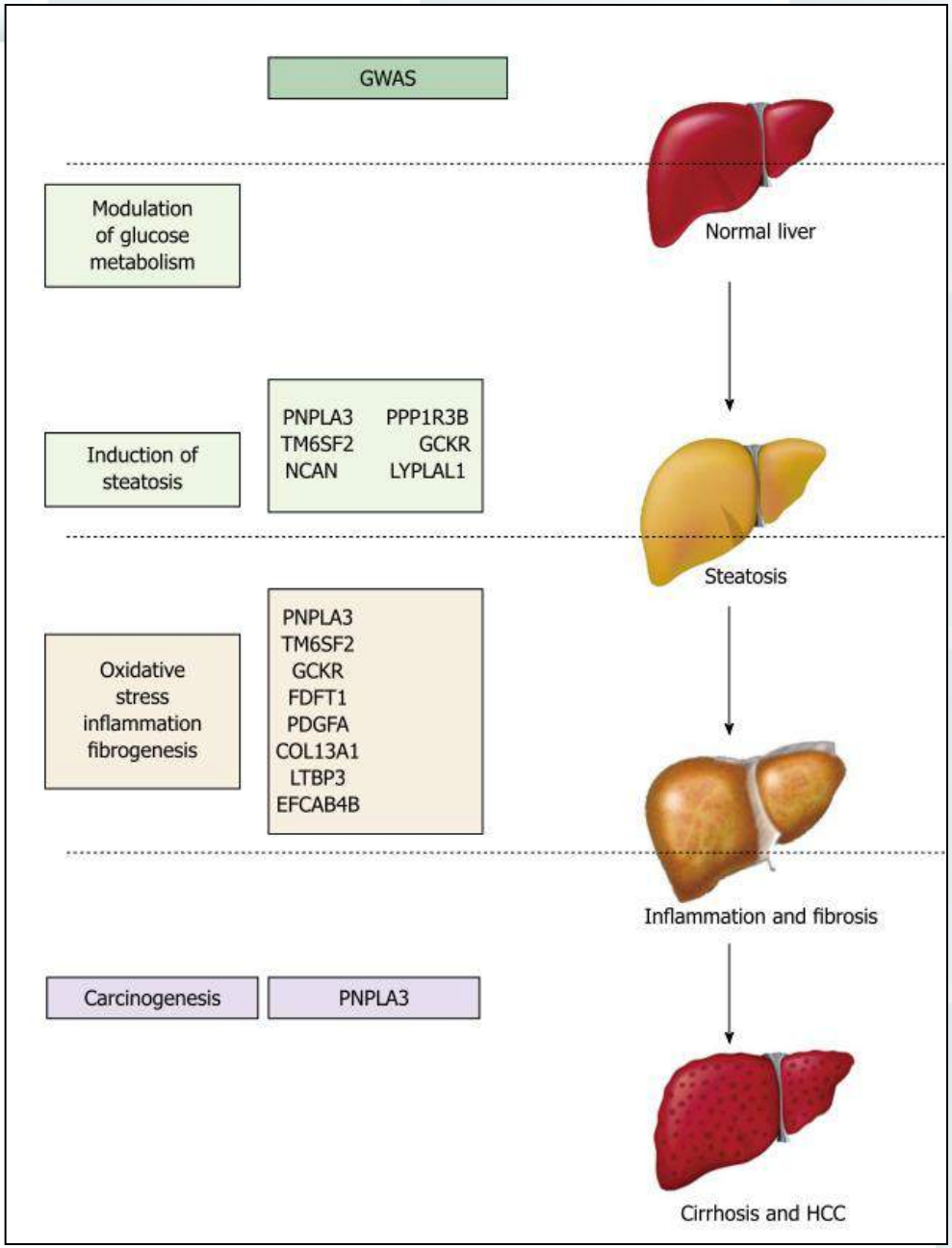
Diyabeti olmayanlarda da NAYKH olabilir

İnsülin direnci olmayan NAYKH hastaları da var

NAYKH birden çok nedeni olan
heterojen bir sendrom

- NAYKH'nın farklı fenotipleri olabileceği düşüncesi son 10 yılda gündeme gelmiş

- Genom çalışmaları ile NAYKH gelişimi ve progresyonu için riskli bir takım polimorfizmler belirlenmiş



Macaluso FS. Et al. World J Gastroenterol 2015 October 21; 21(39): 11088-11111

Table 1 Genetic variants involved in susceptibility and/or progression of nonalcoholic fatty liver disease identified by genome-wide association studies

PNPLA3, patatine-like phospholipase domain containing 3	rs738409	Steatosis NASH/necroinflammation Severity of fibrosis HCC development
TM6SF2, transmembrane 6 superfamily member 2	rs58542926	Steatosis NASH/necroinflammation Severity of fibrosis Reduced cardiovascular risk
PDGFA, platelet-derived growth factor alpha	rs343062	Severity of fibrosis
COL13A1, collagen type XIII alpha1	rs1227756	Lobular inflammation
LTBP3, latent transforming growth factor-beta-protein 3	rs6591182	Lobular inflammation
EFCAB4B, EF-hand calcium binding domain 4B	rs887304	Lobular inflammation

SNP: Single nucleotide polymorphism; NASH: Nonalcoholic steatoh[illegible]is; NAFLD: Nonalcoholic fatty liver disease; HCC: Hepatocellular carcinoma.

