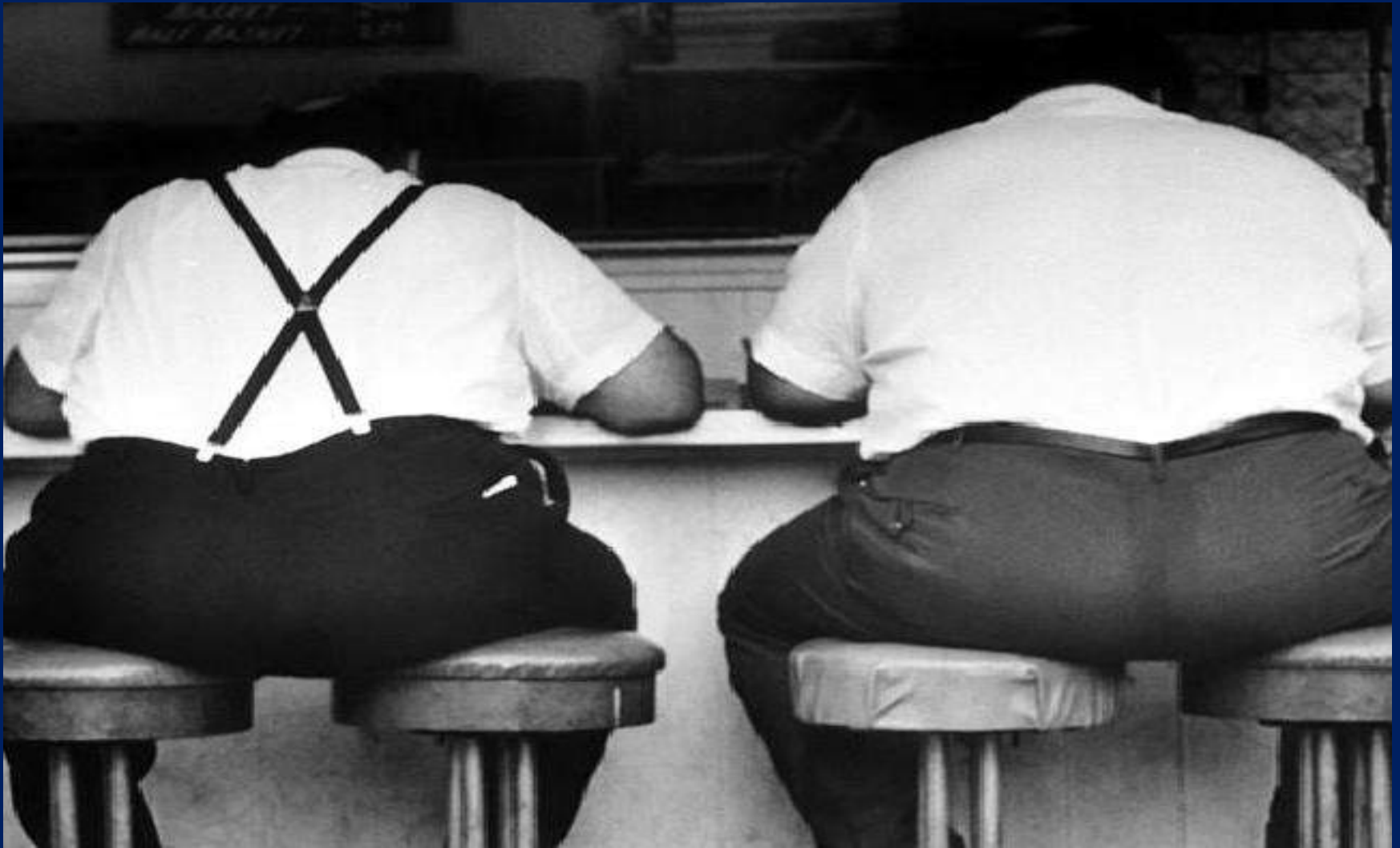


DİRENÇLİ OBEZ HİPERGLİSEMİK TİP 2 DİYABETLİ HASTALARDA TEDAVİ YAKLAŞIMI

Prof. Dr. Engin GÜNEY

Adnan Menderes Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

OBEZİTE



OBEZİTE

➤ WHO 2014 verileri:

❖ 18 yaş üstü

❖ VKİ>25 kg/m²: >1.9 milyar (%39)

Kadın: %40 Erkek: %38

❖ VKİ>30 kg/m²: >600 milyon (%13)

Kadın: %15 Erkek: %11

OBEZİTE



Mean Body Mass Index (kg/m²), ages 20+, age standardized, 1980–2008
Male, 2008

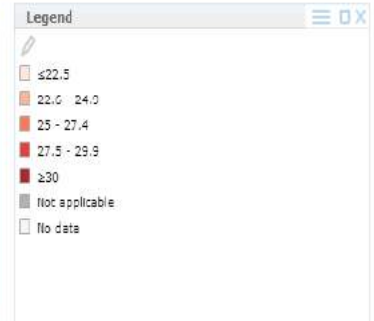
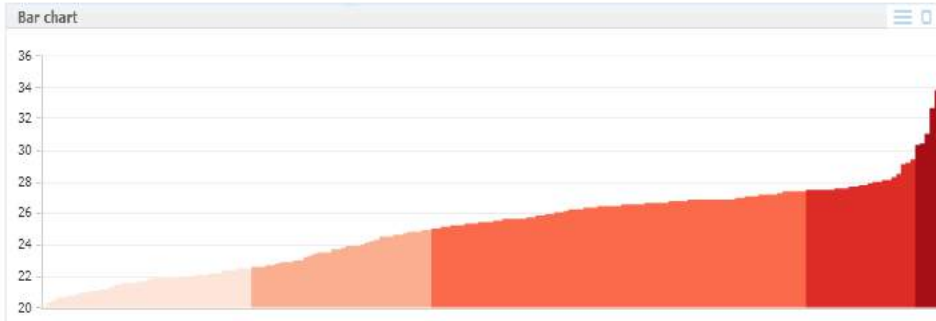
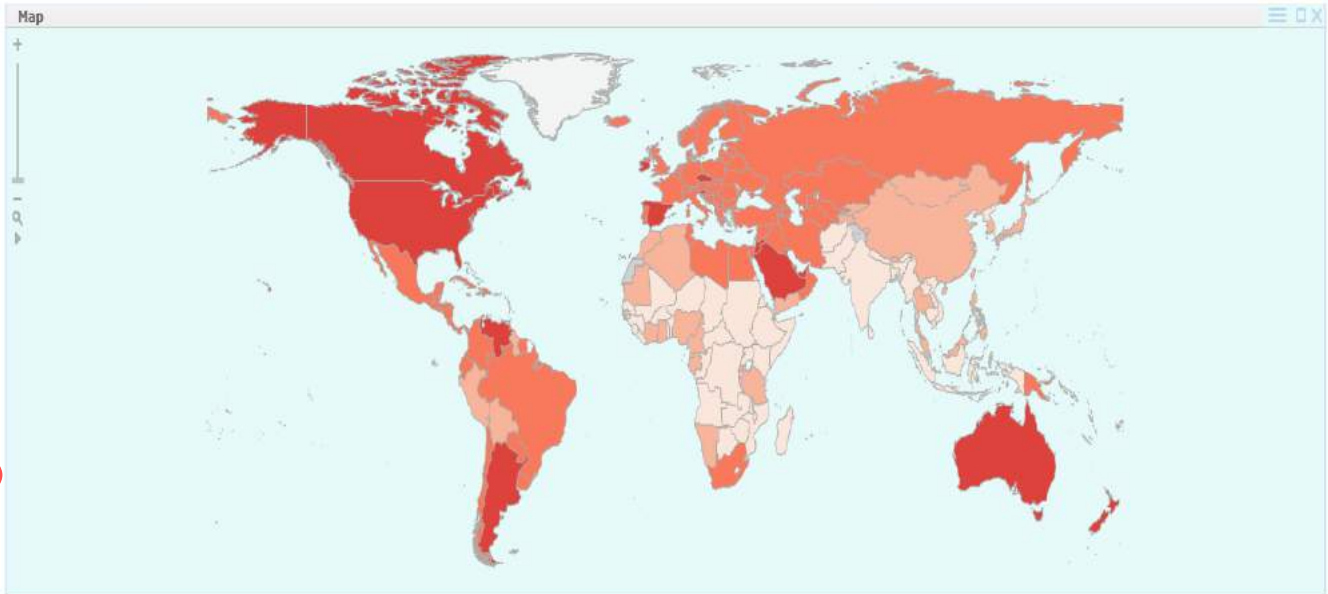
View more indicators

Filter by WHO region

View static maps

Help

Country	Data
Sudan	22.4
Suriname	25.7
Swaziland	23.2
Sweden	26.4
Switzerland	26.2
Syrian Arab Republic	26.9
Tajikistan	23.8
Thailand	23
The former Yugoslav Republic of Macedonia	26.6
Timor-Leste	20.8
Togo	21.9
Tonga	31
Trinidad and Tobago	26.6
Tunisia	25.2
Turkey	26.7
Turkmenistan	25.2
Tuvalu	No data
Uganda	22.5
Ukraine	25.5
United Arab Emirates	28
United Kingdom	27.4
United Republic of Tanzania	22.6
United States of America	28.5
Uruguay	26.4
Uzbekistan	25.3
Vanuatu	26.8
Venezuela (Bolivarian Republic of)	27.5
Viet Nam	21
Yemen	24.5
Zambia	20.7
Zimbabwe	22.1



OBEZİTE



Overweight/obesity, 2008

Prevalence of overweight*, ages 20+, age standardized: Both sexes

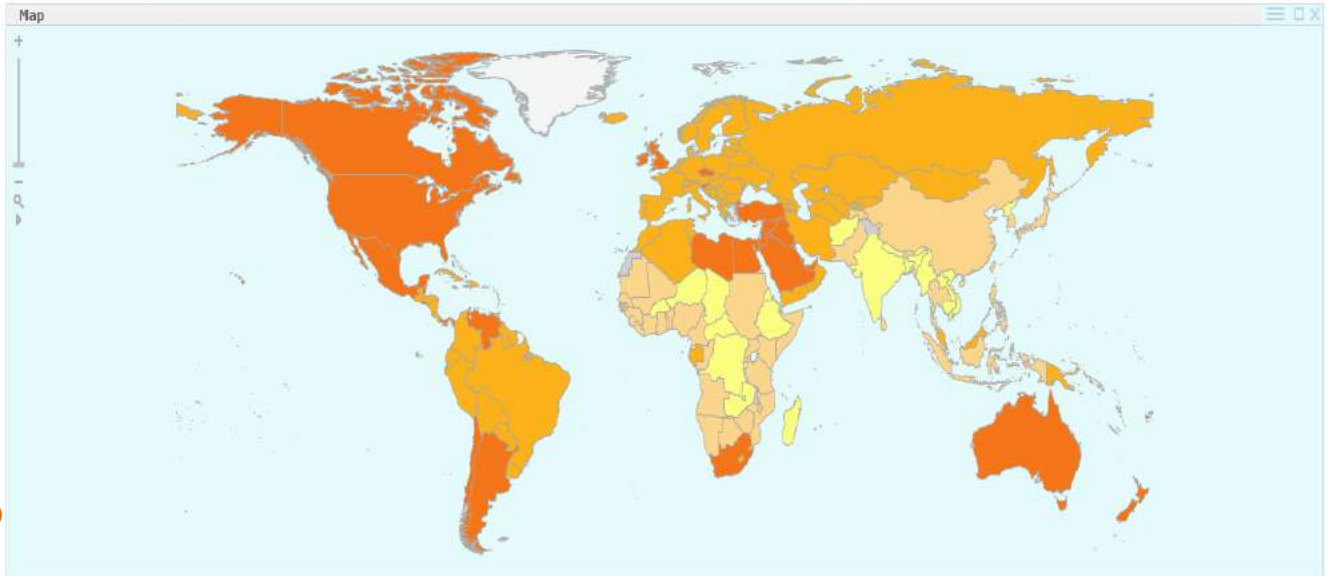
[View more indicators](#)

[Filter by WHO region](#)

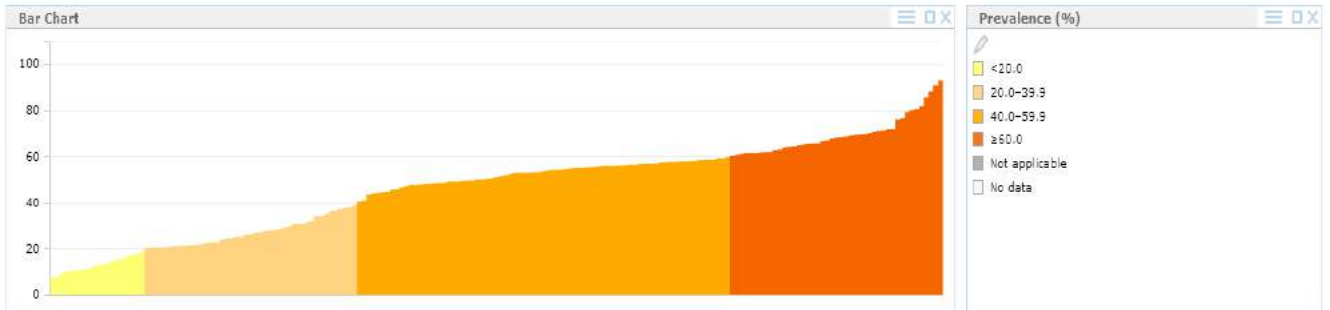
[View static maps](#)

