Kronik Karaciğer Hastalığında Diyabet Tedavisi

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Meram Tıp Fakültesi

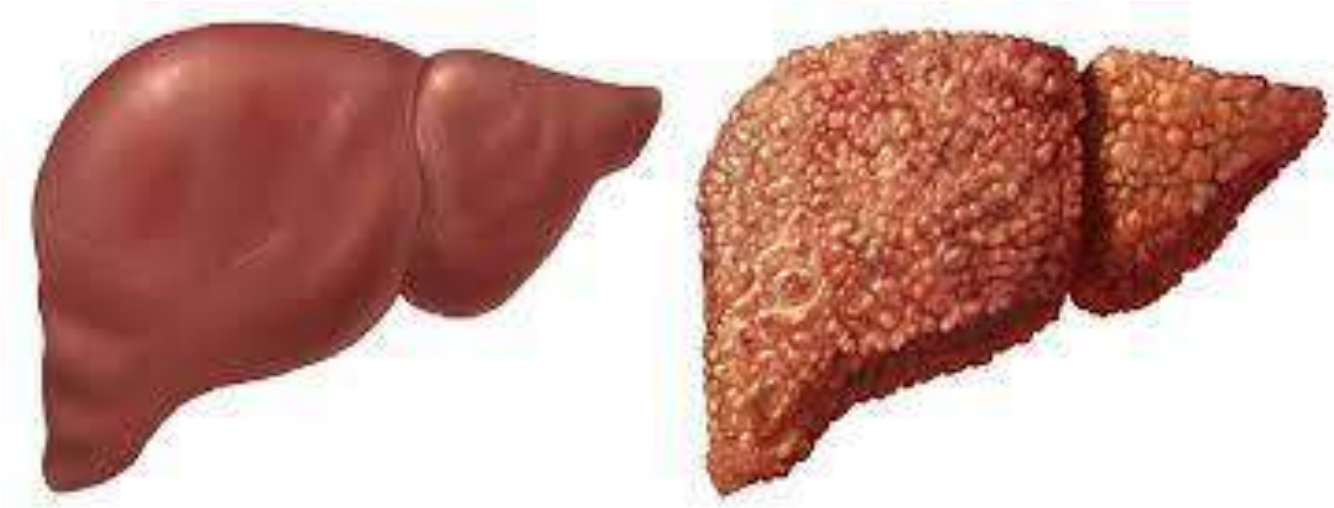
KC Glukoz Metabolizmasındaki Rolü

- Glukoz dengesinde kilit rolde
- Glikojen depolanması (beslenildiğinde)
- Açlıkta glukoneogenez ve glikojenoliz aracılığıyla glukoz üretimi

KC İnsülin Metabolizması

- İnsülin; KC, böbrek ve plasentadaki insülinaz enzimi ile metabolize
- Pankreas tarafından salgılanan insülinin %50'si
- Non-parankimal hücreler; Kupffer hücreleri, sinüziodal endotel hücreler ve hepatik stellate hücreleri aracılığıyla insülin degredasyonu

Kronik KC



Siroz- Portal HT

- Periferik insülin seviyeleri yükseliyor
- Azalmış degredasyon
- Reseptör down regülasyonu
- İnsülin direnci
- Olmasa?
  - Hipoglisemiye bağlı ölüm

- Mann ve Magath:
- Köpekte total hepatotektomi sonrası birkaç saatte ölüm
- Hipoglisemiye bağlı

KC DM ilişkisi

- Diyabetin sonucu ortaya çıkan KC hastalığı
- KC hastalığı sonucu ortaya çıkan, hastalık komplikasyonu ile ilişkili DM
- DM ile koinsidental olarak ortaya çıkan glukoz metabolizma bozukluğu-DM

Diyabetin sonucu ortaya çıkan KC hastalığı

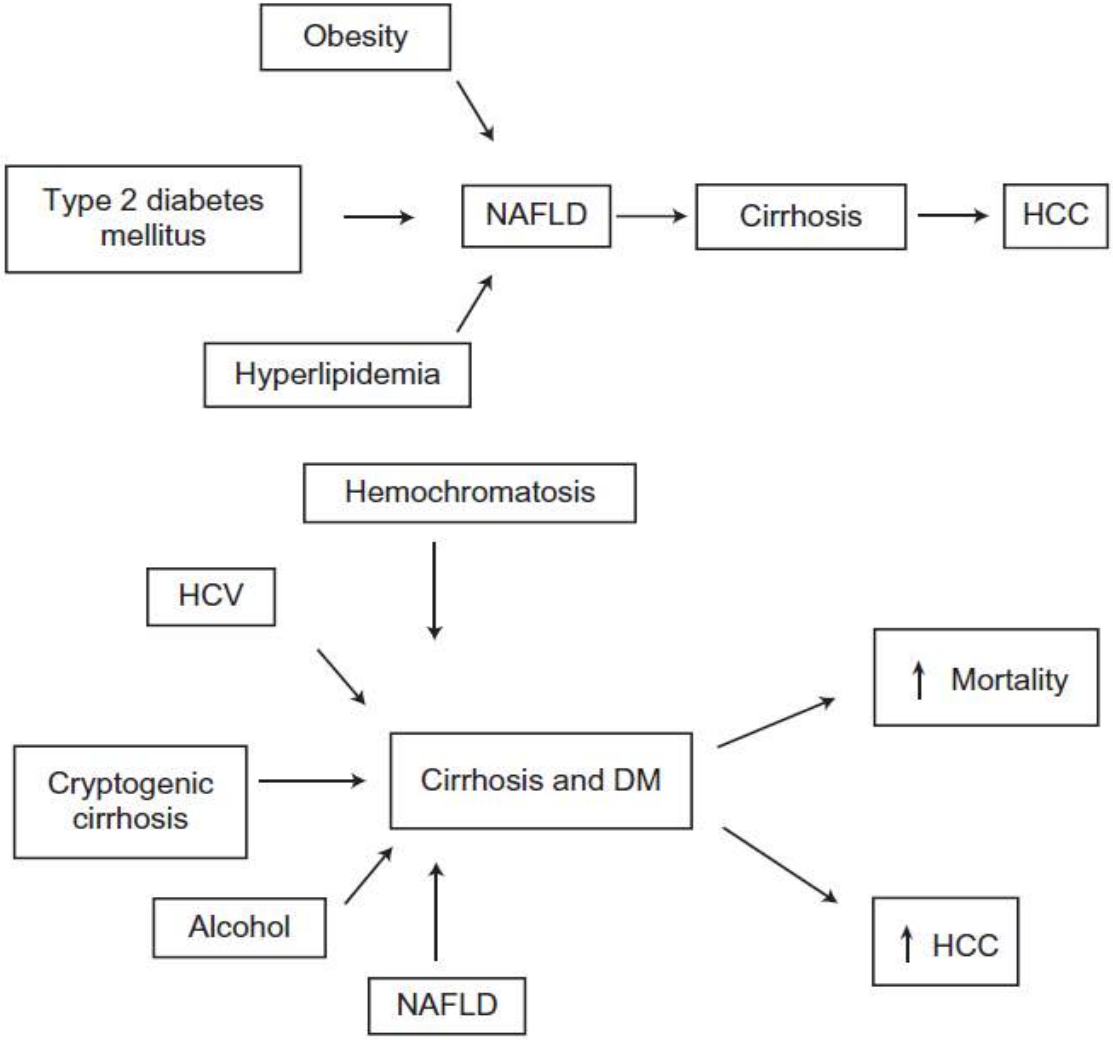
- Glikojen birikimi
- Steatoz ve nonalkolik steatohepatit (NASH)
- Fibrozis ve siroz
- Biliyer hastalık, kolelithiazis, kolesistit
- Diyabet tdv komplikasyonu (kolestatik, nekroinflamatuar)

KC hastalığı sonucu ortaya çıkan, hastalık komplikasyonu ile ilişkili

- Hepatit
- Siroz
- Hepatoselüler ca
- Fulminan KC yetmezliği
- Transplantasyon sonrası

DM ile koinsidental olarak ortaya çıkan glukoz metabolizma bozukluğu-DM

- Hemokromatozis – Bronze DM
- Glikojen depo hastalıkları
- Otoimmün biliyer hastalıklar


Obesity
Type 2 diabetes mellitus
NAFLD
Cirrhosis
HCC
Hyperlipidemia
Hemochromatosis
HCV
Cryptogenic cirrhosis
Cirrhosis and DM
Mortality
Alcohol
NAFLD
HCC

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REVIEW ARTICLE

WILEY Liver INTERNATIONAL

Hepatogenous diabetes: Is it time to separate it from type 2 diabetes?