İnsülin direnci ile ilişkili değil

Macaluso FS., et al World J Gastroenterol 2015; 21(39): 11088-11111

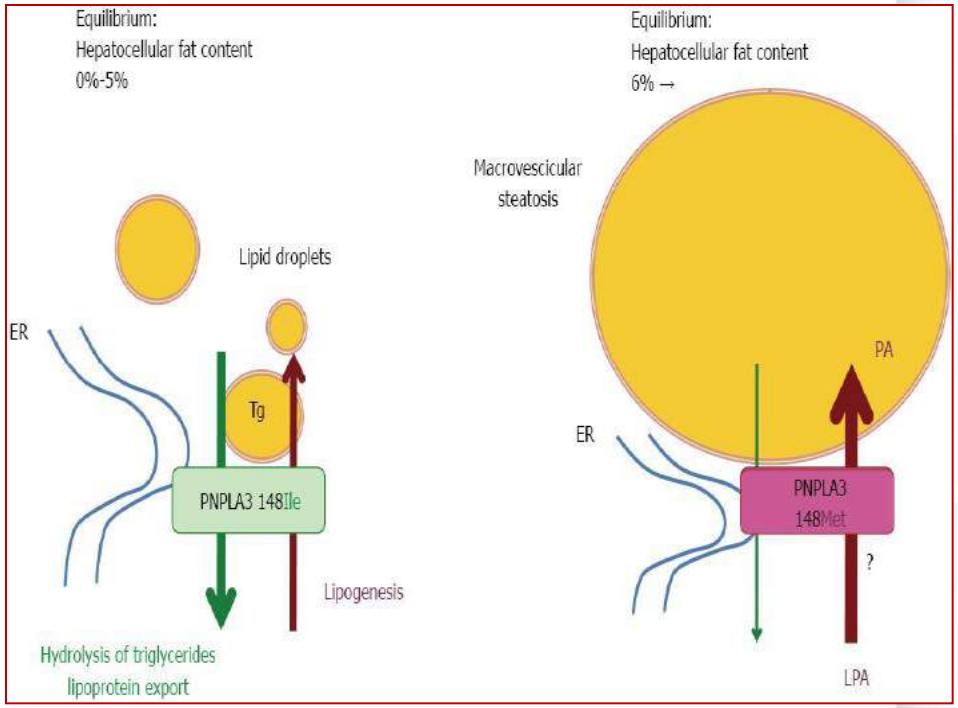
- PNPLA3 (Adiponutrin): Trigliserid hidrolaz aktivitesini yürüten bir polipeptid zincirini kodlar – lipaz olarak etki
- Karaciğer ve yağ dokuda eksprese edilir
- PNPLA3 geninde rs738409 C>G polimorfizmi

↓

Disfonksiyonel PNPLA3

↓

- Triasilgliserollerin lipolizi inhibe olur
- Lipotoksik substrat birikimi ve hepatik yağ miktarında artma