[Help](#)

Country	Data
South Africa	68.0
Spain	58.2
Sri Lanka	21.7
Sudan	25.0
Suriname	58.4
Swaziland	50.3
Sweden	50.0
Switzerland	44.3
Syrian Arab Republic	56.4
Tajikistan	33.8
Thailand	31.4
The former Yugoslav Republic of Macedonia	52.8
Timor-Leste	13.4
Togo	20.5
Tonga	88.1
Trinidad and Tobago	54.7
Tunisia	55.9
Turkey	63.6
Turkmenistan	43.6
Tuvalu	No data
Uganda	21.2
Ukraine	51.8
United Arab Emirates	72.0
United Kingdom	61.5
United Republic of Tanzania	23.9
United States of America	69.4
Uruguay	57.3
Uzbekistan	46.1
Vanuatu	55.4
Venezuela (Bolivarian Republic of)	57.5
Viet Nam	10.1
Yemen	45.7
Zambia	17.8



* BMI ≥ 25 kg/m² | ** BMI ≥ 30 kg/m²



OBEZİTE



Overweight/obesity, 2008

Prevalence of obesity^{**}, ages 20+, age standardized: Both sexes

[View more indicators](#)

[Filter by WHO region](#)

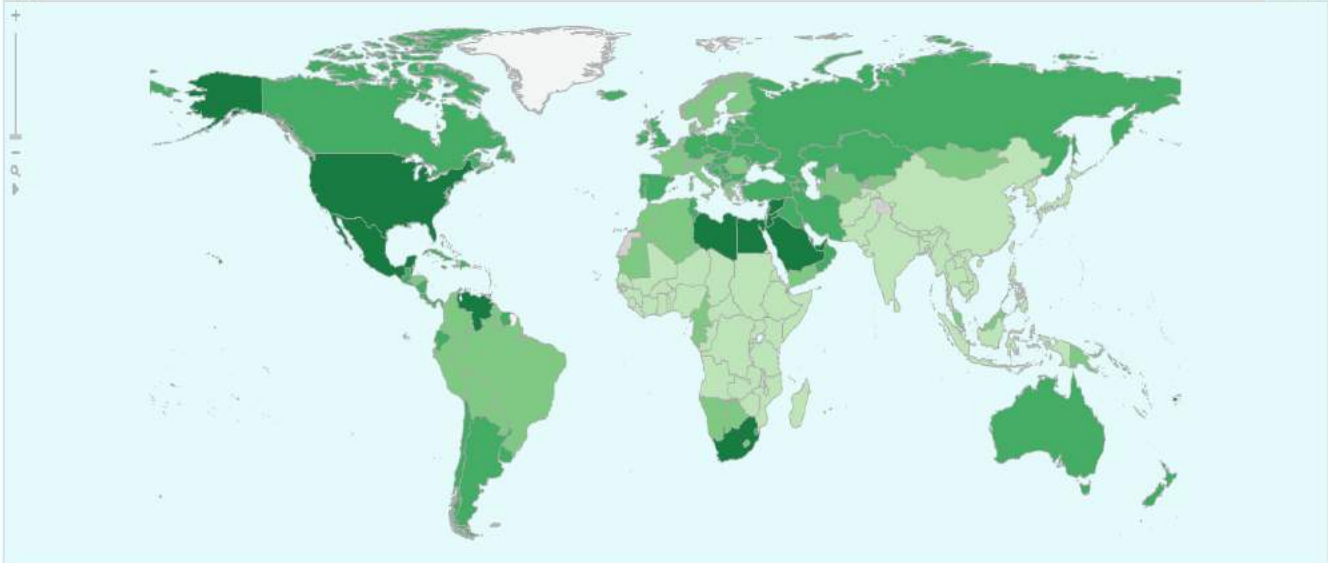
[View static maps](#)

[Help](#)

Table ☰ 🗨 🗪

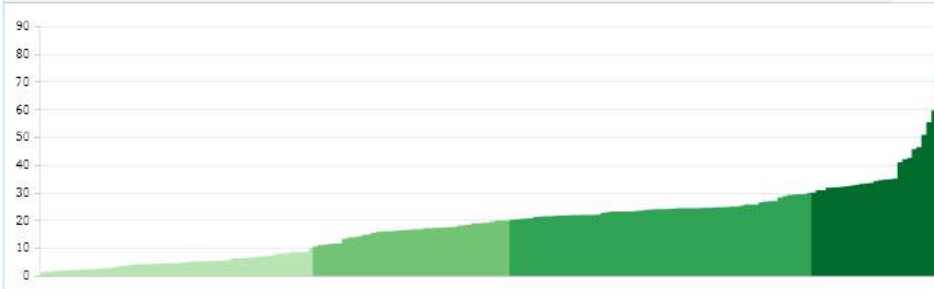
	Country	▲	Data
🔍	Somalia		5.3
🔍	South Africa		33.3
🔍	Spain		24.1
🔍	Sri Lanka		5.0
🔍	Sudan		6.6
🔍	Suriname		25.8
🔍	Swaziland		23.4
🔍	Sweden		16.6
🔍	Switzerland		14.9
🔍	Syrian Arab Republic		31.6
🔍	Tajikistan		9.9
🔍	Thailand		8.5
🔍	The former Yugoslav Republic of Macedonia		20.3
🔍	Timor-Leste		2.9
🔍	Togo		4.6
🔍	Tonga		59.6
🔍	Trinidad and Tobago		20.0
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🔍	Turkey		29.3
🔍	Turkmenistan		14.3
🔍	Tuvalu		No data
🔍	Uganda		4.6
🔍	Ukraine		20.1
🔍	United Arab Emirates		33.7
🔍	United Kingdom		24.9
🔍	United Republic of Tanzania		5.4
🔍	United States of America		31.8
🔍	Uruguay		23.6
🔍	Uzbekistan		17.3
🔍	Vanuatu		29.8
🔍	Venezuela (Bolivarian Republic of)		30.8
🔍	Viet Nam		1.6
🔍	Yemen		16.7
🔍	Zambia		4.2
🔍	Zimbabwe		8.6

Map ☰ 🗨 🗪



* BMI $\geq 25 \text{ kg/m}^2$ | ** BMI $\geq 30 \text{ kg/m}^2$

Bar Chart ☰ 🗨 🗪



Prevalence (%) ☰ 🗨 🗪



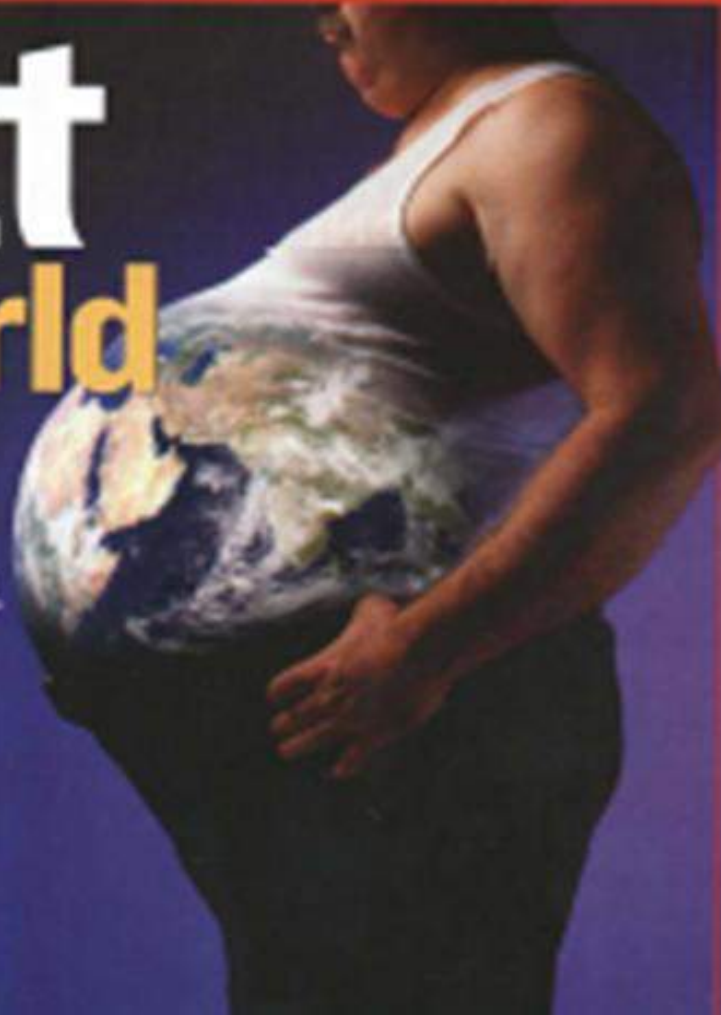
OBEZİTE

Newsweek

Fat World

We're Eating
More Junk
And Getting
Less Exercise.

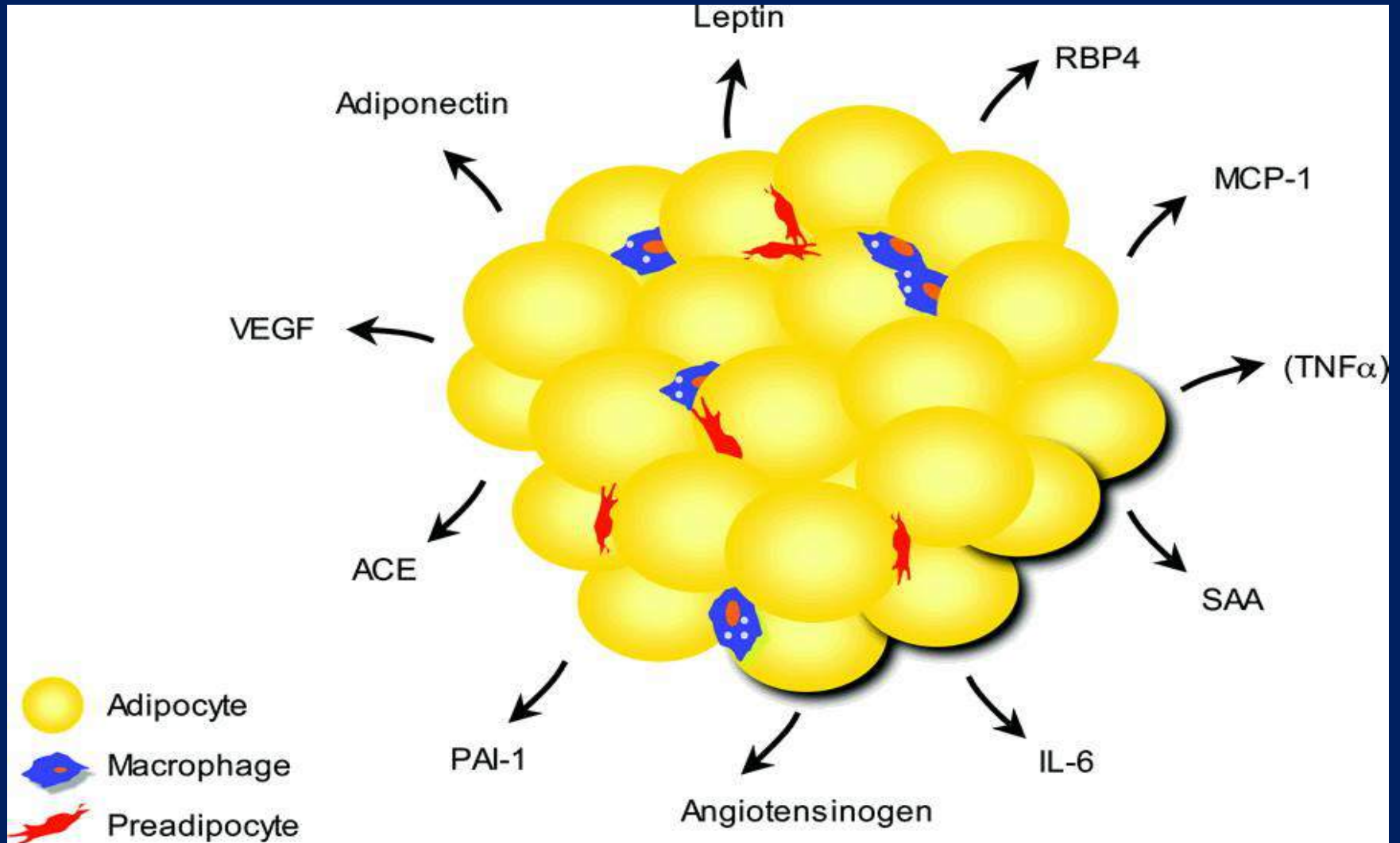
Obesity Is
The Globe's
Newest
Epidemic.