Emanuela Orsi[1,2] | Valeria Grancini[1,2] | Stefano Menini[3,4] | Alessio Aghemo[5] | Giuseppe Pugliese[3,4]

Hepatojenik DM

- Siroz komplikasyonu sonucu oluşan diyabet
- Sirozlu hastaların %30-60'ında
- NAFLD, HCV, Alkolik S

Hepatojenik DM

- Genellikle normal APG ve A1c seviyeleri
- Tanı için OGTT gerekli

García-Compeán D et al. *World J Gastroenterol. 2009*
García-Compeán D, et al. *World J Gastroenterol. 2016*

APG ve A1c seviyelerine göre

Holstein et al. (2002)[14]	52	FPG	NA	17 (32.7)
Wlazlo et al. (2010)[15]	94	FPG	NA	35 (37.2)
García-Compeán et al. (2012)[16]	130	FPG	14 (10.7)	36 (27.6)
Jeon et al. (2013)[17]	195	FPG	NA	67 (34.4)
Lunati et al. (2013)[18]	84	FPG + HbA_{1c}	14 (16.6)	35 (41.7)
Grancini et al. (2015)[19]	206	FPG + HbA_{1c}	7 (3.4)	56 (27.2)
Marselli et al. (2016)[20]	300	FPG	31 (10.3)	92 (30.7)

OGTT

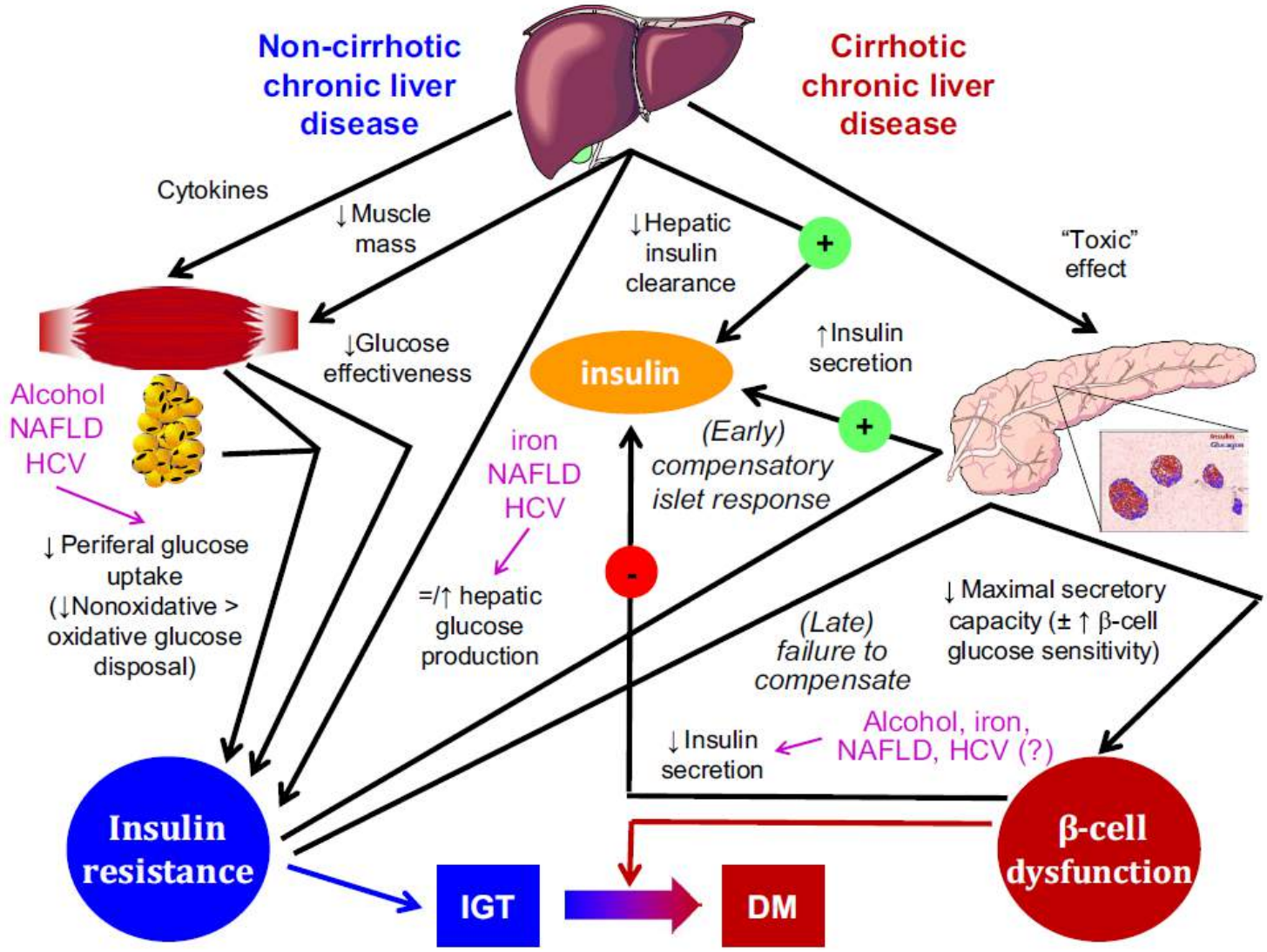
Study	N	Method	IGT (%)	DM (%)
Holstein et al. (2002)[14]	35	OGTT	13 (37.1)	20 (57.2)
Tietge et al. (2004)[20]	100	OGTT	38 (38.0)	35 (35.0)
Nishida et al. (2006)[21]	56	OGTT	13 (23.2)	21 (37.5)
García-Compeán et al. (2012)[16]	80	OGTT	36 (45.0)	27 (33.8)
Jeon et al. (2013)[17]	128	OGTT	61 (47.7)	41 (32.0)
Taguchi et al. (2014)[23]	61	OGTT	12 (19.7)	28 (45.9)
Grancini et al. (2015)[19]	163	OGTT	60 (36.8)	77 (47.2)
Marselli et al. (2016)[20]	205	OGTT	15 (7.2)	13 (6.3)

APG-A1c-OGTT Birlikte

Study	N	Method	AGR (%)	DM (%)
Holstein et al. (2002)[14]	52	FPG + OGTT	50 (96.1)	37 (71.1)
García-Compeán et al. (2012)[16]	130	FPG + OGTT	113 (86.9)	63 (48.3)
Jeon et al. (2013)[17]	195	FPG + OGTT	169 (86.7)	108 (55.4)
Grancini et al. (2015)[19]	206	FPG + HbA_{1c} + OGTT	197 (88.3)	133 (59.6)
Marselli et al. (2016)[20]	300	FPG + OGTT	141 (41.0)	105 (35.0)

KC Hastalığının Ciddiyeti

- Child-Pugh Class A ise %20.5
- Child-Pugh Class B ise %56.1 ,
- Child-Pugh Class C ise %61.2’sinde DM


Non-cirrhotic chronic liver disease
Cirrhotic chronic liver disease
Cytokines
↓Muscle mass
↓Hepatic insulin clearance
+
"Toxic" effect
↓Glucose effectiveness
insulin
↑Insulin secretion
Alcohol NAFLD HCV
iron NAFLD HCV
(Early) compensatory islet response
+
↓ Periferal glucose uptake (↓Nonoxidative > oxidative glucose disposal)
=/↑ hepatic glucose production
-
(Late) failure to compensate
↓ Maximal secretory capacity (± ↑ β-cell glucose sensitivity)
↓Insulin secretion
Alcohol, iron, NAFLD, HCV (?)
Insulin resistance
IGT
DM
β-cell dysfunction