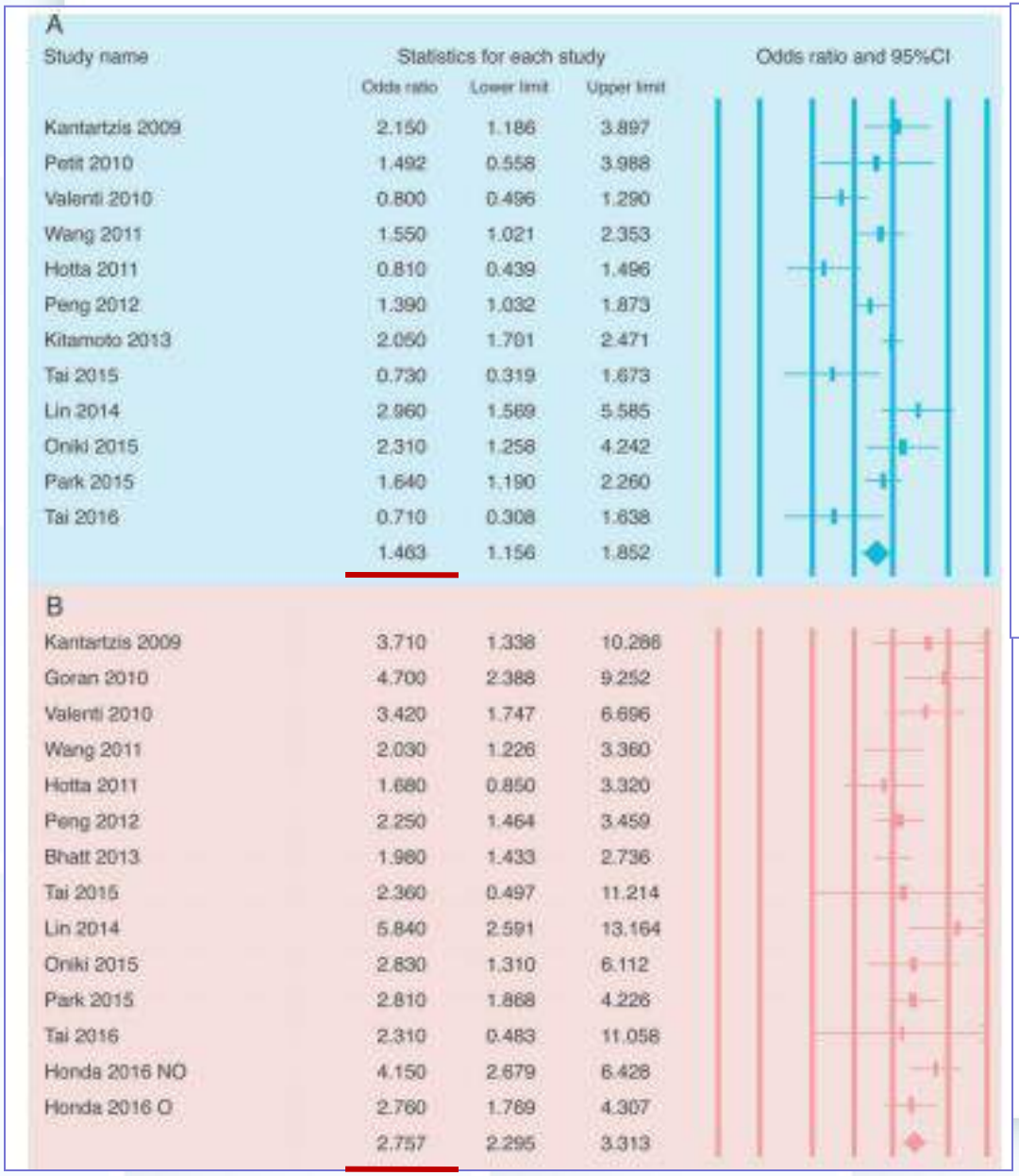


Firneisz G, et al. World J Gastroenterol 2014;20(27):9072-9089

- PNPLA3 I148M varyantı
  - Hispaniklerde %49
  - Avrupa'da %21-28
  - Avrupalı Amerikalılarda %23
  - Afrikalı Amerikalılarda %17

Krawczyk M , et al. Semin Liver Dis 2013; 33: 369-379

PNPLA3 NAYKH ile ilişkili



A

Study name	Odds ratio	Lower limit	Upper limit
Kantartzis 2009	2.150	1.186	3.897
Petit 2010	1.492	0.558	3.988
Valenti 2010	0.800	0.496	1.290
Wang 2011	1.550	1.021	2.353
Hotta 2011	0.810	0.439	1.496
Peng 2012	1.390	1.032	1.873
Kitamoto 2013	2.050	1.701	2.471
Tai 2015	0.730	0.319	1.673
Lin 2014	2.960	1.569	5.585
Oniki 2015	2.310	1.258	4.242
Park 2015	1.640	1.190	2.260
Tai 2016	0.710	0.308	1.638
	1.463	1.156	1.852

B

Kantartzis 2009	3.710	1.338	10.286
Goran 2010	4.700	2.388	9.252
Valenti 2010	3.420	1.747	6.696
Wang 2011	2.030	1.226	3.360
Hotta 2011	1.680	0.850	3.320
Peng 2012	2.250	1.464	3.459
Bhatt 2013	1.980	1.433	2.736
Tai 2015	2.360	0.497	11.214
Lin 2014	5.840	2.591	13.164
Oniki 2015	2.830	1.310	6.112
Park 2015	2.810	1.868	4.226
Tai 2016	2.310	0.483	11.058
Honda 2016 NO	4.150	2.679	6.428
Honda 2016 O	2.760	1.769	4.307
	2.757	2.295	3.313

C

Kantartzis 2009	2.380	1.359	4.167
Soonkoian 2009	2.800	1.504	5.213
Wegenknecht 2010	2.966	1.902	4.625
Wegenknecht 10	9.706	2.784	33.839
Wang 2011	1.440	1.120	1.851
Hotta 2011	1.370	0.879	2.136
Peng 2012	1.770	1.295	2.419
Kawaguchi 2012	1.660	1.425	1.933
Zain 2012	1.370	0.778	2.413
Zain 2012	2.230	1.600	3.109
Li 2012	1.730	1.497	1.999
Kanth 2014	9.860	3.847	25.271
Lin 2014	1.407	1.115	1.776
Tai 2016	1.160	0.658	2.044
Baclig 2014	31.210	0.899	1083.646
Lee 2014	1.990	1.204	3.290
Nishoji 2015	1.980	1.285	3.051
Wei 2015	4.370	2.448	7.802
Xia 2015	1.360	1.192	1.552
	1.905	1.639	2.213

Salameh H, et al. Journal of Clinical and Translational Hepatology 2016 vol. 4 | 175 –191

PNPLA3 as a Genetic Determinant of Risk for and Severity of Non-alcoholic Fatty Liver Disease Spectrum

Habeeb Salameh[1], Muhannad Al Hanayneh[1], Maen Masadeh[2], Mohammed Naseemuddin[3], Tasnia Matin[3], Angelika Erwin[4] and Ashwani K. Singal*[5]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Iowa, Iowa City, IA, USA; [3]Department of Internal Medicine, University of Alabama, Birmingham, AL, USA; [4]Genomic Medicine Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [5]Division of Gastroenterology and Hepatology, University of Alabama, Birmingham, AL, USA