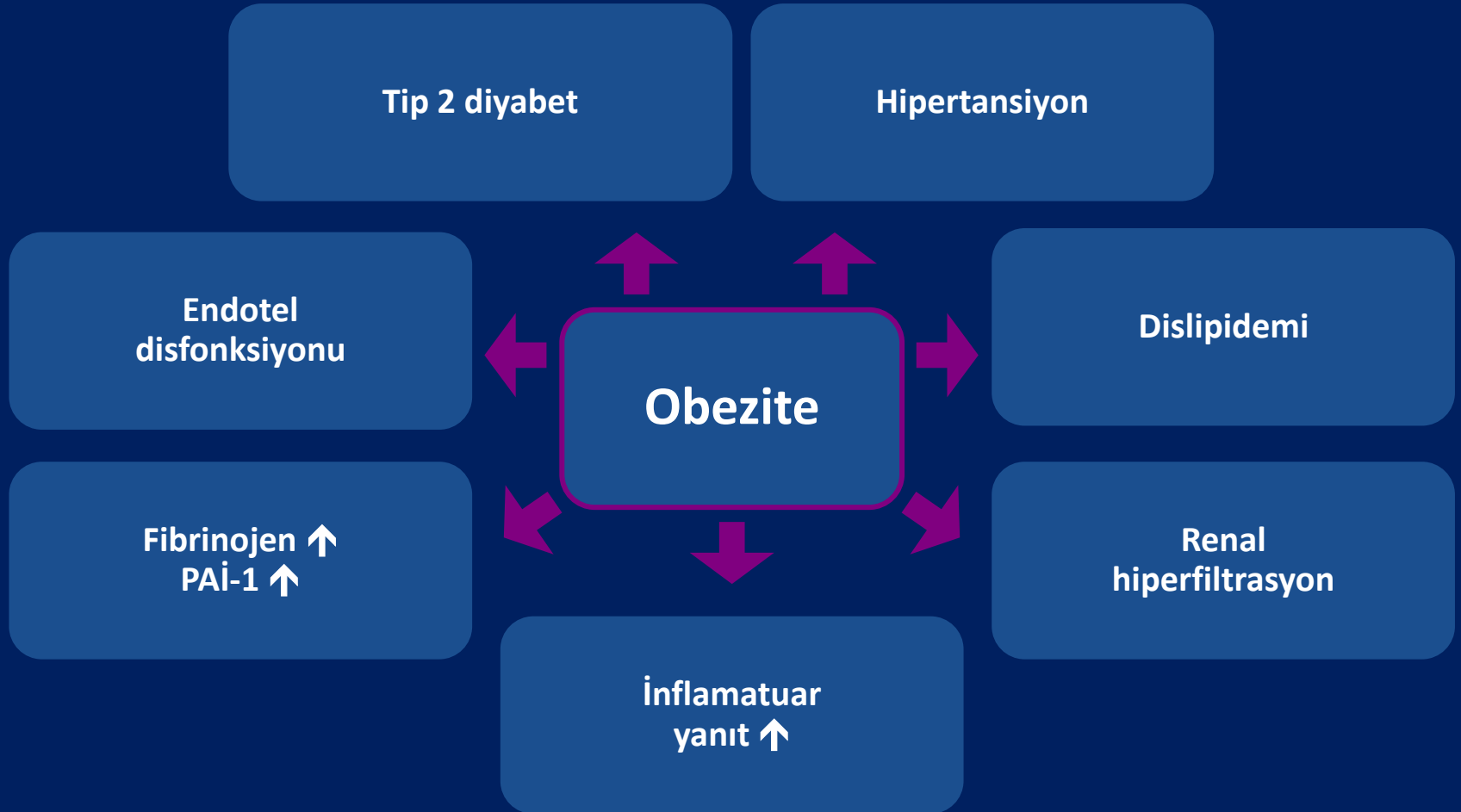
OBEZİTE

- ❖ Obezite prevalansı 1980'den 2014'e kadar 2 kattan fazla artmıştır.
- ❖ Obezite vücutta sağlığı bozacak şekilde aşırı veya anormal yağ birikmesi olarak tanımlanmaktadır.

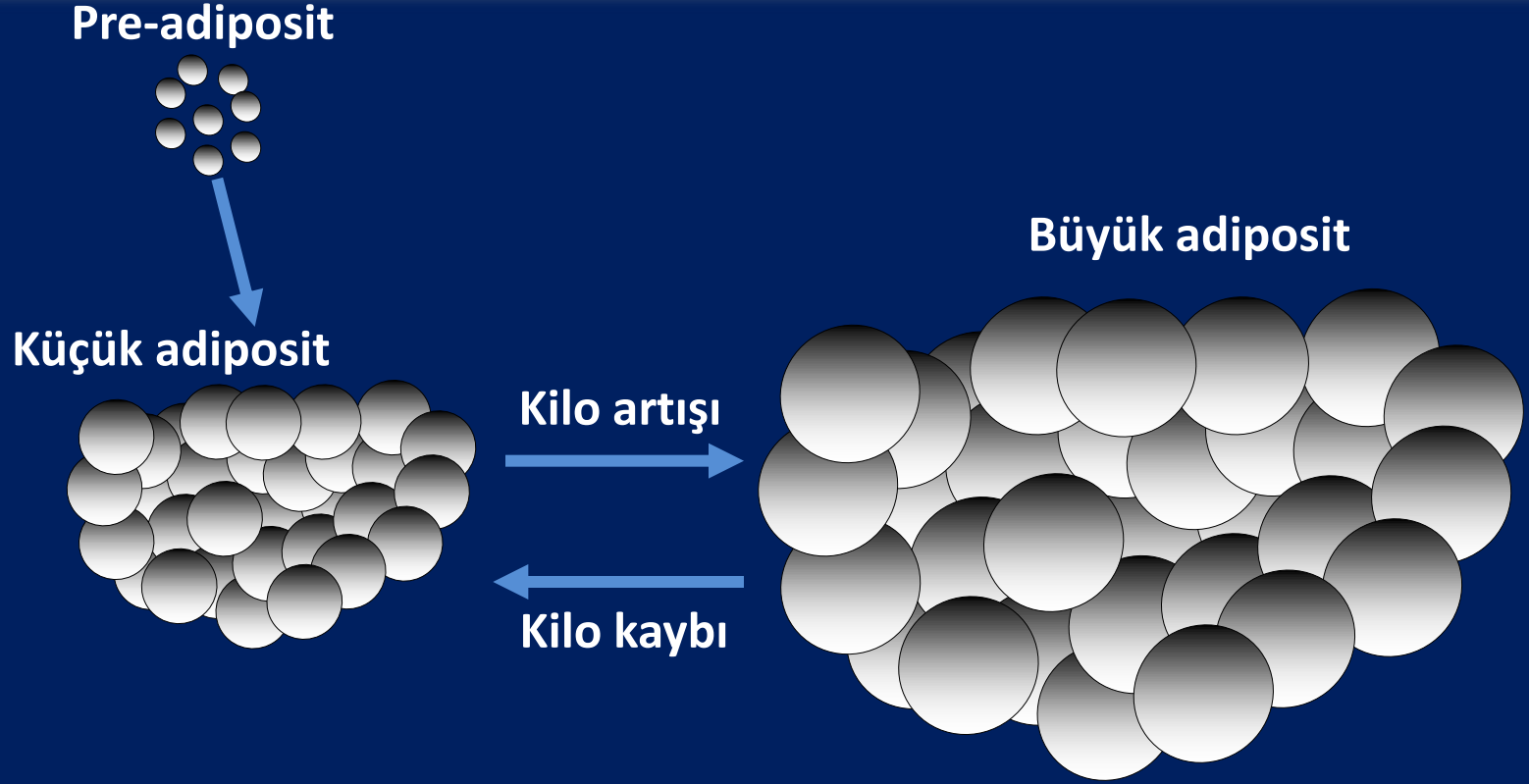
YAĞ DOKUSU: ENDOKRİN HÜCRE



METABOLİK SENDROM



İNSÜLİN DİRENCİ



↑ Adiponektin

↓ Serbest yağ asitleri

↓ IL-6

Azalmış insülin direnci

↓ Adiponektin

↑ Serbest yağ asitleri

↑ IL-6

Artmış insülin direnci

İNSÜLİN DİRENCİ



METABOLİK SENDROM

İnsülin
direnci

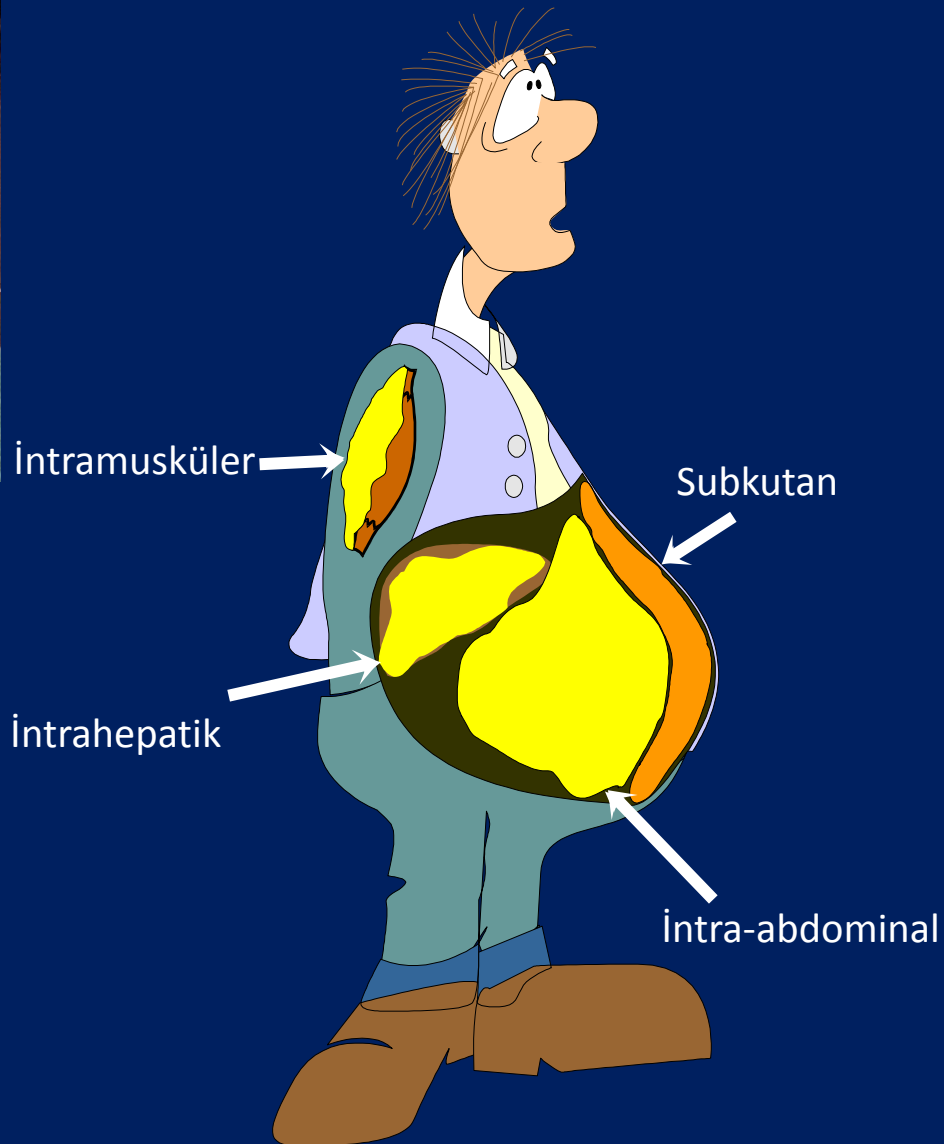
- ◆ Obezite
- ◆ Hipertansiyon
- ◆ Diyabet
- ◆ Hipertrigliseridemi
- ◆ Küçük, yoğun LDL
- ◆ Düşük HDL
- ◆ Hiperkoagülabilite
(PAI-1 ↑, fibrinojen ↑)