	Hepatogenous diabetes	T2DM
Onset	After cirrhosis onset	Before cirrhosis onset
Presentation	Subclinical DM (normal FPG and HbA_{1c}, abnormal response to OGTT)	Overt DM (increased FPG and HbA_{1c})
Hypoglycema and MALA	Higher risk	Lower risk
Effect of OLT	Reversal or amelioration (?)	Persistence
Traditional risk factors for DM	Less frequently present	More frequently present
Complications of DM	Lower incidence	Higher incidence
Complications of liver disease	Higher than in non-diabetic cirrhotic subjects	Higher than in non-diabetic cirrhotic subjects
Mortality	Higher than in non-diabetic cirrhotic subjects	Higher than in non-diabetic cirrhotic subjects

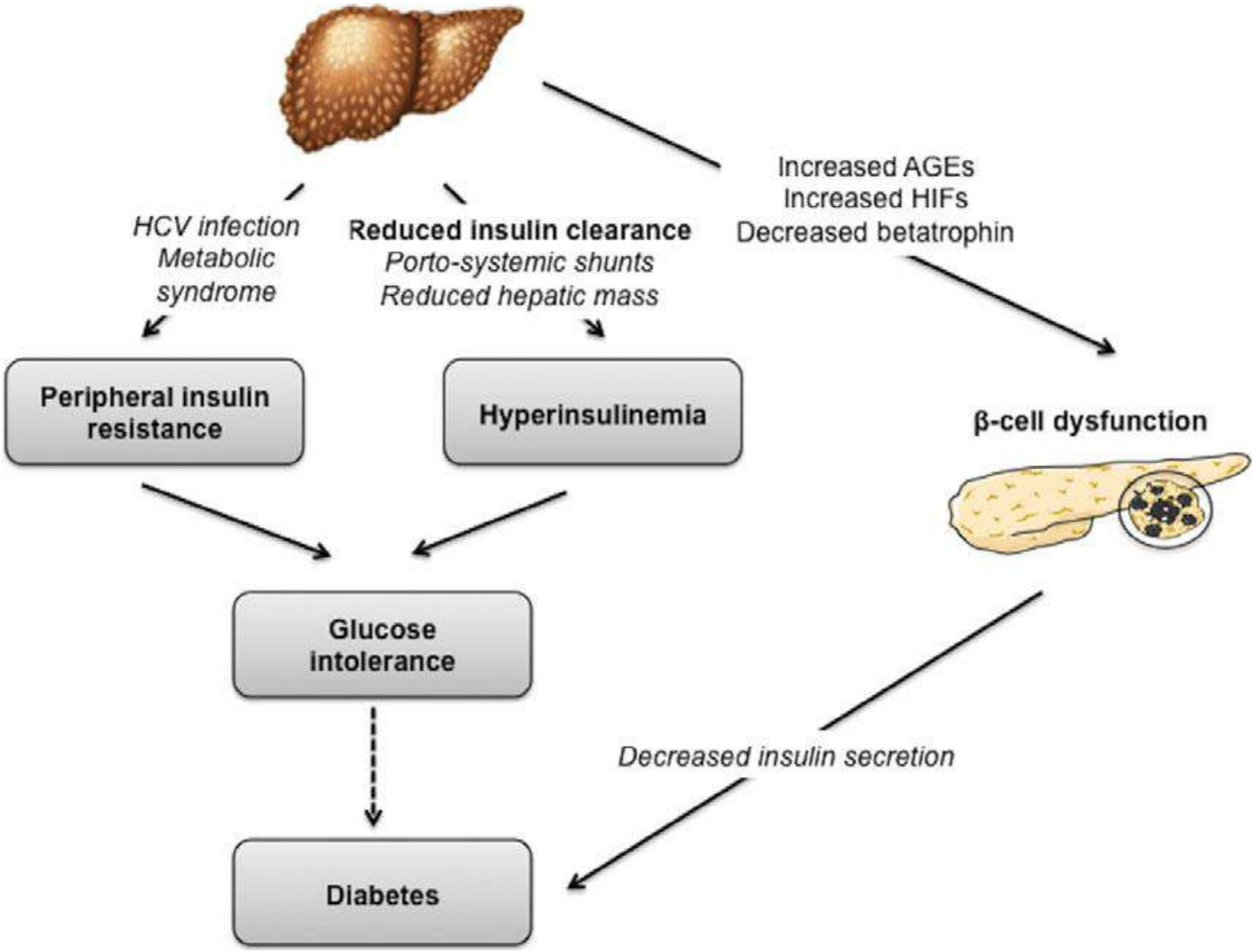
T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; OGTT, oral glucose tolerance test; MALA, metformin-associated lactic acidosis; OLT, orthotopic liver transplant; DM, diabetes mellitus; ?, debated.

HCV-DM

- HCV ile enfekte olanların % 85'i kronik aktif hepatit ve %20'si siroz
- NHANES çalışmasında, >20 yaş 9,841 hastanın %8.4'ünde DM
- 3.7 kat artmış DM riski

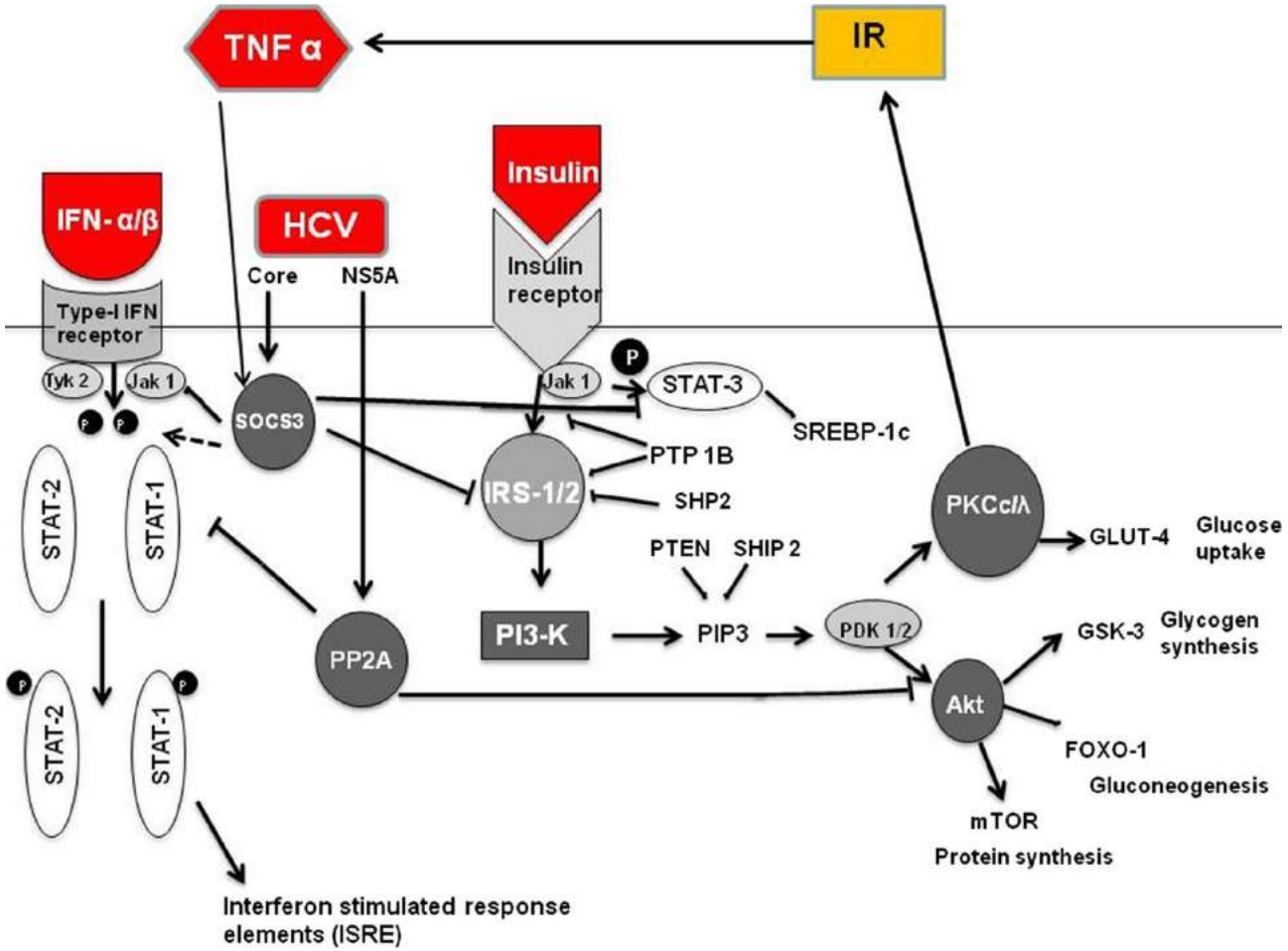
HCV nasıl DM yapıyor

- Artmış serum TNF-alpha seviyeleri
- Artmış IL-6 seviyeleri, GLUT4, IRS-1 ve PPAR reseptörlerinin transkripsiyonunu inhibe ederek insülin direnci