35 çalışma

Journal of Clinical and Translational Hepatology **2016** vol. 4 | 175–191

NASH

Steatoz derecesi

NAS, lobuler inflamasyon, hepatositerde balonlaşma

Fibrosis, siroz

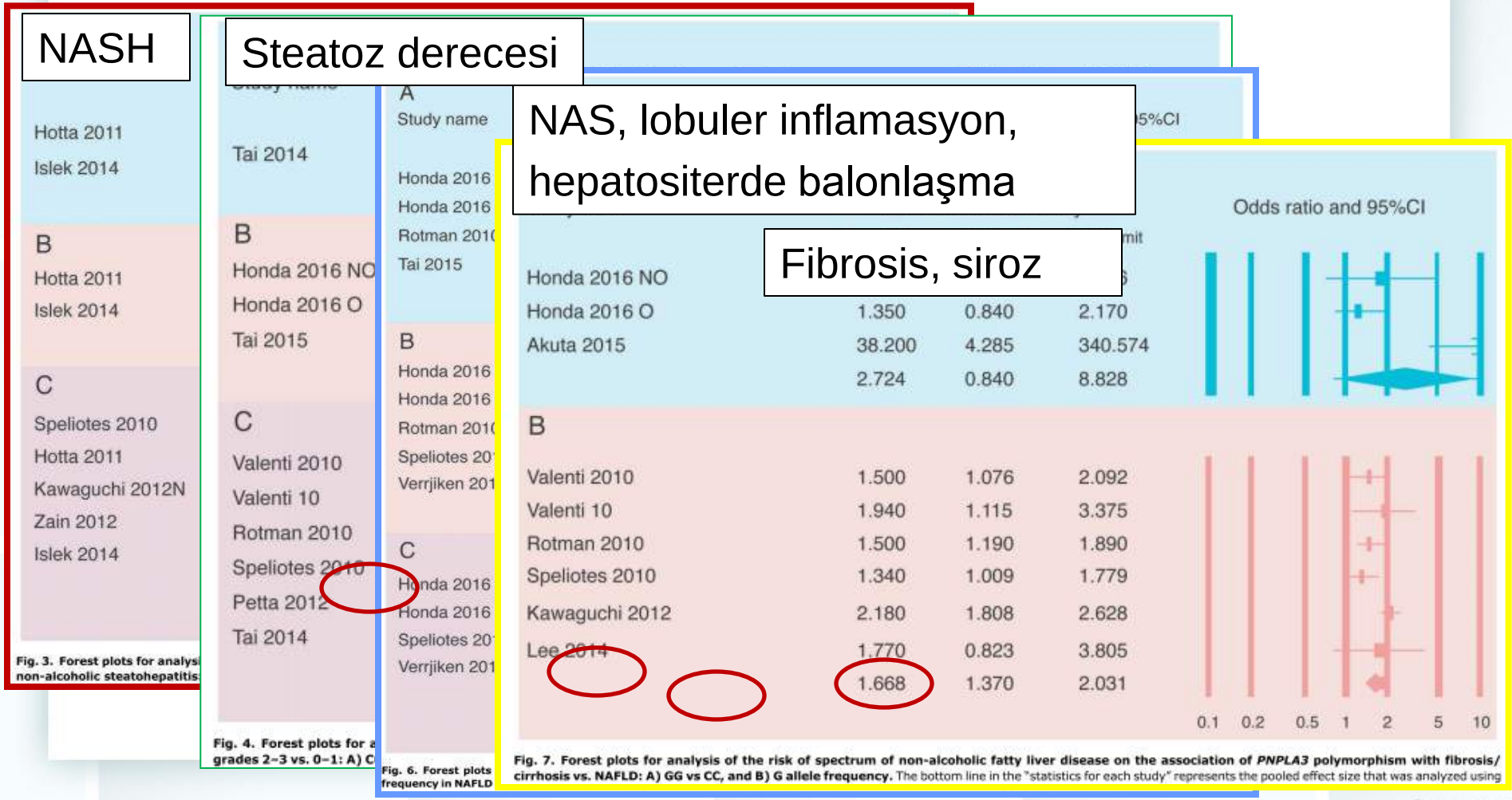


Fig. 7. Forest plots for analysis of the risk of spectrum of non-alcoholic fatty liver disease on the association of *PNPLA3* polymorphism with fibrosis/cirrhosis vs. NAFLD: A) GG vs CC, and B) G allele frequency. The bottom line in the "statistics for each study" represents the pooled effect size that was analyzed using

- PNPLA3 risk alleli varlığına dayalı yeni bir klinik durum olarak **“PNPLA3 ilişkili steatohepatit**”

Krawczyk M , et al Semin Liver Dis 2013; 33: 369-379

Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease

Panu K. Luukkonen[1,2,*,†], You Zhou[1,†], Sanja Sädevirta[1,2], Marja Leivonen[3], Johanna Arola[4], Matej Orešič[5], Tuulia Hyötyläinen[5], Hannele Yki-Järvinen[1,2]