Ateroskleroz



Endotel
disfonksiyonu

ABDOMİNAL OBEZİTE



SYA

TNF-alfa

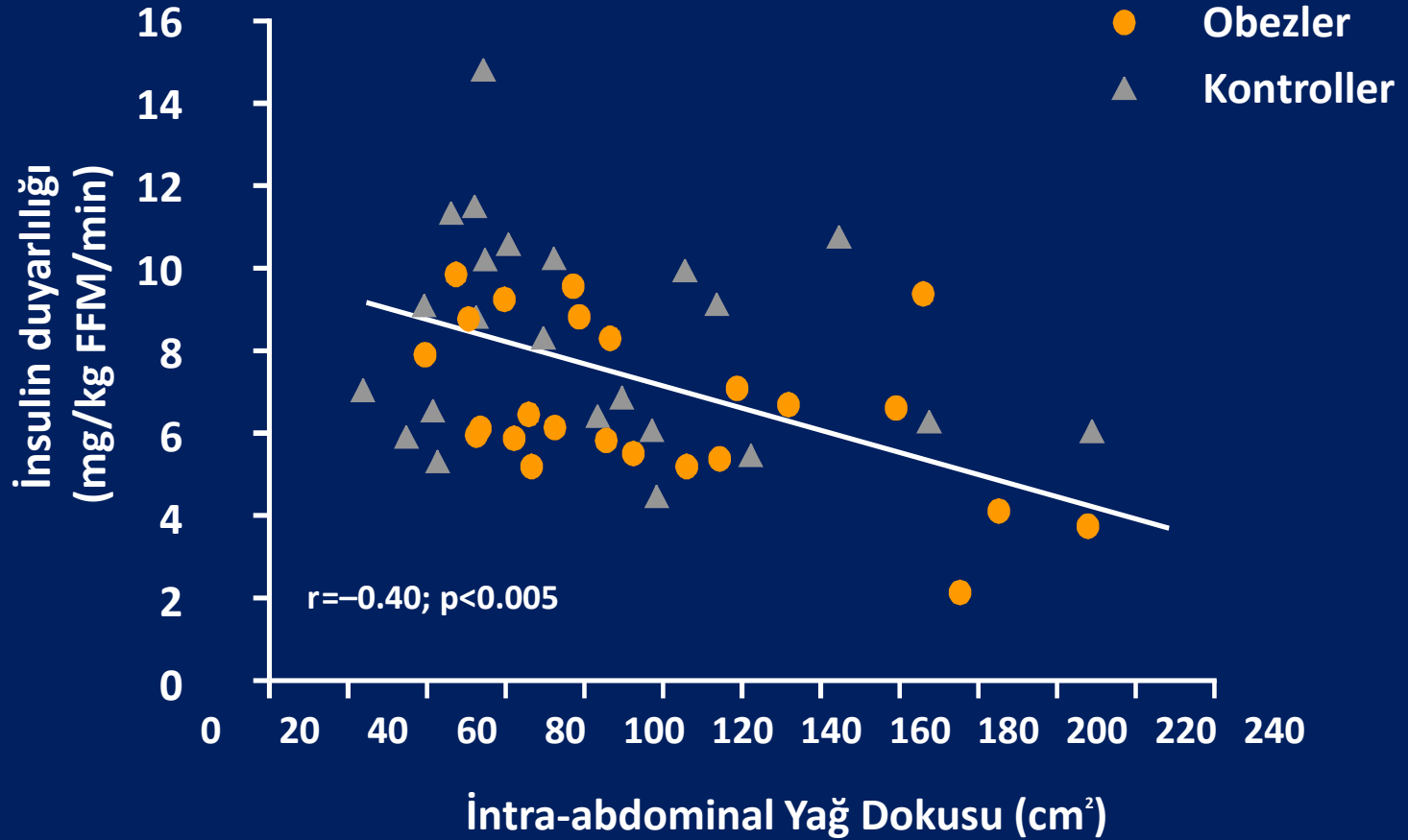
Leptin

IL-6

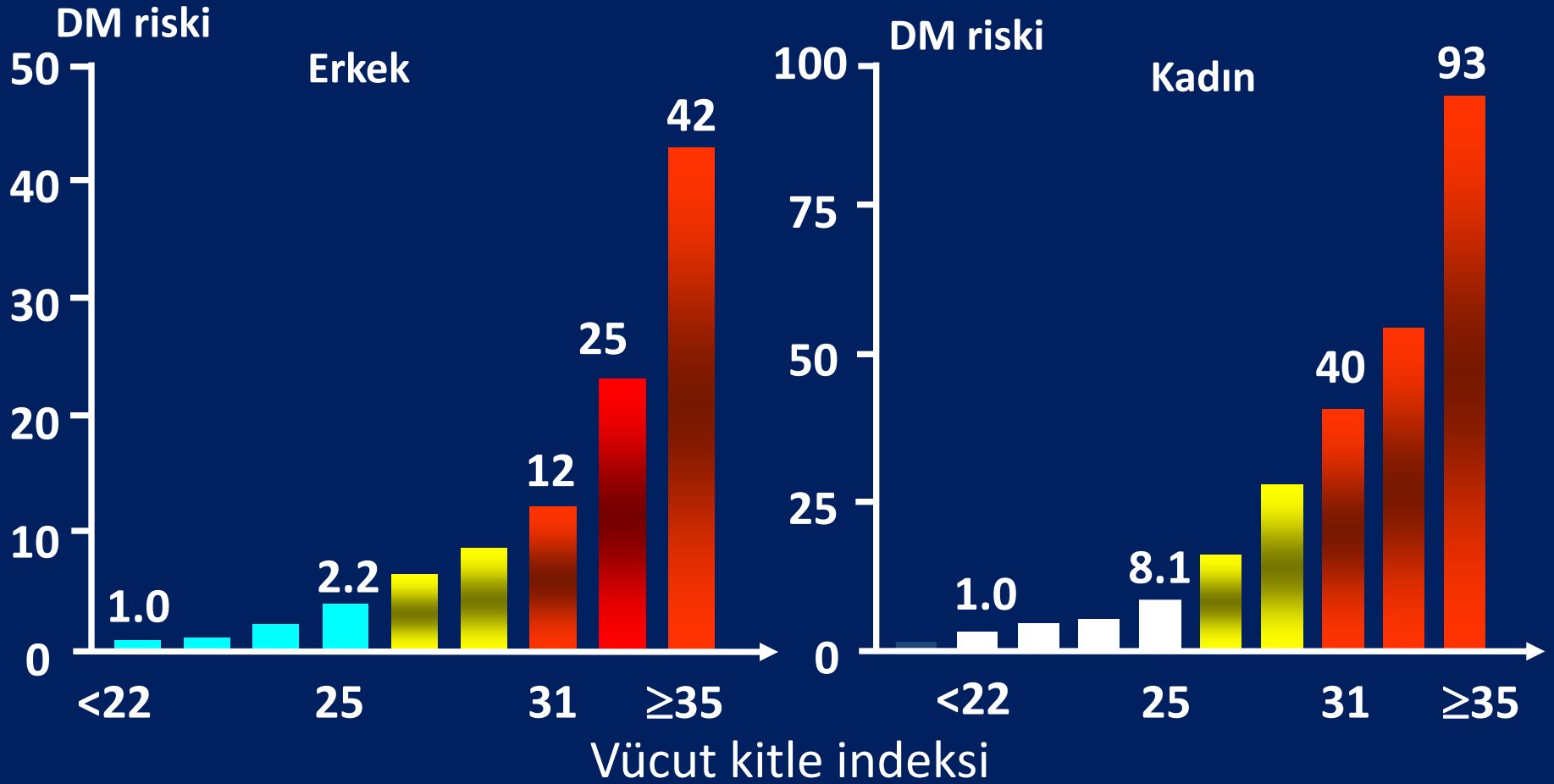
PAI-1

Anjiotensinojen

ABDOMİNAL OBEZİTE

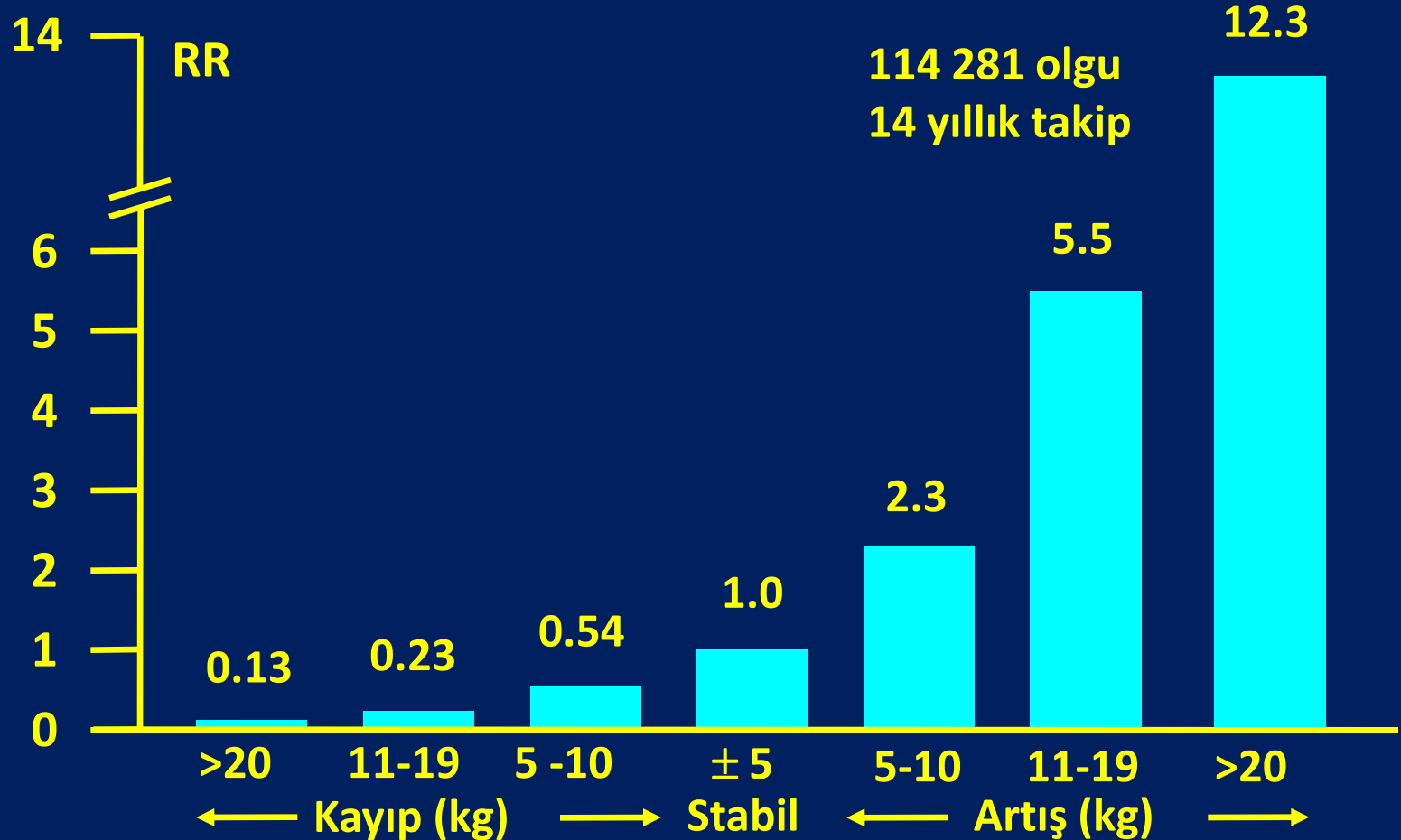


DM GELİŞME RİSKİ

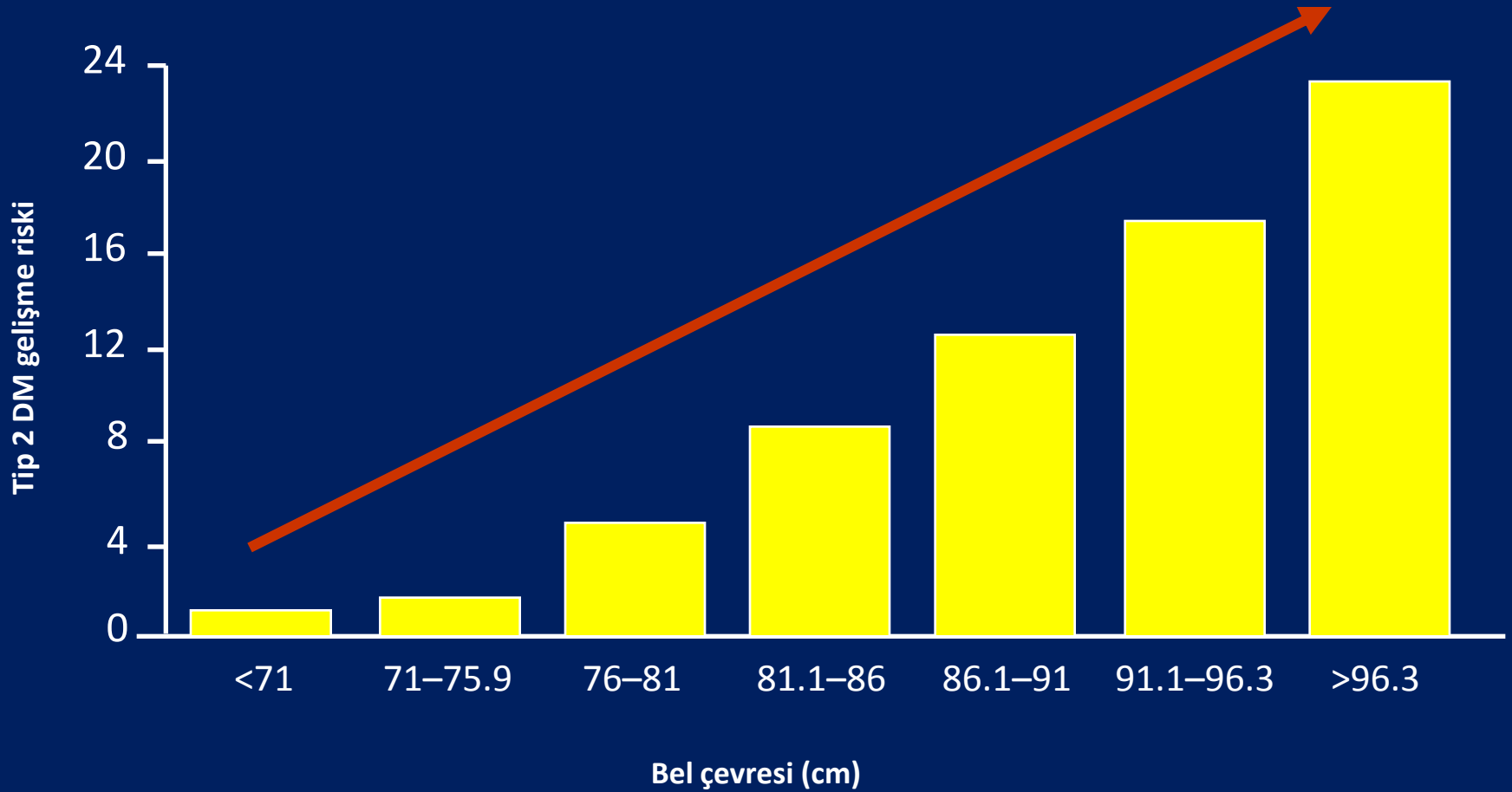


DM GELİŞME RİSKİ

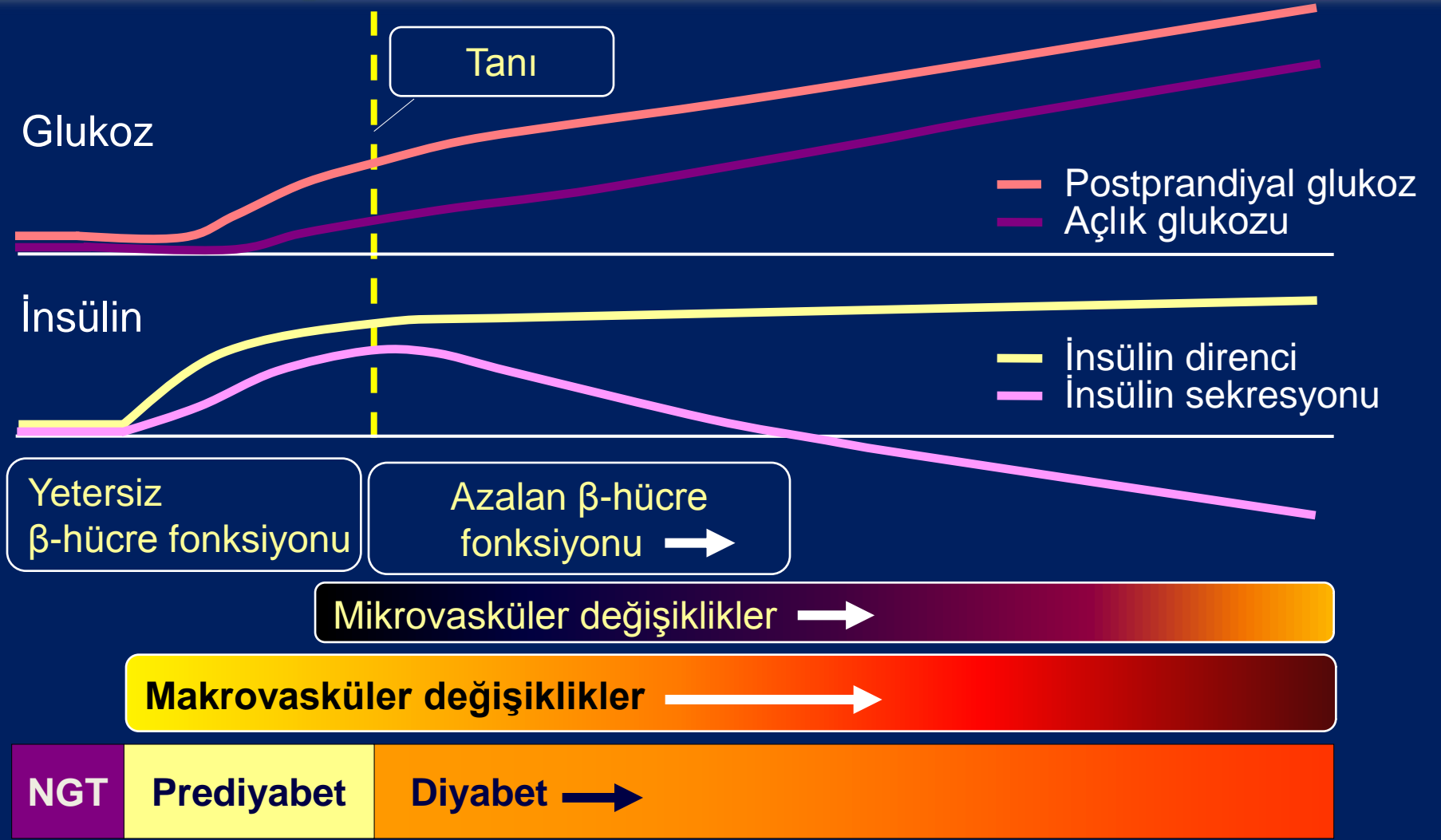
Vücut ağırlığı değişimine göre DM ortaya çıkma riski



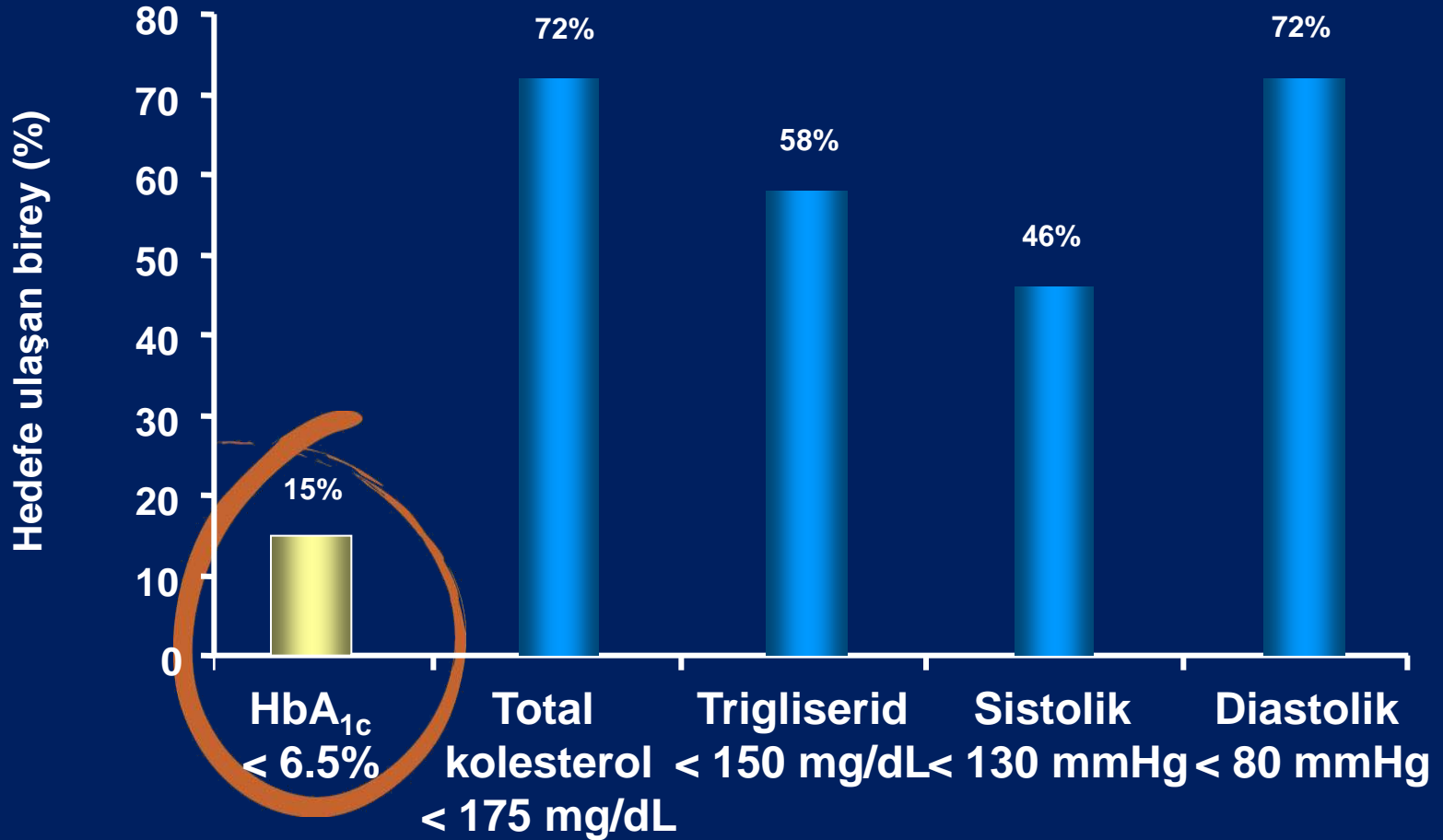
DM GELİŞME RİSKİ