Laure Elkrief et al. Liver International 2016

HCV – İD Mekanizmaları



DPP-4

- CD26 , T- hücrelerinin yüzeyinde yer alan immünoregülatuar bir molekül
- HCV ile enfekte olunca DPP-4 ekpresyonunu arttırıyor
- IF tdv ile DPP-4 aktivitesi normale dönüyor
- Ama, DPP-4 aktivitesi hepatojenik diyabette değişmiyor

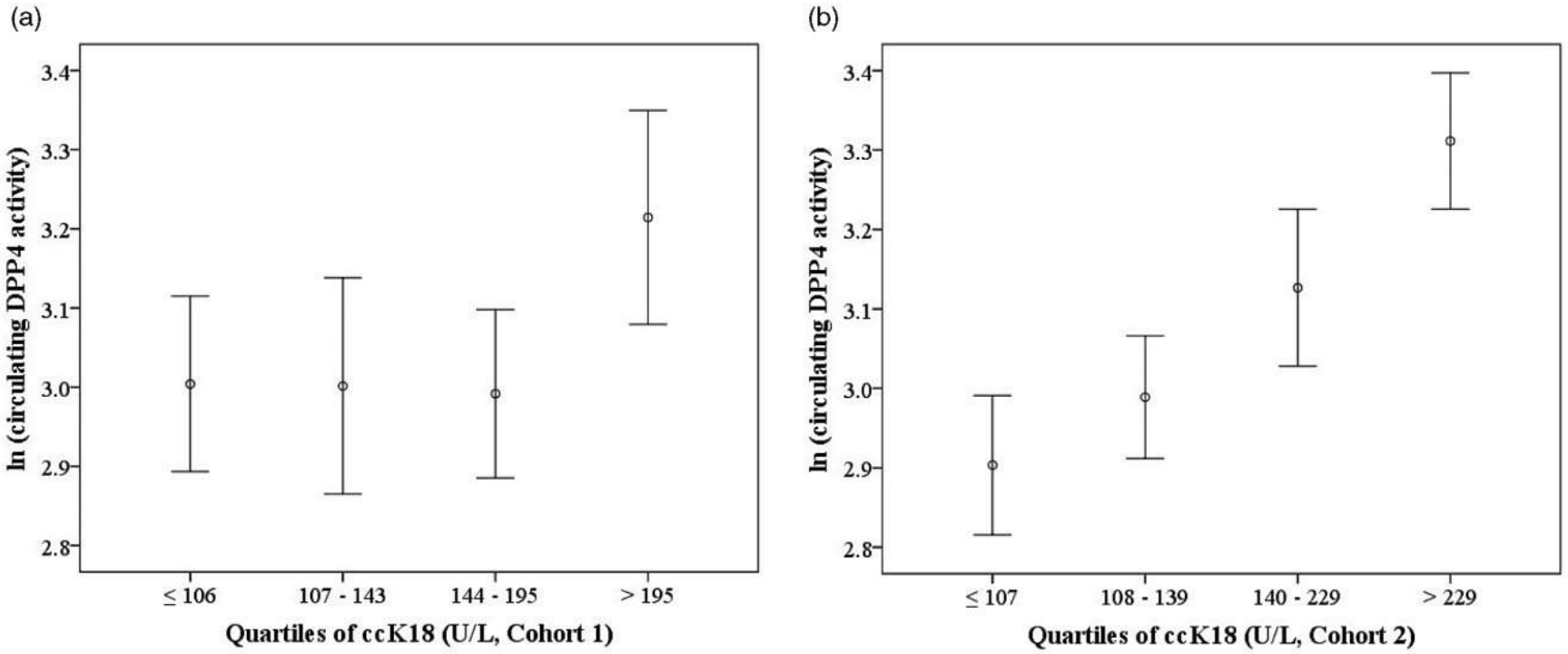
Journal of Diabetes 7 (2015) 809–819

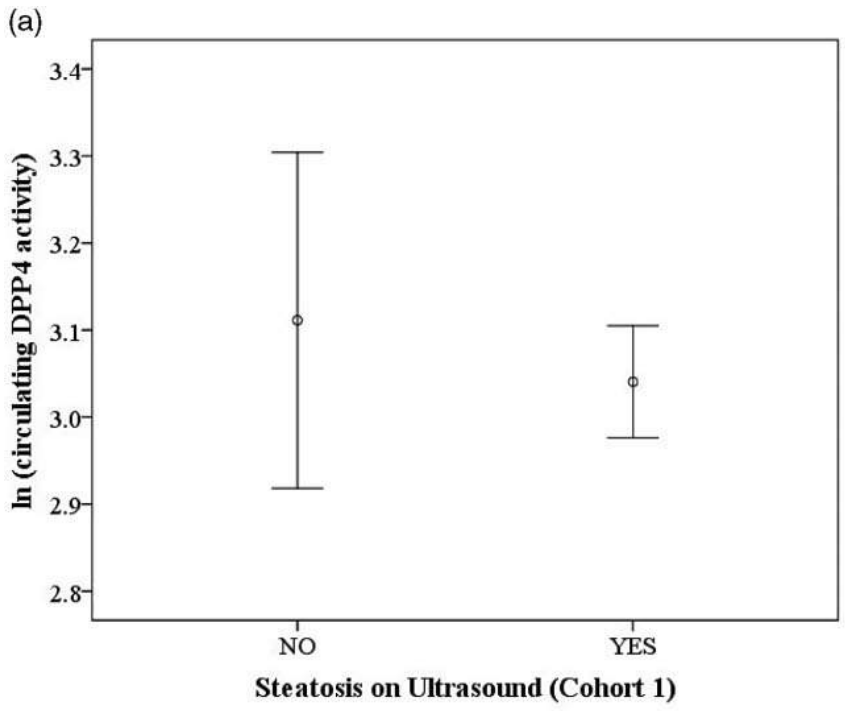
ORIGINAL ARTICLE

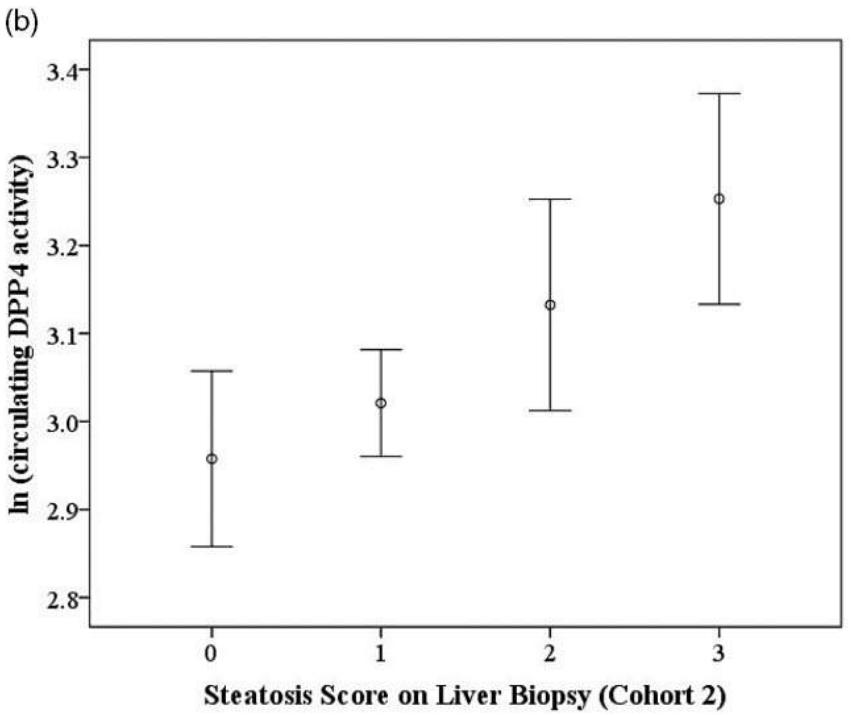
Circulating dipeptidyl peptidase-4 activity correlates with measures of hepatocyte apoptosis and fibrosis in non-alcoholic fatty liver disease in type 2 diabetes mellitus and obesity: A dual cohort cross-sectional study