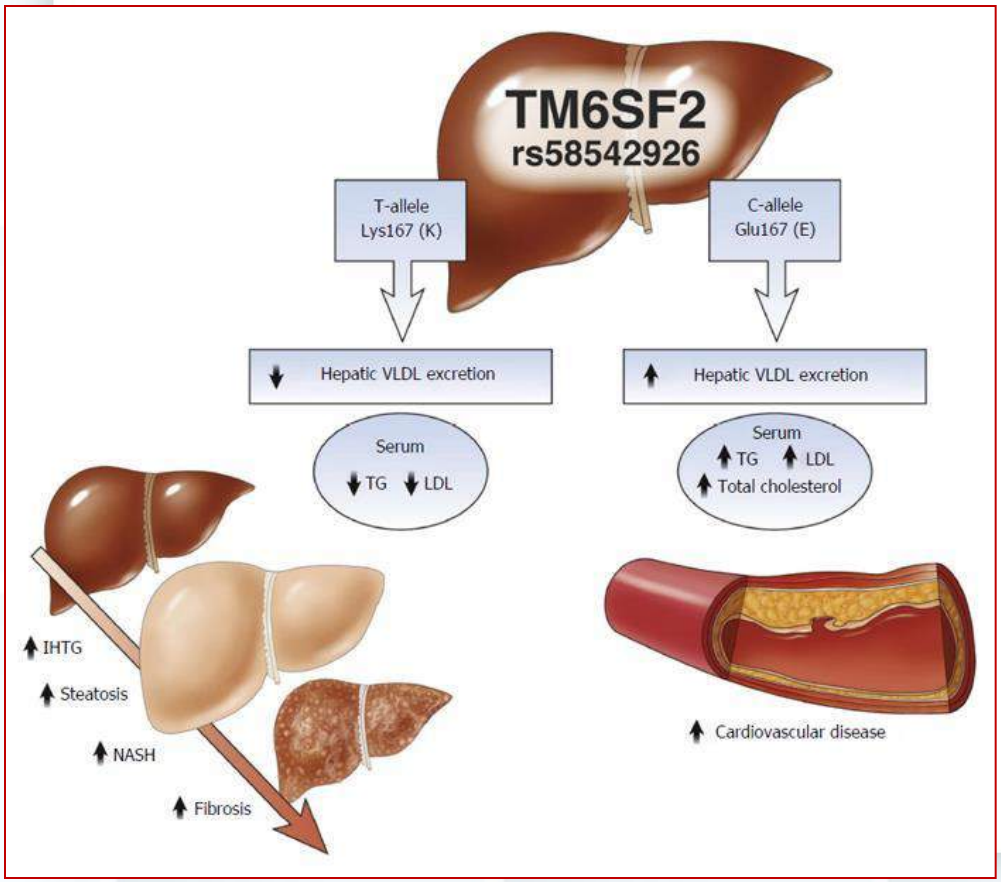
[1]*Minerva Foundation Institute for Medical Research, Helsinki, Finland;* [2]*Department of Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [3]*Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [4]*Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [5]*Steno Diabetes Center, Gentofte,*

Journal of Hepatology **2016** vol. 64 | 1167–1175

- Metabolik NAYKH'da karaciğerde doymuş ve tekli doymamış serbest yağ asitleri ve triasilgliserol ↑
- PNPLA3 NAYKH'da çoklu doymamış triasilgliseroller ↑

- **"Metabolik NAYKH"** ve **"PNPLA3 NAYKH"** olmak üzere 2 farklı fenotip

- TM6SF2 gen E167K varyantı yakın zamanda tanımlanmış
- Hepatik trigliserid salınımını düzenliyor
- Disfonksiyonu durumunda hem NAYKH gelişimi hem de steatoz ve fibrosis riski ↑