TİP 2 DİABETES MELLİTUS



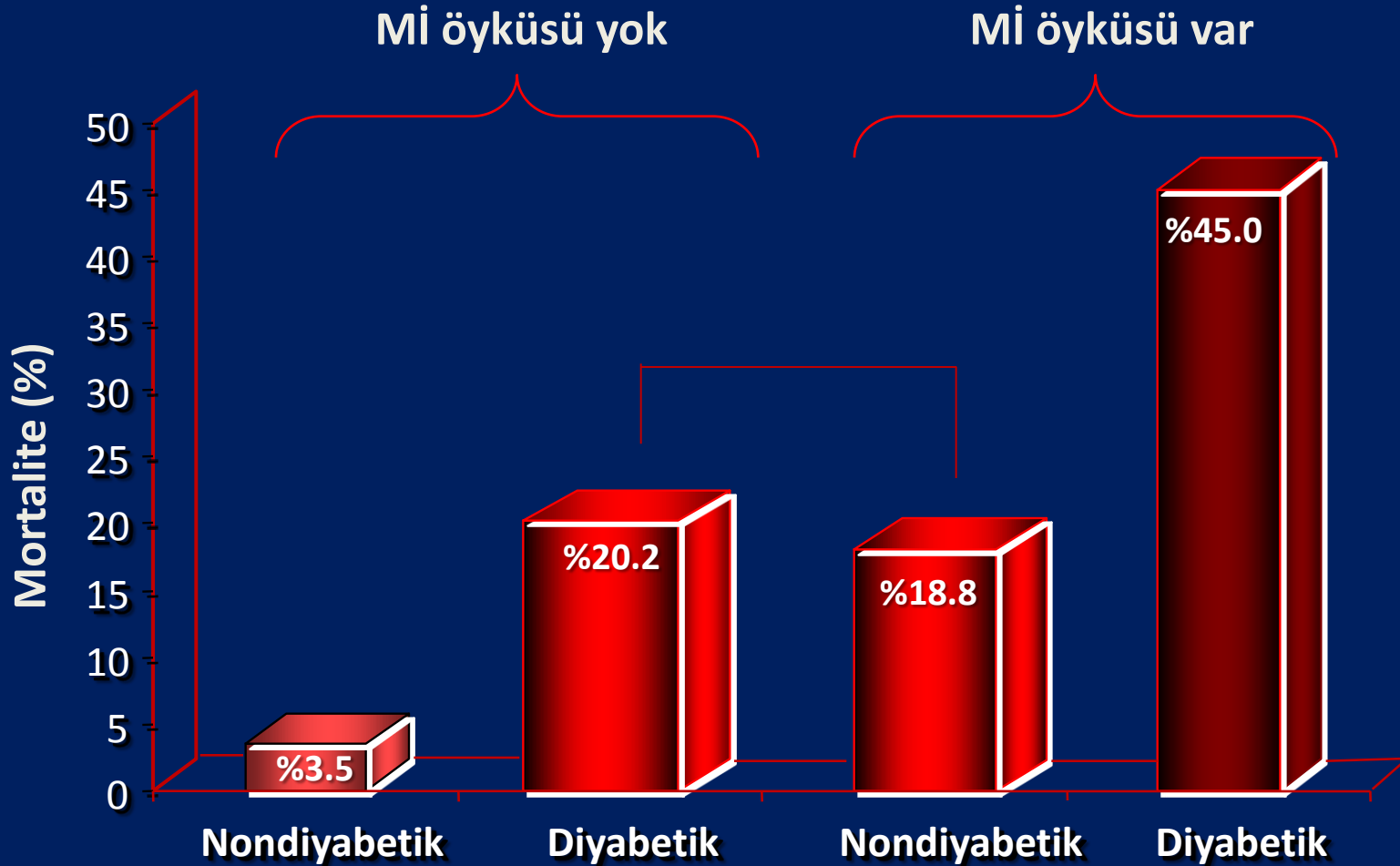
TEDAVİ SONUÇLARI



DIYABET KOMPLİKASYONLARI



MORTALİTE



DIABEZİTE

- From the NIH: Successful diet and exercise therapy is conducted in Vermont for "diabesity".
JAMA 1980;243(6):519-20.
- Astrup A, Finer N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'?
Obes Rev. 2000;1(2):57-9.
- Efrat S. Beta-cell expansion for therapeutic compensation of insulin resistance in type 2 diabetes.
Int J Exp Diabesity Res 2003;4(1):1-5.