Kathryn H. WILLIAMS,[1,2,3,4] Ana Júlia VIEIRA DE RIBEIRO,[1,5] Emilia PRAKOSO,[1,2,5] Anne-Sophie VEILLARD,[1,4] Nicholas A. SHACKEL,[1,2,5] Belinda BROOKS,[2,6] Yangmin BU,[7] Erika CAVANAGH,[2] Jim RALEIGH,[2] Susan V. MCLENNAN,[1,2,3] Geoffrey W. MCCAUGHAN,[1,2,5] Fiona M. KEANE,[1,5] Amany ZEKRY,[7,8] Mark D. GORRELL[1,5] and Stephen M. TWIGG[1,2,3]

DPP-4 Aktivitesi




(a)
3.4
3.3
3.2
3.1
3.0
2.9
2.8
ln (circulating DPP4 activity)
NO
YES
Steatosis on Ultrasound (Cohort 1)


(b)
3.4
3.3
3.2
3.1
3.0
2.9
2.8
ln (circulating DPP4 activity)
0
1
2
3
Steatosis Score on Liver Biopsy (Cohort 2)

Digestive and Liver Disease 48 (2016) 105–111

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: Myth or reality?

Ester Vanni[a], Elisabetta Bugianesi[a], Giorgio Saracco[b,*]

[a] Gastro-hepatology Unit, Department of Medical Sciences, University of Turin, Turin, Italy
[b] Gastroenterology Unit, Oncology Department, University of Turin, Italy

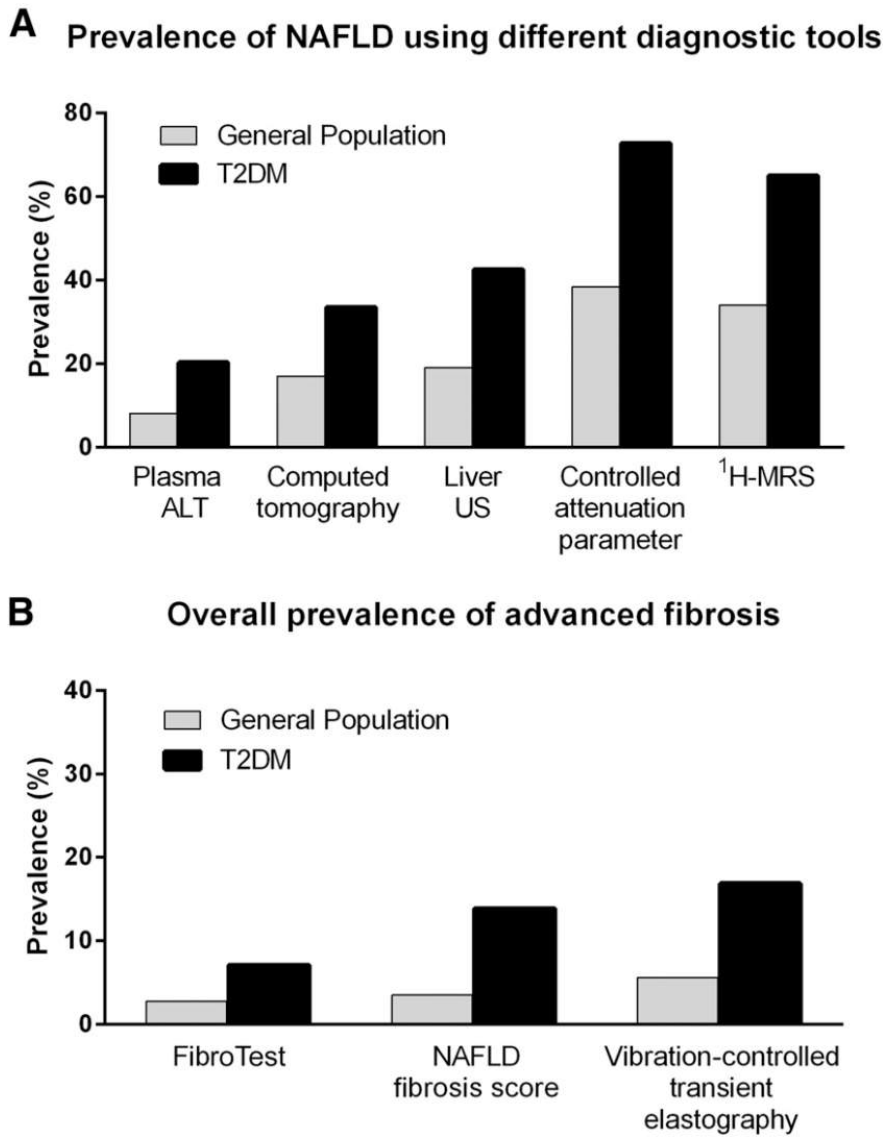
Author, year (ref)	Type of study	Genotype	IR improvement	DM incidence reduction	Comments
Romero-Gomez, 2005 [41]	Prospective	1–4	Yes	–	No follow-up data
Simò, 2006 [52]	Retrospective	1–4	Probable	Yes	No measurement of insulin resistance
Kawaguchi, 2007 [53]	Prospective	1,2	Yes	–	– Genotype 1–2 only – Small sample size – Baseline IR not considered in the analysis
Romero-Gomez, 2008 [55]	Prospective	1–4	Probable	Yes	No measurement of insulin resistance
Giordanino, 2008 [60]	Retrospective	1–4	n.a.	No	– Small sample size – Low number of cirrothics
Kawaguchi, 2009 [54]	Prospective	1,2	Yes	–	– Genotype 1–2 only – Small sample size
Arase, 2009 [59]	Retrospective	1,2	–	Yes	– No data on confounding variables (family history, smoking habits, BMI at f.u.)
Delgado-Borrego, 2010 [56]	Prospective	n.a.	Yes	–	– Genotype 3 excluded – No data regarding SVR
Aghemo, 2012 [58]	Prospective	1–4	Yes	–	Small sample size
Thompson, 2012 [57]	Retrospective	1–3	Partially	–	Genotype 4 excluded