• Nekroinfalamasyon, balonlaşma ve ilerlemiş karaciğer fibrosisi ile ilişkili

•Serum LDL, Tg ↓

•Kanıtlar henüz PNPLA3 kadar birikmemiş

Kozlitina J, et al. Nat Genet 2014;46 : 352-356

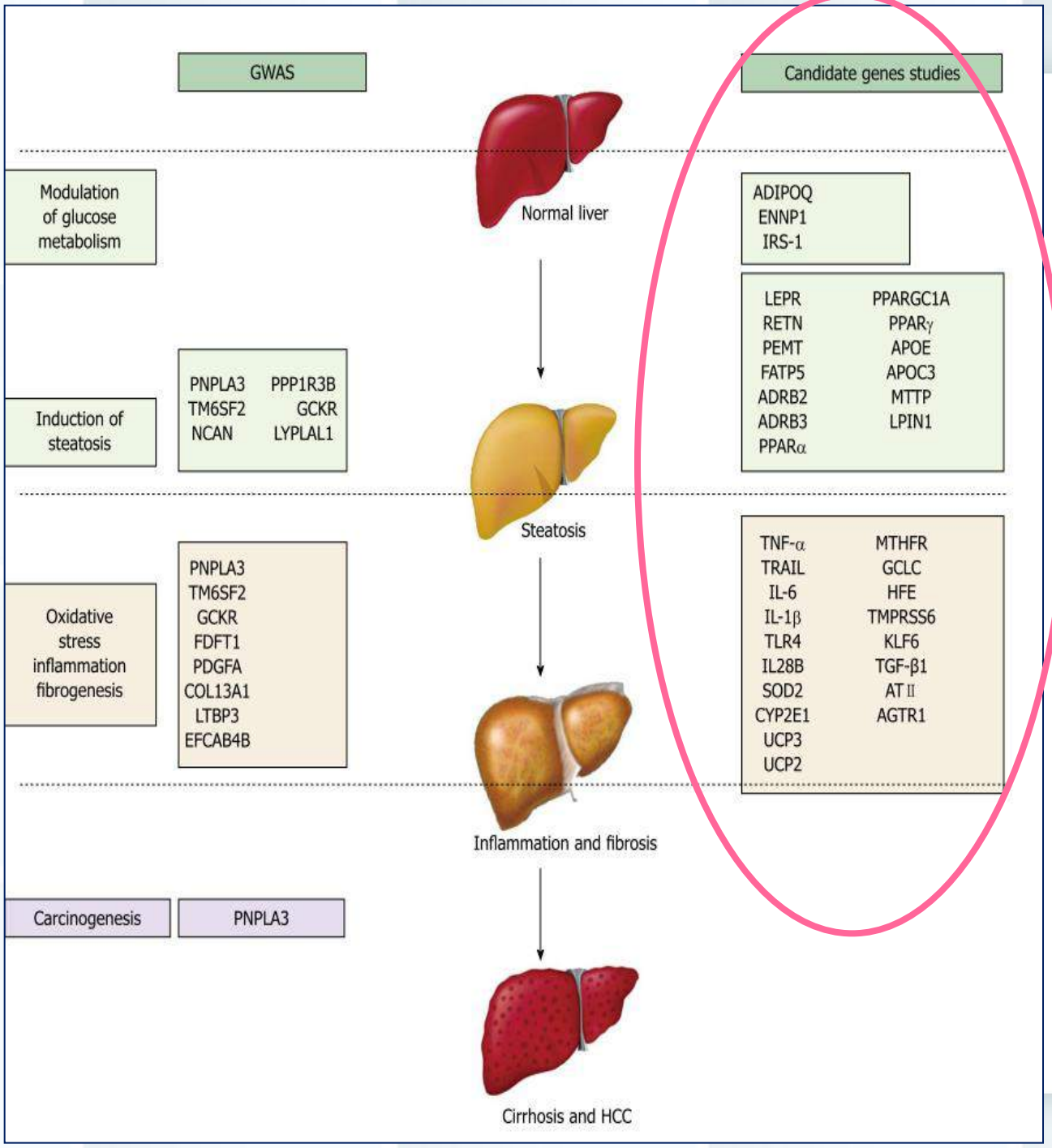
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

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

- PNPLA3 ve TM6SF2 polimorfizmi sağlıklı kontrollere göre NAYK ve NASH riskinde artış, daha ciddi NAYKH spektrumu (steatoz derecesi, NAS, histopatolojik bulgular, siroz) ile ilişkili

Gene (Reference)	Steatosis	NASH	Fibrosis	HCC	% Europids with allele
PNPLA3 [1-3]	Yes	Yes	Yes	Yes	40
TM6SF2 [4-6]	Yes	Yes	Yes	No	15

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of Hepatology 2016 vol. xxx j xxx–xxx



Aday gen çalışmalarında yağlı karaciğer patogenezinde ve progresyonunda rol oynadığı gösterilen birçok genetik faktör var

Table 2 Genes influencing glucidic or lipid metabolism with a potential role in nonalcoholic fatty liver disease pathogenesis evaluated by candidate gene studies

Gene	Functions of encoded protein	SNP
ENPP1, ectonucleotide pyrophosphatase/ phosphodiesterase1 or PC-1	Interaction with the insulin receptor with consequent reduction of insulin receptor activity	rs1044498
IRS-1, insulin receptor substrate 1	Part of the machinery involved in insulin pathway as transductor of insulin receptor signaling	rs1801278
ADIPOQ, adiponectin	Relevant adipocytokine associated with insulin resistance, type 2 diabetes, and NAFLD pathogenesis	rs2241766 rs1501299
LEPR, leptin receptor	Receptor of leptin, a hormone synthesized by adipocytes that regulates food intake, insulin action, thermogenesis, and immune system	rs62589000 rs6700986 rs1137100 rs1137101 rs8179183
RETN, Resistin	Adipocytokine involved in lipid metabolism, hepatic insulin resistance, inflammatory cascade reactions, and fibrogenesis	rs3745367
PEMT, phosphatidylethanolamine N-methyltransferase	Enzyme involved in the *de novo* synthesis of phosphatidylcholine in the liver, a biochemical pathway essential for VLDL formation	rs7946
FATP5, Fatty Acid Transport Protein 5	Transporter involved in the hepatic uptake of fatty acids	rs56225452
ADRB2 and *ADRB3*, β-adrenergic receptor 2 and 3	β-adrenergic receptors, with several functions including regulation of basal metabolism and induction of lipolysis	rs4994 rs1042714 rs2053044 rs11168070 rs11959427 rs1042711
PPARα, peroxisome proliferative activated receptor α	Transcription factor whose activation improves steatosis, inflammation, and fibrosis in pre-clinical models of NAFLD	rs1800206
PPARGC1A, peroxisome proliferator-activated receptor γ coactivator 1-α	PGC-1α, involved in mitochondrial functions, oxidative stress, gluconeogenesis, and lipogenesis	rs8192678 rs2290602
PPARγ, peroxisome proliferative activated receptor γ	Transcription factor whose activation improves IR, restores adipose tissue insulin sensitivity, and decreases fatty free acids flux to the liver	rs1801282
APOE, apolipoprotein E	Mediator of remnant lipoprotein binding to LDL receptors to favor the clearance of chylomicrons and VLDL	N/A
APOC3, apolipoprotein C-Ⅲ	A constituent of plasma VLDL, chylomicrons, and HDL-C that inhibits lipoprotein lipase and triglycerides clearance	rs2854116 rs2854117
MTTP, microsomal triglyceride transfer protein	Transfer protein involved in apoB-lipoprotein assembly	rs1800591 rs1800804 rs1057613 rs3805335
LPIN1, lipin 1	Phosphatase specifically involved in metabolic pathways between adipose tissue and liver	rs13412852