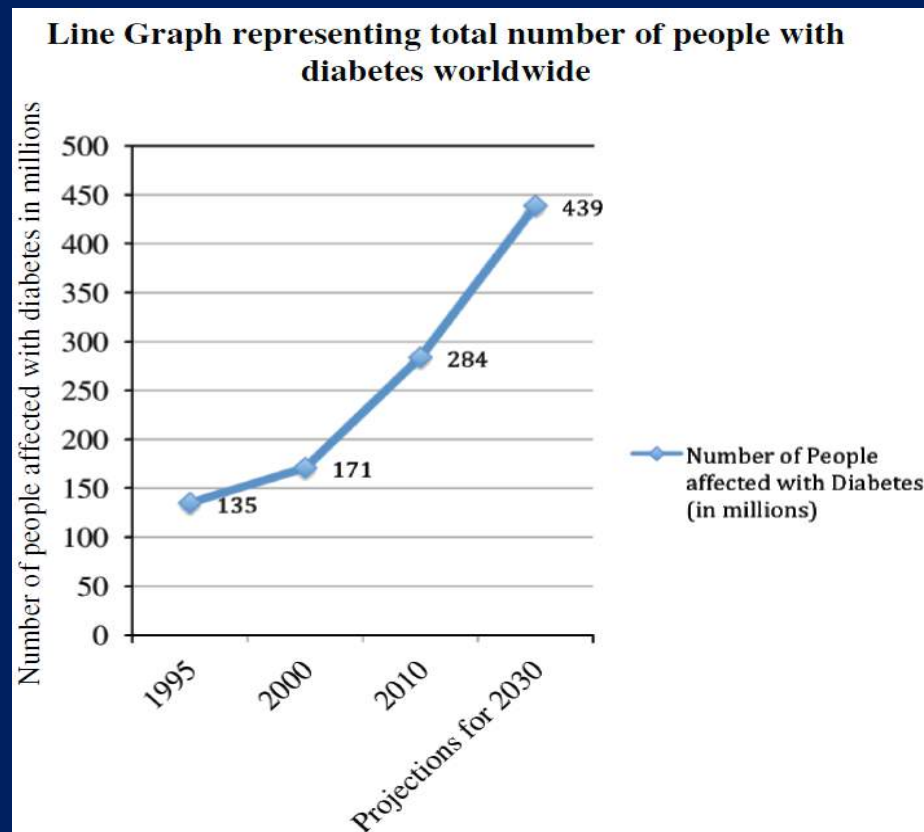
DIABEZITE

Diabetes: an overview of a rising epidemic

Youssef M.K. Farag¹ and Mahmoud R. Gaballa²

¹Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA and ²Department of Internal Medicine, Ain Shams University Hospital, Cairo, Egypt

Nephrol Dial Transplant (2011) 26: 28–35

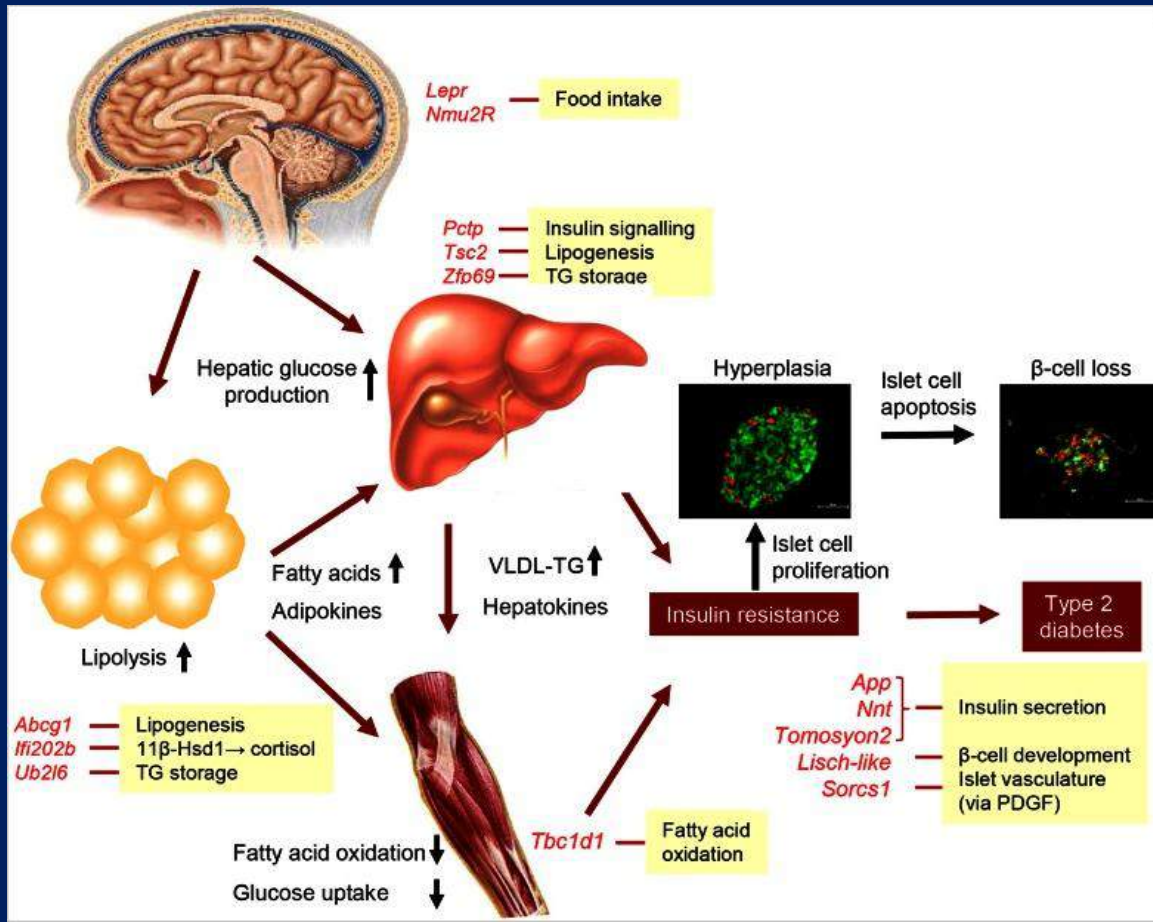


DIABEZİTE

Mamm Genome (2014) 25:401–412
DOI 10.1007/s00335-014-9514-2

The genetic basis of obesity-associated type 2 diabetes (diabesity) in polygenic mouse models

Hans-Georg Joost · Annette Schürmann

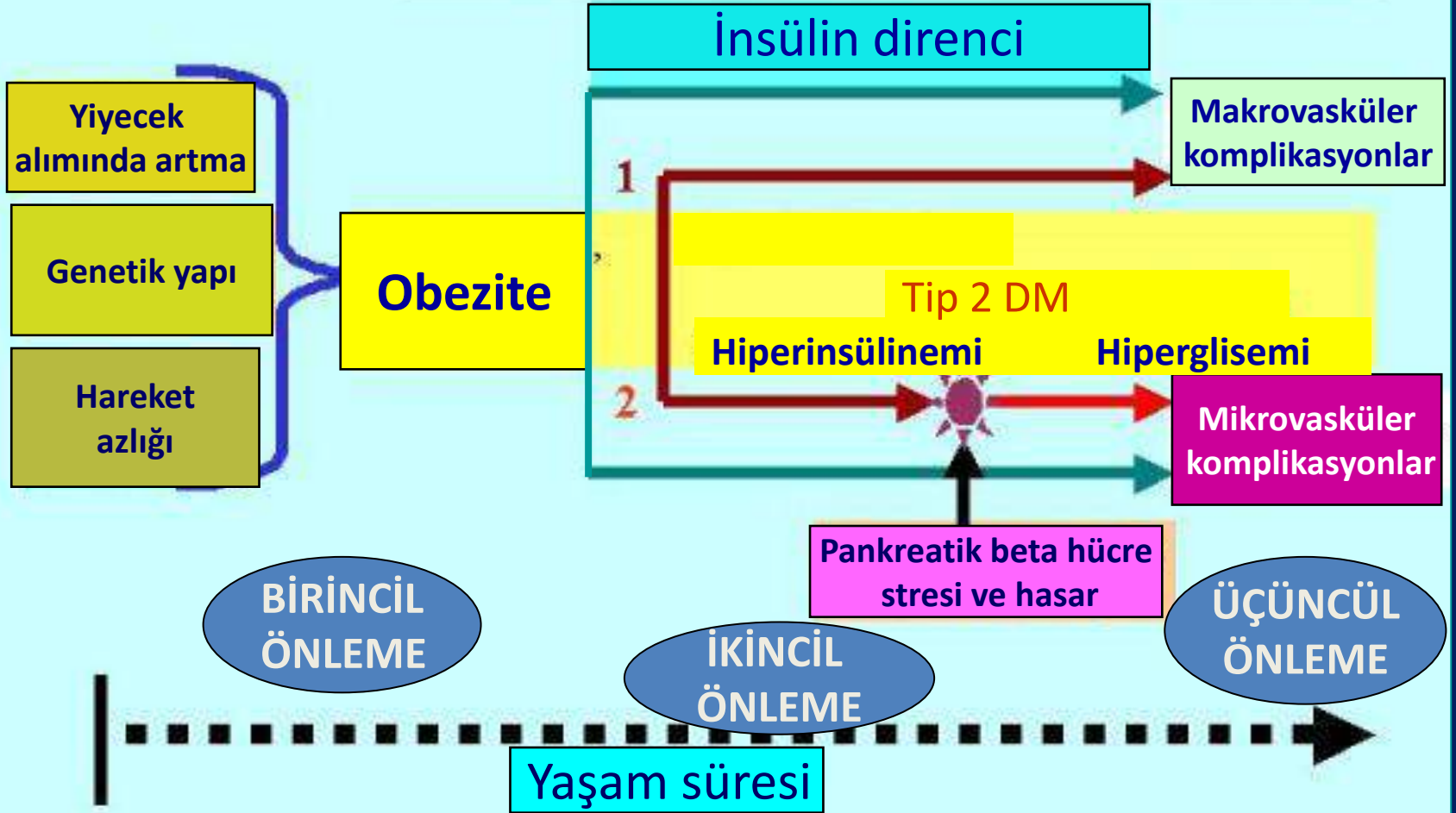


ÖNLEME

Bazı şeyler geri döndürülemez,
ancak önlenabilir!



METABOLİK SENDROM



OLGU - 1

- ❖ G.T. 51 yaş K, Ev Hanımı, Marmaris
- ❖ Yakınma: Ayaklarda ağrı, duyu kaybı, bacaklarda şişlik
- ❖ 13 yıldır diyabetik olan hastanın kan şekeri yüksek seyrediyormuş. Yakınmaları artan hastanın insülin dozları artırılmasına rağmen kan şekeri kontrol altına alınamadığı için bize sevk edilmiş
- ❖ Hipertansiyon ve hiperlipidemi var
- ❖ Babasında DM öyküsü var
- ❖ Sigara ve alkol kullanımı yok

OLGU - 1

- ❖ Fizik muayene:
 - TA: 160/100 mm Hg
 - Obez
 - Pretibial ödem++
 - Boy: 160 cm VA: 89 kg
 - VKİ: 34.7 kg/m²
 - Bel çevresi: 102 cm
- ❖ Vücut yağ oranı: %38.0

OLGU - 1

❖ Kullandığı ilaçlar:

Novorapid 3x16 U Lantus 34 U

Diaformin 1000 mg 2x1 Glucobay 100 mg 3x1

Ator 20 mg 1x1 Hipersar plus 20/12.5 mg 1x1

❖ Laboratuvar:

AKŞ:285 mg/dl TKŞ:356 mg/dl A1C:%9.5

LDL:89 mg/dl Trigliserid:169 mg/dl

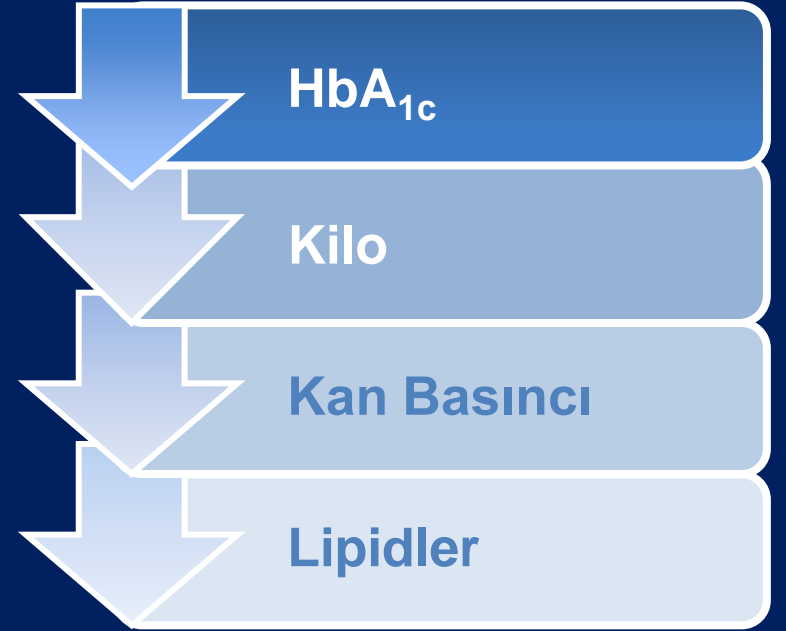
Kreatinin:0.69 mg/dl ALT: 14 U/L

TSH: 2.3 mIU/L

OLGU - 1

❖ Bu hastaya yaklaşımda ilk olarak aşağıdakilerden hangisini yapmayı düşünürsünüz?