Diabetes Care Volume 40, March 2017

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

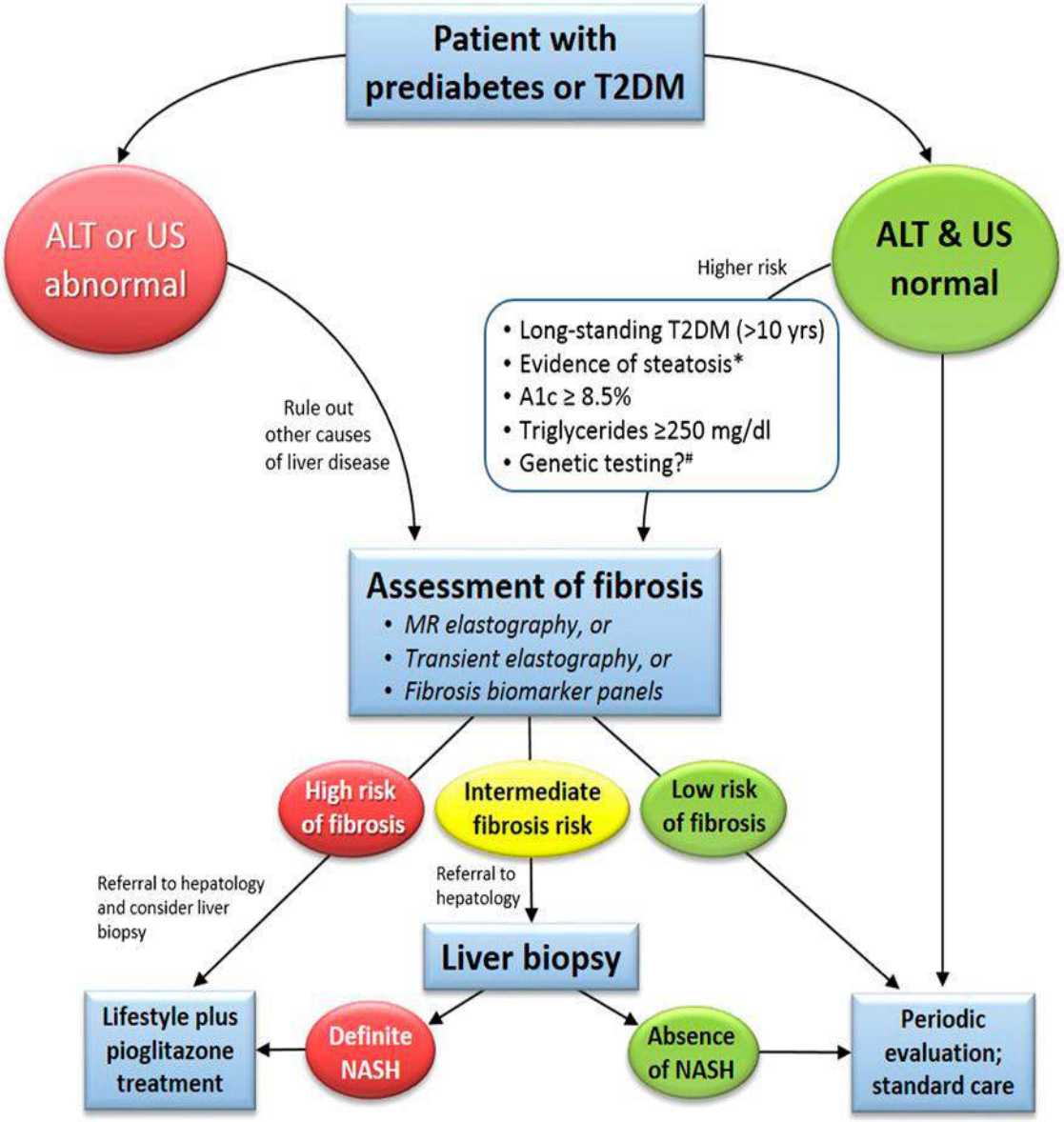
Fernando Bril[1] *and Kenneth Cusi*[1,2]

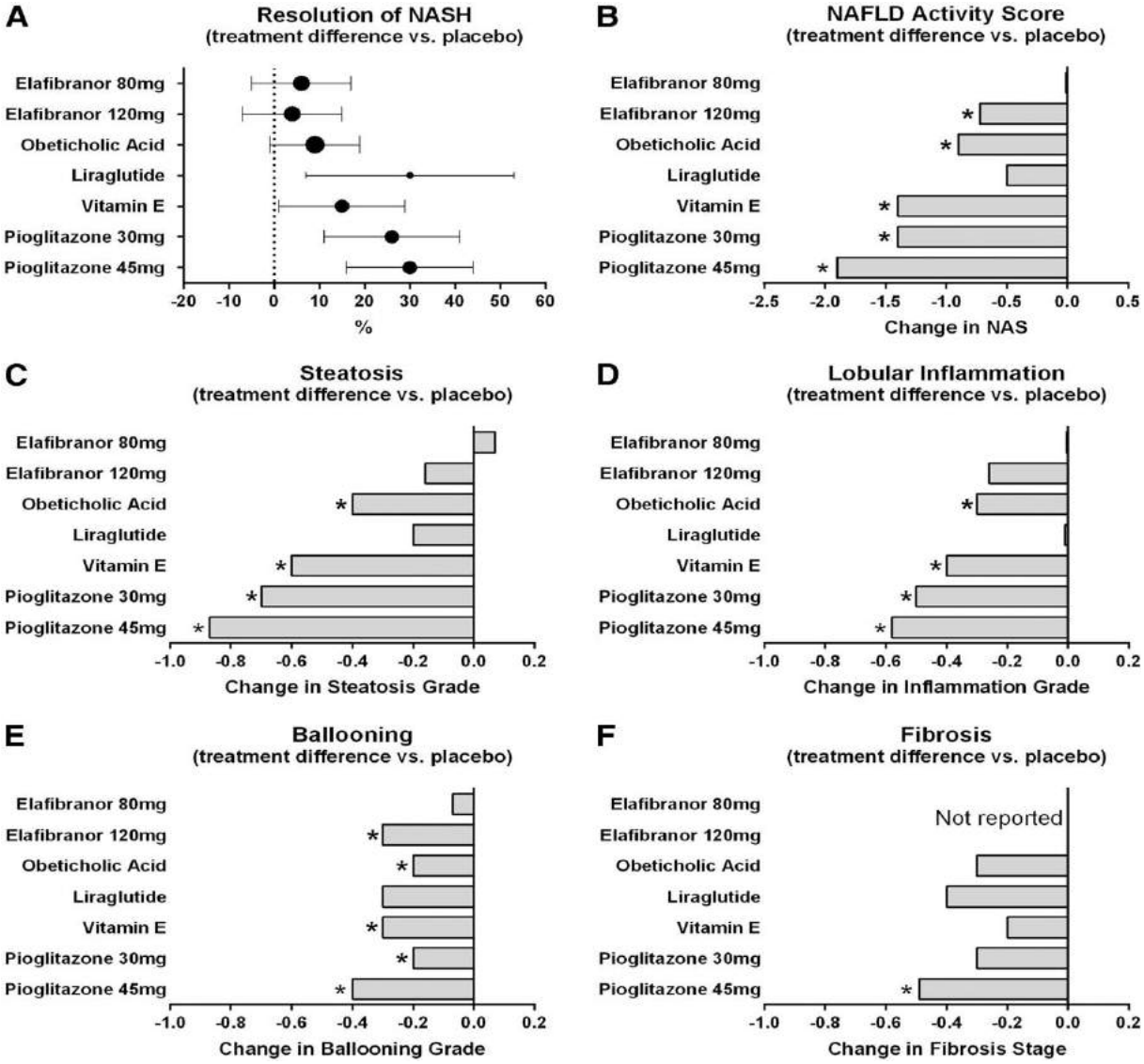
Diabetes Care 2017;40:419–430 | DOI: 10.2337/dc16-1787