Macaluso FS., et al World J Gastroenterol 2015; 21(39): 11088-11111

- **NAYKH patogenezinde rolü olduğu düşünülen genler**

Glukoz metabolizmasını etkileyen ve diyabet gelişimi için de risk oluşturan ve lipid metabolizmasını etkileyen genler

Table 3 Genes potentially involved in mechanisms of liver injury in nonalcoholic fatty liver disease evaluated by candidate gene studies

Gene	Functions of encoded protein	SNP
TNF-α, tumor necrosis factor-α	Proinflammatory cytokine also involved in the regulation of insulin resistance, release of free fatty acids, and apoptosis in hepatocytes	rs1800629 rs361525 rs1799964 rs1800630
TRAIL, TNF-related apoptosis -inducing ligand	Protein functioning as a ligand that induces celluar apoptosis	rs6763816 rs4491934
IL-6, interleukin-6	Proinflammatory cytokine produced by adipocytes, hepatocytes, and immune cells also involved in the modulation of insulin resistance	rs1800795
IL-1β, interleukin-1β	Member of IL-1 family cytokine, mainly produced by adipose tissue	rs16944
TLR4, toll-like receptor 4	Receptor involved in the interaction with bacterial endotoxins capable to favor hepatic injury and a proinflammatory systemic status	rs4986790
IL28B, interleukin-28B	Cytokine belonging to the type Ⅲ Interferon family	rs12979860
SOD2, superoxide dismutase 2	Manganese-dependent mitochondrial enzyme involved in protection from cellular injury induced by superoxide radicals	rs4880
CYP2E1, cytochrome P450 2E1	Part of the cytochrome P450 complex	rs2031920
UCP3, uncoupling protein 3	Mitochondrial anion carrier involved in the metabolism of superoxide radicals and in the modulation of lipid homeostasis	rs1800849 rs11235972
UCP2, uncoupling protein 2	Similar to uncoupling protein 3	rs695366
MTHFR, methylenetetrahydrofolate reductase	Enzyme involved in the methylation of homocysteine to methionine	rs1801133 rs1801131
GCLC, Glutamate-cysteine ligase catalytic subunit	Limiting enzyme in the formation of glutathione, a relevant endogen antioxidant	rs17883901
HFE, hemochromatosis	Crucial protein for the regulation of iron homeostasis *via* the modulation of the expression of hepcidin	rs1800562 rs1799945
TMPRSS6, trans-membrane protease serine 6	Matriptase-2, which cleaves the membrane-bound hemojuvelin, the co-receptor required for hepcidin expression in the liver	rs855791
KLF6, kruppel-like factor 6	One of the Kruppel-like factors, a family of transcriptional factors that regulate cellular proliferation, differentiation, and apoptosis	rs3750861
TGF-β1, transforming growth factor β1	In the liver, a promoter of hepatic fibrosis *via* the activation of hepatic stellate cells	rs1800471
ATⅡ, angiotensin Ⅱ	Part of the renin-angiotensin system, also advocated as an inducer of TGF-β1 production and accumulation of extracellular matrix in the liver	rs699
AGTR1, Angiotensin Ⅱ Type 1 Receptor	Type 1 Receptor of Angiotensin Ⅱ	rs3772622 rs3772633 rs2276736 rs3772630 rs3772627

- **NAYKH varlığında karaciğer hasarının ilerlemesinde rolü olduğu düşünülen genler**

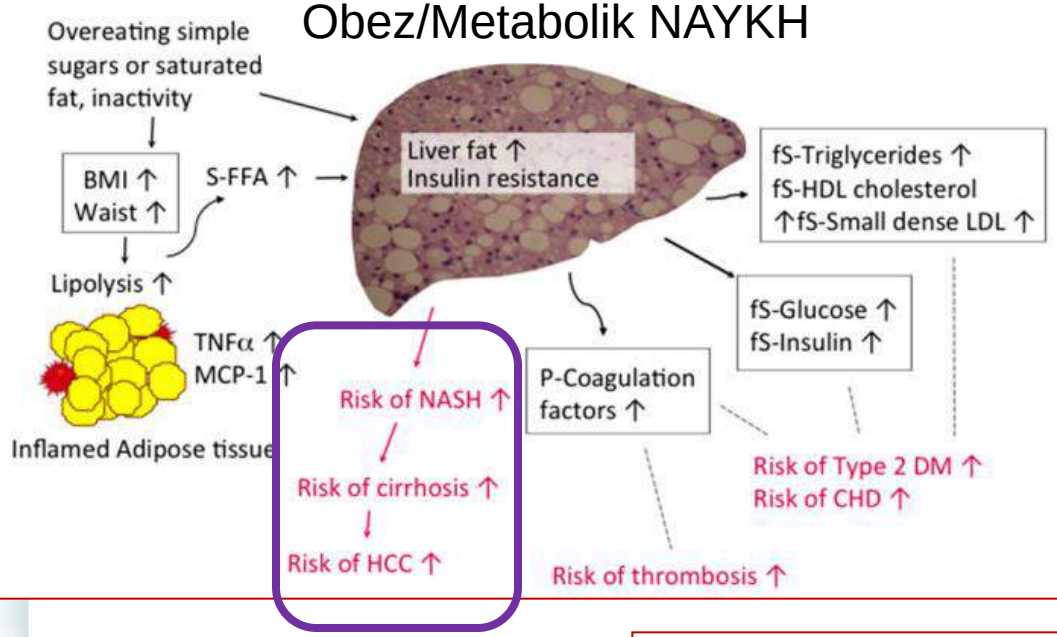
Macaluso FS., et al World J Gastroenterol 2015; 21(39): 11088-11111