- Kan şekeri regülasyonu
- Obeziteye yönelik tedavi
- Kan basıncı ve lipidlerin düzenlenmesi
- Hepsi
- Hiçbiri



CUSHİNG SENDROMU

Tablo 2. Cushing sendromu belirti ve bulguları (%prevalans)

Belirti

Kilo alma %91
Menstruel düzensizlik %84
Hirsutizm %81
Psikiyatrik bozukluk %62
Sırt ağrısı %43
Kas zayıflığı %29
Kırık %19
Saç dökülmesi %13

Bulgu

Obezite %97
Pletora %94
Aydede yüz %88
Hipertansiyon %74
Kolay zedelenme %62
Stria %56
Kas zayıflığı %56
Bilekte ödem %50
Hiperpigmentasyon %4

Diğer bulgular

Diabetes %50
Aşikar %13
Bozulmuş Glukoz Toleransı %37
Osteoporoz %50
Böbrek taşı %15

CUSHİNG SENDROMU

Tablo 1. Cushing sendromu nedenleri

ACTH - bağımlı olanlar

- Hipofiz adenomu (Cushing hastalığı)
- Ektopik ACTH sendromu
- Ektopik CRH sendromu

ACTH-bağımlı olmayanlar

- Adrenal neoplazma (adenom, karsinom)
- Noduler adrenal hiperplazi
 - Primer pigmente nodüler hastalık
 - Massif makronodüler adrenonodüler hiperplazi
 - Besinlere bağılı (GİP-aracılı)

Psödo-Cushing sendromu

- Obezite
- Depresyon
- Alkolizm

OLGU - 1

- ❖ 1 mg deksametazon testi:
Kortizol: 5.2 $\mu\text{g}/\text{dl}$
- ❖ Gece kortizol düzeyi: 8.5 $\mu\text{g}/\text{dl}$
- ❖ 24 saatlik idrar kortizol düzeyi: 320 $\mu\text{g}/\text{gün}$
- ❖ 2 mg deksametazon testi:
Kortizol: 6.4 $\mu\text{g}/\text{dl}$
- ❖ ACTH: 4 pg/ml
- ❖ Abdomen BT: Sağ sürrenalde 33x21 mm adenom
- Tedavi: Sağ sürrenalektomi

OLGU - 1

Kemik dansite ölçümü			
L1	- 3,6	Neck	- 2,6
L2	- 3,9	Troch	- 2,2
L3	- 3,9	Inter	- 1,5
L4	- 3,5	Wards	- 3,0
L1-L4	- 3,8	Total	- 1,9

OLGU - 1

- ❖ Yakınma: yok
- ❖ FM: TA:110/70 mm Hg
- ❖ Boy:160 cm VA:66 kg VKİ:25.7 kg/m²
- ❖ A1C: %6.1
- ❖ Sık hipoglisemi tanınıyor

Sabah açlık	S abah tokluk	Öğle tokluk	Akşam tokluk
81	122	115	149
78	92	153	137

OLGU - 1

❖ Kullandığı ilaçlar:

Genkort 10 mg 2x1 Lantus 18 U

Diaformin 1000 mg 2x1 Novonorm 2 mg 3x1

Hipersar plus 20/12.5 mg 1x1 Ator 20 mg 1x1

Fosavance Haftada bir



OLGU - 2

- ❖ M.D. 56 Yaş E, Restoran işletmecisi, Kuşadası
- ❖ Yakınma: Halsizlik, baş ağrısı, kilo alma
- ❖ Öykü: 2 aydır stresli bir dönem geçirdiğini ifade eden hasta bu dönemde sağlıksız beslenmiş, tedavilerini aksatmış ve daha önce de olan yakınmaları artmış. 2 ayda 12 kg almış.
- ❖ 10 yıldır DM, hipertansiyon ve hiperlipidemi tanıları ile izleniyormuş.
- ❖ Baba ve kardeşlerinde DM öyküsü var
- ❖ Sigara: 1p/gün Alkol: Haftada 3-4 kez

OLGU - 2

- ❖ Fizik muayene:
 - TA: 130/85 mm Hg.
 - Tiroid sağ lobunda 3 cm nodül ele geliyor
 - Obez
 - Boy: 170 cm VA: 135 kg
 - VKİ: 46.7 kg/m²
 - BÇ: 136 cm
- ❖ Vücut yağ oranı: %42.4

OLGU - 2

❖ Kullandığı ilaçlar:

Humalog mix 25 48+44 U Glifor 1000 mg 2x1

Crestor 10 mg 1x1 Coveram 10/5 mg 1x1

Coraspin 100 mg 1x1

❖ Laboratuvar:

AKŞ:159 mg/dl TKŞ:251 mg/dl A1C:%7.9

LDL:85 mg/dl Trigliserid:112 mg/dl

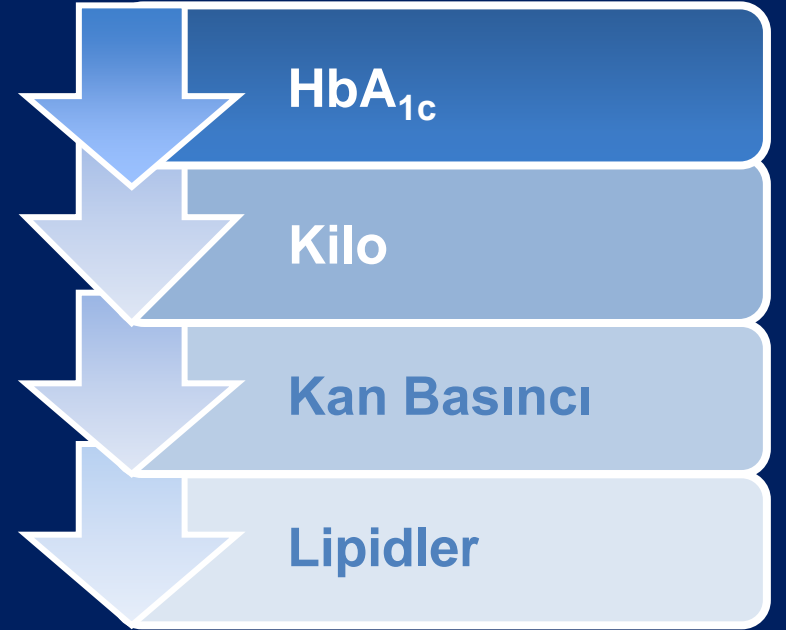
Kreatinin:1.0 mg/dl ALT: 34 U/L TSH: 1.6 mIU/L

1 mg deksametazon testi: Kortizol: 1.1 µg/dl

OLGU - 2

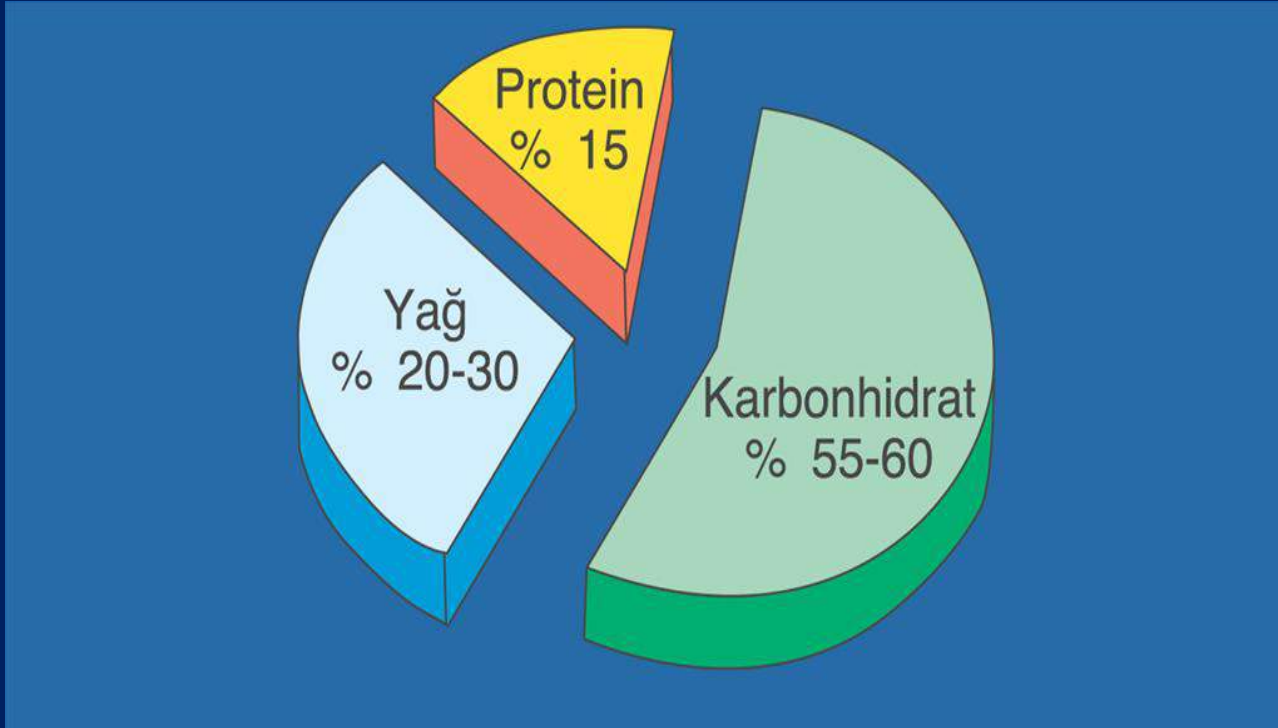
❖ Bu hastaya yaklaşımda ilk olarak aşağıdakilerden hangisini yapmayı düşünürsünüz?

- Kan şekeri regülasyonu
- Obeziteye yönelik tedavi
- Kan basıncı ve lipidlerin düzenlenmesi
- Hepsi
- Hiçbiri



SAĞLIKLI BESLENME

Dengeli Diyette Enerji Kaynakları (Günlük Toplam)



Diyetin toplam kalorisi günlük harcanan kaloriden 500-1000 kcal eksik olmalıdır.

FİZİK AKTİVİTE

Televizyon veya bilgisayar başında geçen zaman sınırlanmalı !



HAFTADA EN AZ 2 KEZ



Güçlendirme ve fleksibilite egzersizleri

Aerobik egzersiz

- Yürüyüş
- Bisiklet
- Koşu



HAFTADA EN AZ
3 KEZ



Eğlenceli takım sporu



HERGÜN
Olabildiğince aktif
olunmalı !