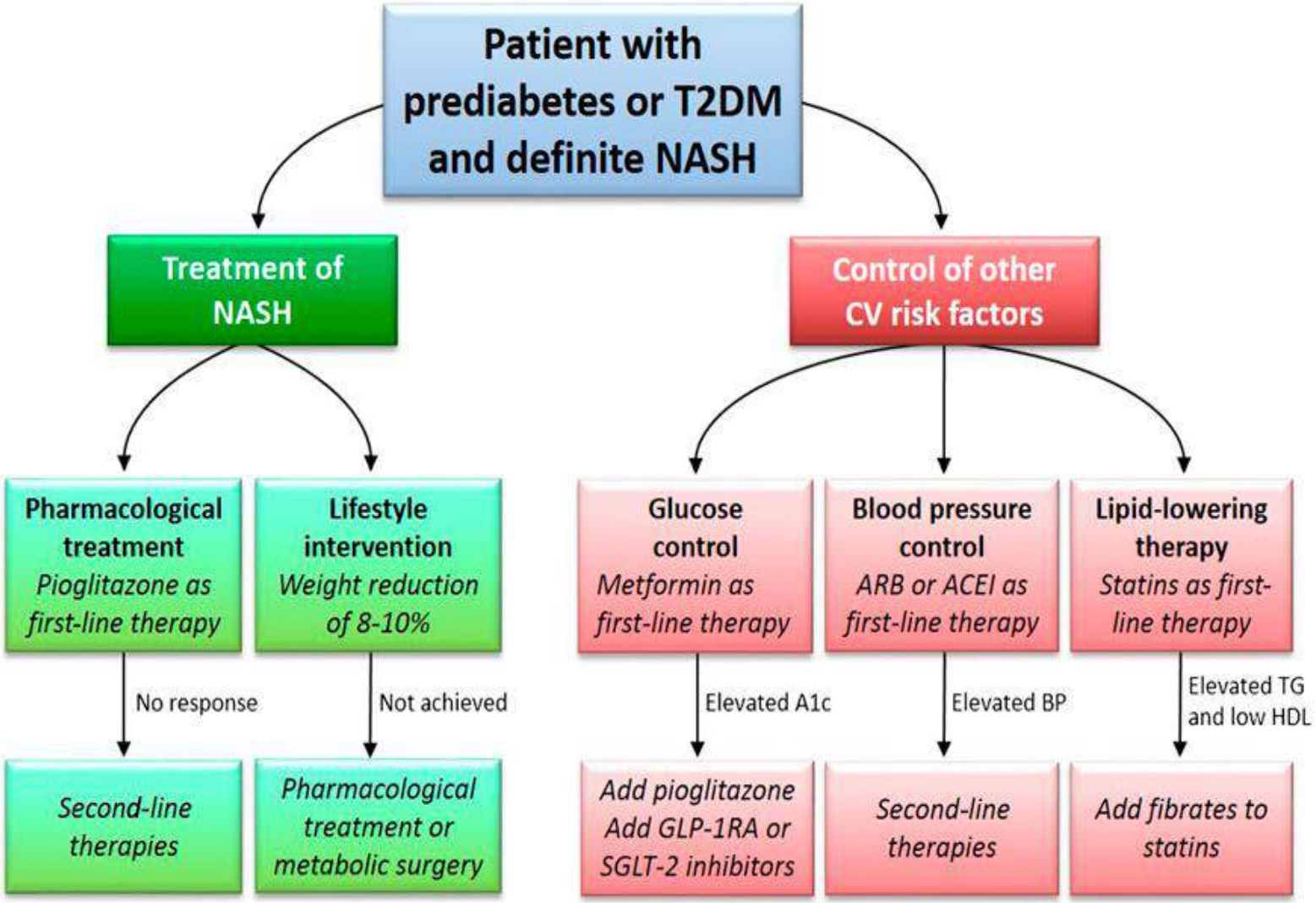

A
Prevalence of NAFLD using different diagnostic tools
Prevalence (%)
80
60
40
20
0
General Population
T2DM
Plasma ALT
Computed tomography
Liver US
Controlled attenuation parameter
1H-MRS
B
Overall prevalence of advanced fibrosis
Prevalence (%)
40
30
20
10
0
General Population
T2DM
FibroTest
NAFLD fibrosis score
Vibration-controlled transient elastography

- Yağlı KC (NAFLD), diyabetli hastaların %34 ile % 74'ünde mevcut
- Nonalcoholic steatohepatitis (NASH), yağlı karaciğer hastalarının % 17–25'inde
- T2DM varlığı 2-5 kat artmış NAFLD

Trombetta M, et al. Aliment Pharmacol Ther 2005
Ludwig J, et al. Mayo Clin Proc 1980


Patient with prediabetes or T2DM
ALT or US abnormal
ALT & US normal
Higher risk
• Long-standing T2DM (>10 yrs)
• Evidence of steatosis*
• A1c ≥ 8.5%
• Triglycerides ≥250 mg/dl
• Genetic testing?#
Rule out other causes of liver disease
Assessment of fibrosis
• MR elastography, or
• Transient elastography, or
• Fibrosis biomarker panels
High risk of fibrosis
Intermediate fibrosis risk
Low risk of fibrosis
Referral to hepatology and consider liver biopsy
Referral to hepatology
Liver biopsy
Lifestyle plus pioglitazone treatment
Definite NASH
Absence of NASH
Periodic evaluation; standard care


A
Resolution of NASH
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
-20 -10 0 10 20 30 40 50 60
%
B
NAFLD Activity Score
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
-2.5 -2.0 -1.5 -1.0 -0.5 0.0 0.5
Change in NAS
C
Steatosis
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2
Change in Steatosis Grade
D
Lobular Inflammation
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2
Change in Inflammation Grade
E
Ballooning
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2
Change in Ballooning Grade
F
Fibrosis
(treatment difference vs. placebo)
Elafibranor 80mg
Elafibranor 120mg
Obeticholic Acid
Liraglutide
Vitamin E
Pioglitazone 30mg
Pioglitazone 45mg
Not reported
-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2
Change in Fibrosis Stage


Patient with prediabetes or T2DM and definite NASH
Treatment of NASH
Control of other CV risk factors
Pharmacological treatment
Pioglitazone as first-line therapy
Lifestyle intervention
Weight reduction of 8-10%
Glucose control
Metformin as first-line therapy
Blood pressure control
ARB or ACEI as first-line therapy
Lipid-lowering therapy
Statins as first-line therapy
No response
Not achieved
Elevated A1c
Elevated BP
Elevated TG and low HDL
Second-line therapies
Pharmacological treatment or metabolic surgery
Add pioglitazone Add GLP-1RA or SGLT-2 inhibitors
Second-line therapies
Add fibrates to statins

Tip 2 DM Siroz arasındaki Morbidite-Mortalite

- Asiti olan, KC transplantasyonu bekleyen hastalarda diyabet varlığı mortalite için bağımsız risk faktörü
- Diyabeti olanlarda; 1- ve 2-yıl yaşam şansı: %32 ile %18
- Diyabeti olmayanlarda oran %62 ‘ye %58

Moreau R, et al. Liver Int 2004

HCC ve DM

- DM hastalarda x4 artmış HCC riski
- HCC'li hastalarda da benzer oranda artmış DM riski

Adami HO, et al. J Natl Cancer Inst 1996
Wideroff L, et al. J Natl Cancer Inst 1997

Tedavi- Yaşam Tarzı Değişiklikleri

- Kilo kaybını hedefleyen; düşük glisemik yüklü, düşük kalorili diyetler
- Kötü beslenmiş kişilerde sorun
- Yaşam tarzı değişiklikleri; en iyi NAFLD, HCV +, ve transplantasyon bekleyenlerde

İlaç Tedavisi

- Oral antidiyabetikler dekompanse KC yetmezliği olan asitli veya ensefalopatili hastalarda çok dikkatli kullanılmalı

Akarboz

- Hepatik ensefalopatili hastalarda, A-TKŞ, A1c düşüşü
- Kan amonyak seviyelerinde düşüş
- Artmış bağırsak hareketleri
- Saccharolitik bakteri proliferasyonunda artış

Gentile S, et al. Diabetes Obes Metab 2001
Gentile S, et al. Clin Gastroenterol Hepatol 2005