✓ **NAYKH'nın bir kısmı genetik zeminde, bir kısmı çevresel faktörlerle gelişmekte**

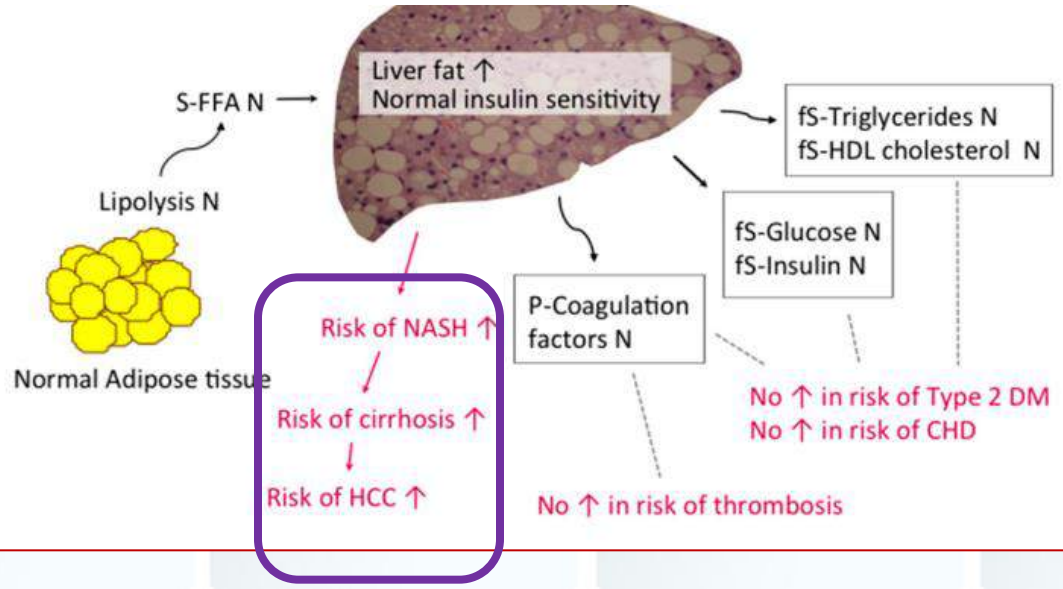
- NAYKH gelişimindeki ve NASH'e ilerlemesindeki bireyler arasındaki geniş değişkenlik kalıtımsallıkla ilgili

- Etnik kökenlerdeki NAYKH prevalansındaki farklar da genetik PNPLA3 varyantı ile açıklanabilir

Obez/Metabolik NAYKH



TM6SF2 veya PNPLA3 gen varyantlarının neden olduğu NAYKH



Petäjä EM, et al Int J Mol Sci. 2016;17(5):633

NAYKH – Farklı subtipler?

Metabolik sendrom (+)

- Daha çok yaşam tarzının bir sonucu gibi
- NASH, siroz ve HCC riski ↑
- Tip 2 DM riskinde ↑
- Kardiyovasküler hastalık riskinde ↑

Metabolik sendrom (-)

- Belirli genetik bozukluklarla ilişkili

  [Metabolik sendromun erken safhası ?]
- NASH, siroz ve HCC riski ↑
- Tip 2 DM riskinde ↑ YOK
- Kardiyovasküler hastalık riskinde ↑ YOK

SONUÇ

- Tip 2 diyabetli hastalarda >%70 NAYKH mevcut

- NAYKH ve NASH tip 2 diyabetin genellikle atlanan bir komplikasyonu
- Diyabetin diğer komplikasyonları gibi taranmalı mıdır? Ne ile?

- NAYKH saptanması metabolik sendrom ve diyabet varlığının araştırılmasını gerektirir

SONUÇ

- NAYKH metabolik sendromun hepatik bulgusu/öncülü?
- Heterojen bir durum
- Bütün NAYKH olanlar tip 2 diyabet için risk altında değil
- Hem bu genetik durumların hem de metabolik sendromun sık olduğu düşünülürse her iki duruma da sahip ve NAYKH için daha yüksek risk altında olan ayrı bir grup (**double trouble NAYKH)**

TEŞEKKÜRLER