İnsülin Sekratogogları

- Gliclazide, KC'de metabolize
- Repa-Nate glinid çalışma? HT değil

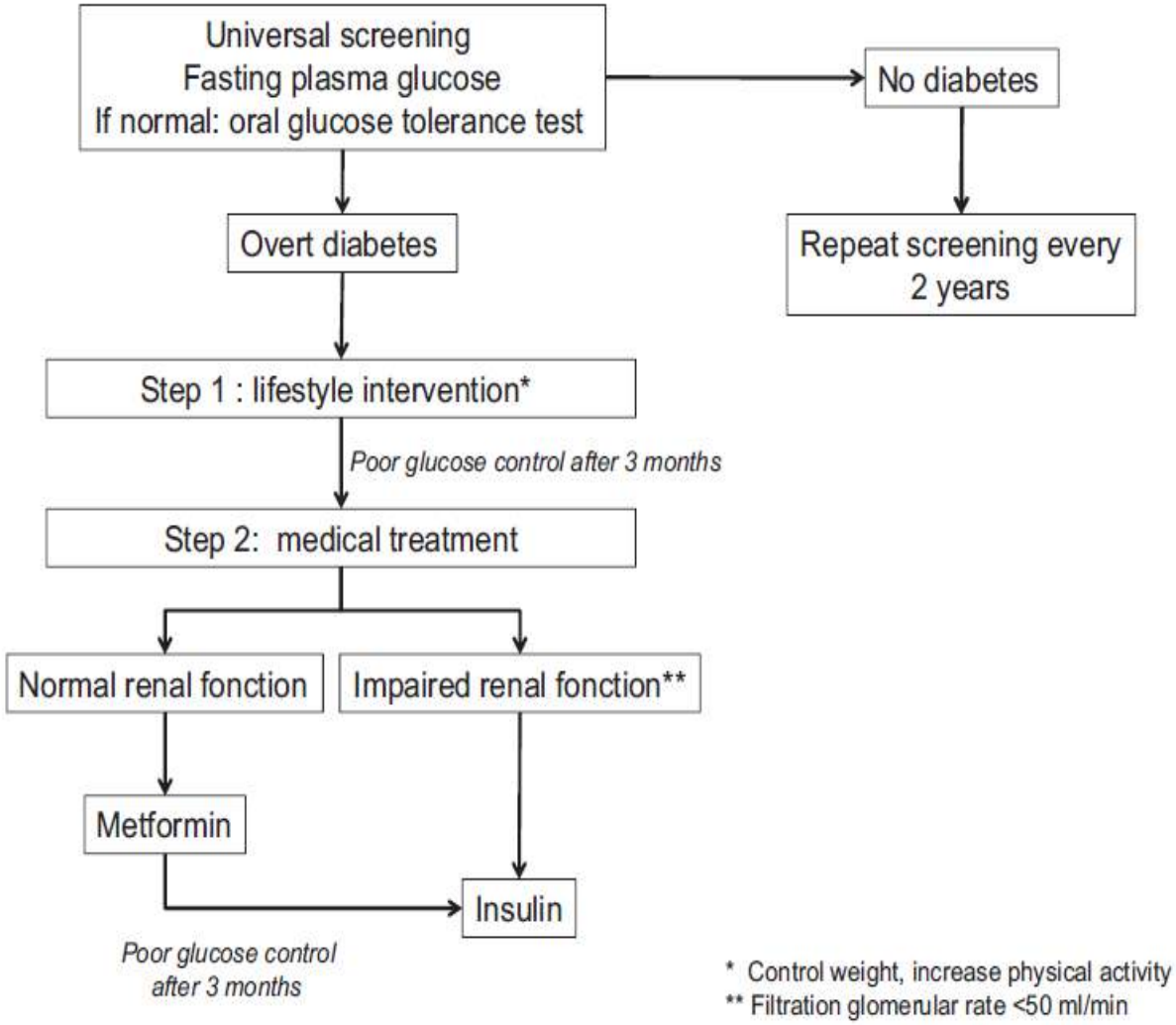
Medikal Tdv

References	Study design	*n*	Treatments (*n*)	Length of treatment	Results on glycemia	Clinical outcomes	Side effects
Gentile et al. [69]	Double-blinded randomized trial	100	Acarbose: 52 versus placebo: 48	28 weeks	Improvement of fasting and postprandial glycemia, HbA1c and C-peptide	Not assessed	None
Kwon et al. [68]	Retrospective and descriptive	434 (88 HCV; 346 HBV)	Insulin: 48 % HCV and 66 % HBV; OHGA: 39 % HCV and 22 % HBV	Mean 20.5 months	Control of glycemia in 34.2 % HCV and in 23.5 % in HBV patients	Control of hyperglycemia and Child–Pugh score were predictors of survival only in HCV patients	Not reported
Nkontchou et al. [70]	Prospective cohort study. Observational	100 pts with HCV cirrhosis	Metformin: 26 Insulin or OHGA: 74	3.8–9.5 years	Not assessed	Metformin use reduced incidence of HCC and liver-related death/transplantation	Any case of lactic acidosis
Gundling et al. [67]	Observational retrospective	285	Insulin or OHGA: 87 No treatment: 198	3 years	Satisfactory control of glycemia in 28.7 % of cases	The control of hyperglycemia was associated only with reduction in hepatic encephalopathy	Hypoglycemia in 12.6 % in Child–Pugh B and C patients treated with insulin
Zhang et al. [71]	Observational retrospective	250	Metformin: 172 No treatment: 78	3.1–151.0 months	Not assessed	The use of metformin was associated with significant increase in survival	Any case of lactic acidosis

Drug Class	Example	Mechanism of Action	Normal Dosage	Dosage Adjustment in Patients with CLD
Biguanide	Metformin	Insulin sensitization leading to increased glucose uptake in muscle and reduced hepatic gluconeogenesis	500–3000 mg daily	Maximum dose, 1500 mg daily
Sulfonylurea	Gliclazide; glyburide; repaglinide	Stimulation of insulin release from pancreatic islet cells	80–320 mg daily; 2.5–20 mg daily; 4–16 mg daily	Dosage halved, especially if patient is not abstinent from alcohol
Alpha-glucosidase inhibitor	Acarbose	Inhibit disaccharidases to reduce glucose absorption in bowel	50–100 mg 3 times daily with meals	No dose adjustment
Thiazolidinedione	Pioglitazone	Insulin sensitization via PPAR-γ agonist effect	15–45 mg daily	Maximum, 30 mg daily with careful monitoring of liver function
Insulin	Long acting, intermediate acting, mixed, and short acting	Replacement of insulin deficiency	Variable between patients	Reduction in dose by 25% in patients with CLD, with clear warnings about risk of hypoglycemia
GLP-1 analog	Exenatide; liraglutide	GLP-1 stimulates insulin release and reduces appetite	10 μg twice daily; 0.6–1.8 mg daily	Little experience of use; hence, no dose recommendation. Use with caution.
DPP-4 inhibitor	Saxagliptin; linagliptin	Inhibit DPP-4 thereby elevating endogenous GLP-1	2.5–5 mg daily; 5 mg daily	No dose adjustment

Roaid Khan, et al. Postgraduate Medicine, 2012

Therapy	Mechanism of action	Useful in type 2 DM	Useful in patients with cirrhosis and DM	Side-effects/risks
Lifestyle interventions *Low fat diet* *Physical exercise*	Decrease liver and adipose fat Increase insulin sensitivity	Very useful	Potentially useful	Malnutrition frequent in patients with cirrhosis Physical exercise may not be feasible in patients with advanced cirrhosis (edema, ascites)
Metformin	Increase insulin sensitivity	Very useful	Very useful	Contraindicated in patients with renal dysfunction Theoretical risk of lactic acidosis
Thiazolidinediones	Increase insulin sensitivity	Useful	No available data	Reported hepatotoxicity Usefulness in patients with NASH has not been demonstrated
Secretagogues *Sulphonyureas* *Glinides*	Increase endogenous production of insulin	Useful	Not useful	Contraindicated in patients with advanced cirrhosis because of the risk of hypoglycaemia
Incretins *GLP-1 receptor analogues* *DPP-4 inhibitors*	Increase insulin sensitiviy	Very useful Obese patients (weight loss)	No available data	
Alpha-glucosidase inhibitors	Decrease carbohydrate absorption in the bowel	Useful	May be useful in patients with HE	Benign digestive side-effects
Insulin	Substitutive treatment	Often necessary	Often necessary	Risk of hypoglycaemia


Universal screening
Fasting plasma glucose
If normal: oral glucose tolerance test
No diabetes
Repeat screening every 2 years
Overt diabetes
Step 1 : lifestyle intervention*
Poor glucose control after 3 months
Step 2: medical treatment
Normal renal fonction
Impaired renal fonction**
Metformin
Insulin
Poor glucose control after 3 months
* Control weight, increase physical activity
** Filtration glomerular rate <50 ml/min

DM+ KC-S Tdv

- Bireysel tdv hedefini belirle (A1c %7.5-8)
- Sirozda birçok OAD'nin onayı yok
- Hipoglisemik molekül kullanımında dikkatli ol (SU, insülin)
- KC hastalığının ciddiyetini belirle (Child-Pugh)
- Renal hastalık, alkol alımını dolayısıyla dekompanzasyon riskini belirle
- Primer amaç: Semptomatik olmasından kaçın: hipoglisemi, dehidrate, kognitif bozuklukta ilerleme

Diyabet ve Siroz birlikteliğinde Tdv

- Child A Siroz: Onayı olmamasına rağmen OAD'ler güvenli olarak kullanılabilir
- Metformin: Alkol kullanımı yoksa ve GFR< 30 ml/dk üstünde ise
- Pioglitazon özellikle NASH varsa
- Akarboz özellikle ensefalopati eğilimi olan hastalarda
- DPP-4 inhibitörleri güvenli olarak görünüyor, özellikle HCV +
- GLP-1 analogları: exenatide, dulaglutide, liraglutide'in KC yetmezliğinde doz ayarlamasına gerek yok
- İnsülin: Hızlı etkili olanlar tercih
- Child B ve C Sirozda: Metformin özelleşmiş merkezlerde, GLP-1-RA, ve basit insülin rejimleri

- KC transplantasyonu
- Bariatrik cerrahi