YAŞAM TARZI DEĞİŞİKLİĞİ

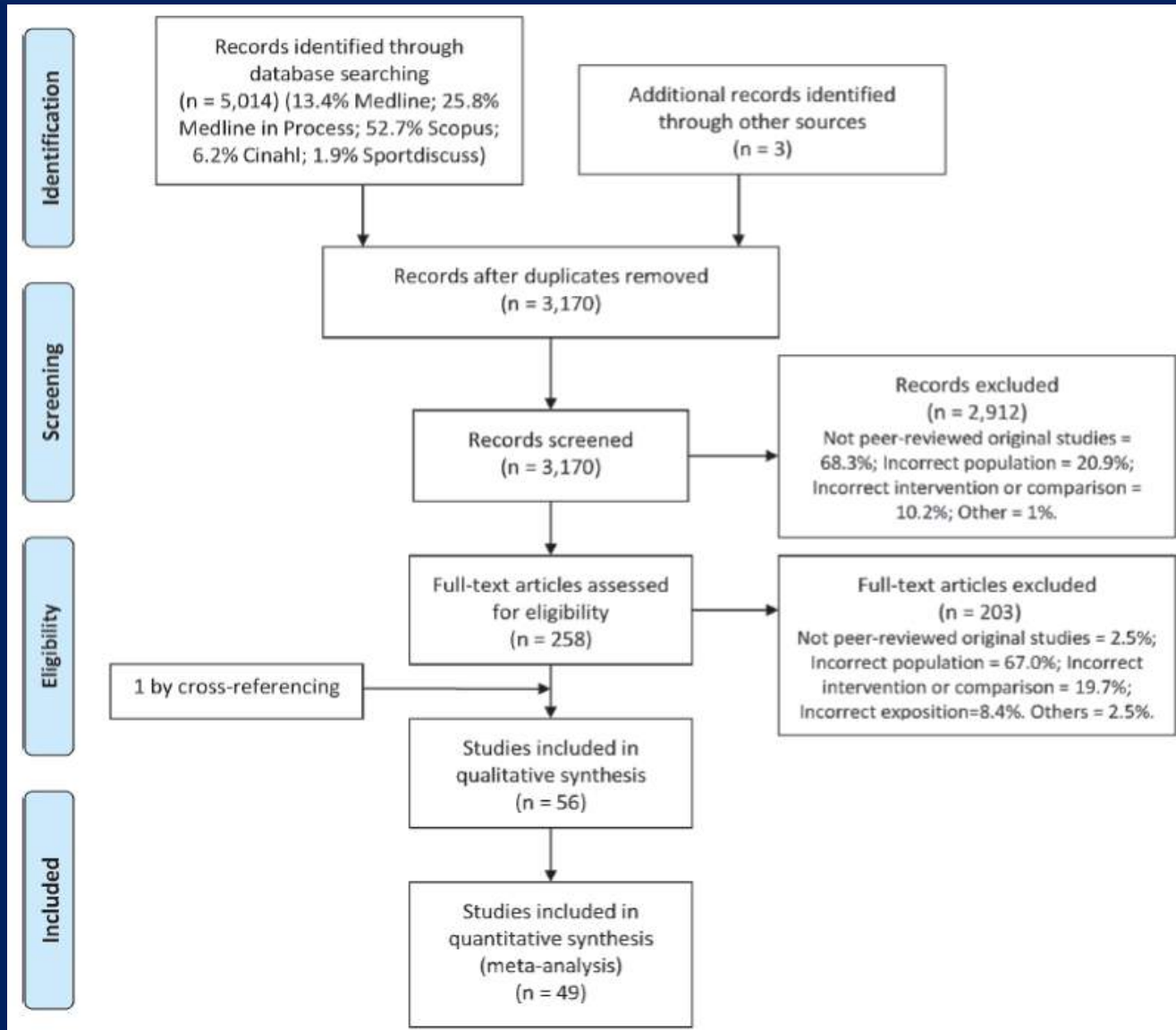
RESEARCH ARTICLE

Effects of Lifestyle Interventions That Include a Physical Activity Component in Class II and III Obese Individuals: A Systematic Review and Meta-Analysis

Aurélie Baillot^{1,2}, Ahmed J. Romain³, Katherine Boisvert-Vigneault^{4,5}, Mélisa Audet^{4,5}, Jean Patrice Baillargeon^{1,2}, Isabelle J. Dionne^{4,5}, Louis Valiquette⁶, Claire Nour Abou Chakra⁶, Antoine Avignon^{3,7}, Marie-France Langlois^{1,2*}

1 Research Center of the Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Quebec, Canada, **2** Department of Medicine, Division of Endocrinology, Université de Sherbrooke, Sherbrooke, Quebec, Canada, **3** Unit of Nutrition and Diabetes, Department of Endocrinology-Nutrition and Diabetes, University Hospital of Montpellier, Montpellier, France, **4** Research Centre on Aging, Health and Social Services Centre, Institute of Geriatrics, Université de Sherbrooke, Sherbrooke, Quebec, Canada, **5** Faculty of Physical Education and Sports, Université de Sherbrooke, Sherbrooke, Quebec, Canada, **6** Department of Microbiology and Infectious Diseases, Université de Sherbrooke, Quebec, Canada, **7** INSERM U1046, Physiology and experimental medicine of heart and muscles, University of Montpellier, Montpellier, France

YAŞAM TARZI DEĞİŞİKLİĞİ



YAŞAM TARZI DEĞİŞİKLİĞİ

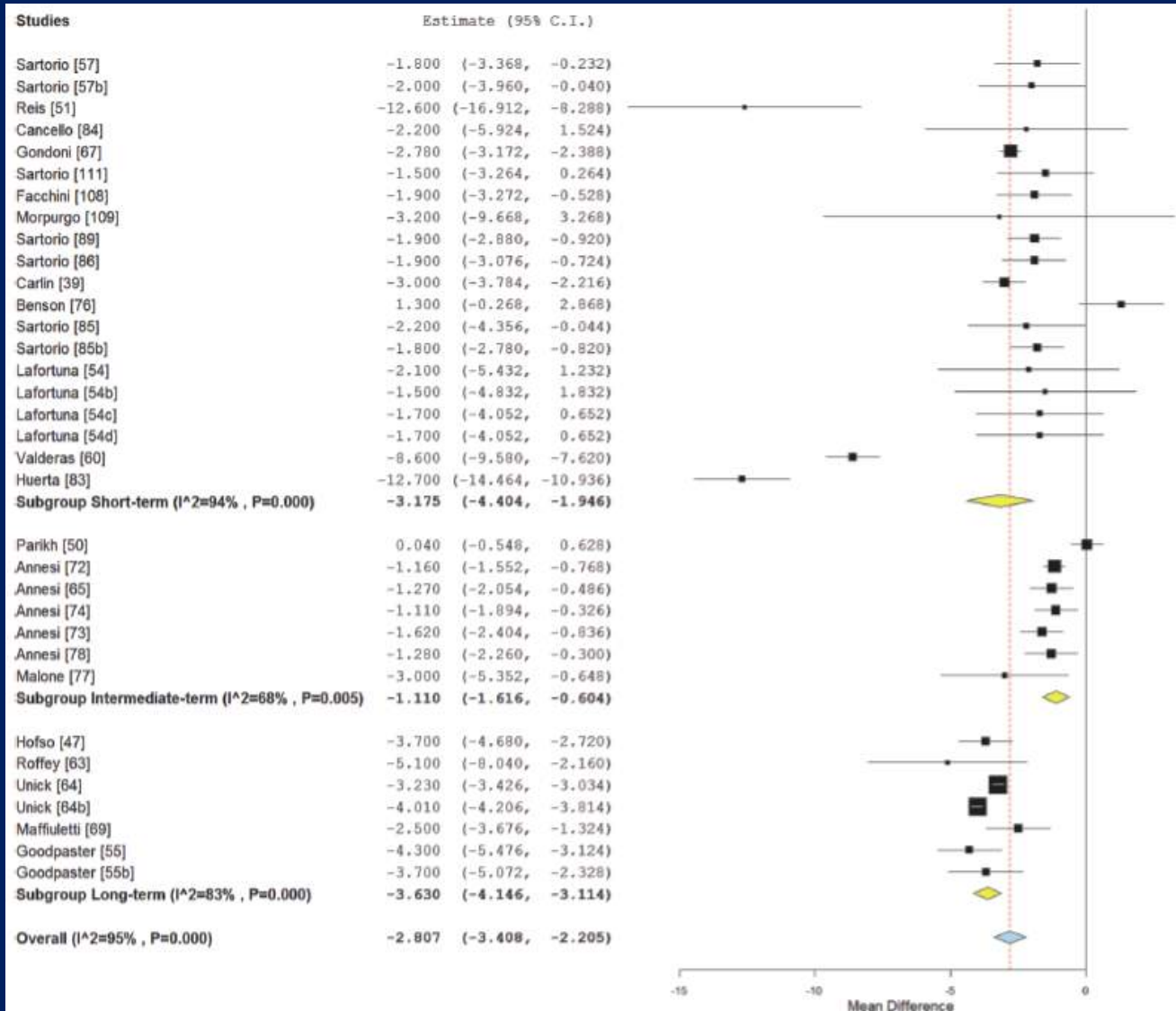


Fig 2. Forest plot of mean body mass index changes according to the intervention length in class II and III obese individuals.

YAŞAM TARZI DEĞİŞİKLİĞİ

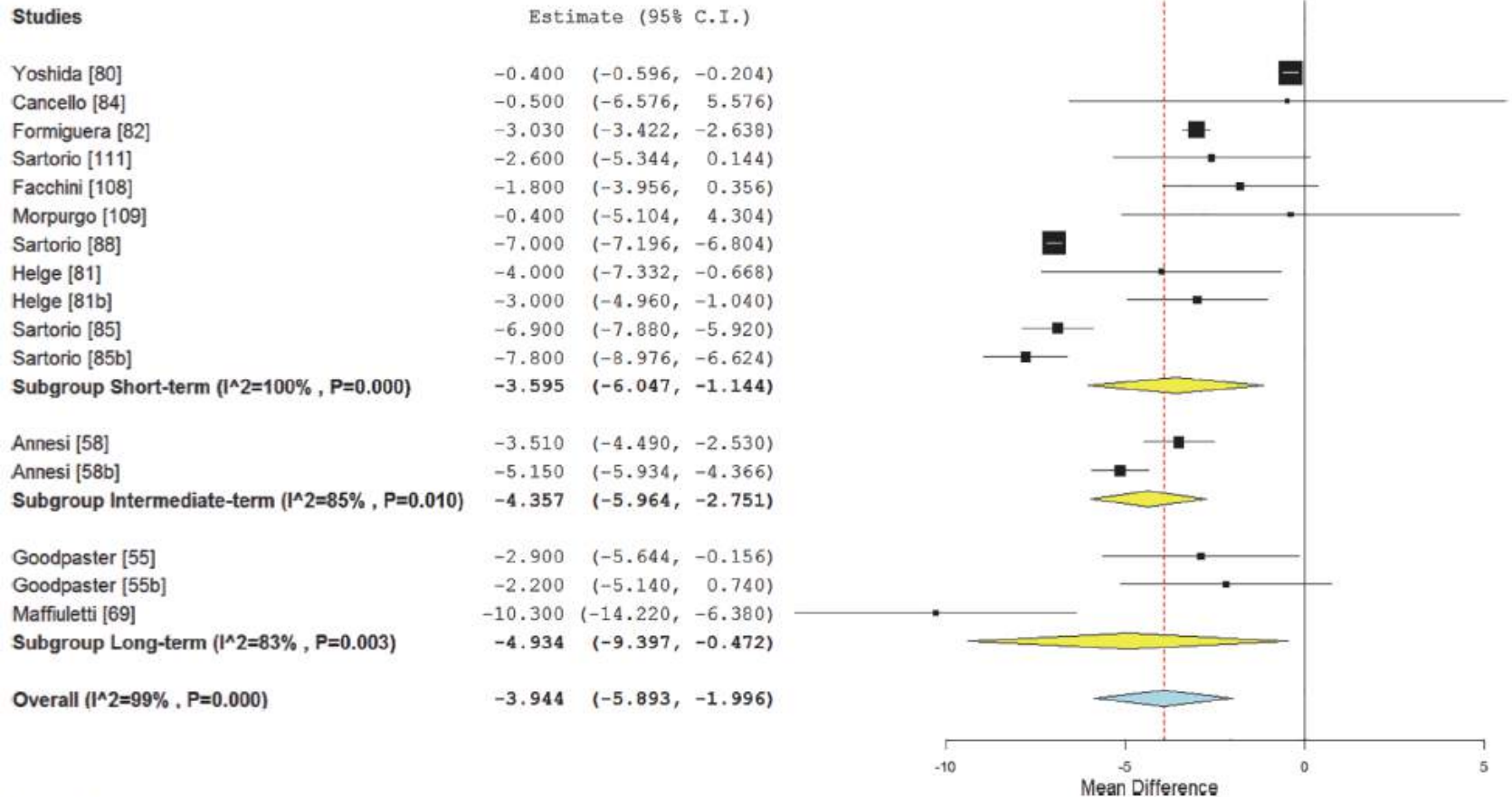


Fig 3. Forest plot of mean fat mass changes according to the intervention length in class II and III obese individuals.

YAŞAM TARZI DEĞİŞİKLİĞİ

- ❖ Çalışma süreleri: 3 hafta-61.5 ay
- ❖ Kilo kaybı sonuçları:
 - Kısa süreli çalışmalar:
-7.20 kg, 95% CI [-8.88; -5.53], $p < 0.01$
 - Orta süreli çalışmalar:
-7.96 kg, 95% CI [-10.82; -5.09], $p < 0.01$
 - Uzun süreli çalışmalar:
-11.33 kg, 95% CI [-13.07; -9.59], $p < 0.01$

YAŞAM TARZI DEĞİŞİKLİĞİ

- ❖ Bel çevresi sonuçları:
 - Kısa süreli çalışmalar:
-4.78 cm; 95% CI [-8.01; -1.55], $p = 0.004$
 - Orta süreli çalışmalar:
-6.26 cm; 95% CI [-11.82; -0.70], $p < 0.01$
 - Uzun süreli çalışmalar:
-7.52 cm; 95% CI [-9.42; -5.61], $p < 0.01$

YAŞAM TARZI DEĞİŞİKLİĞİ

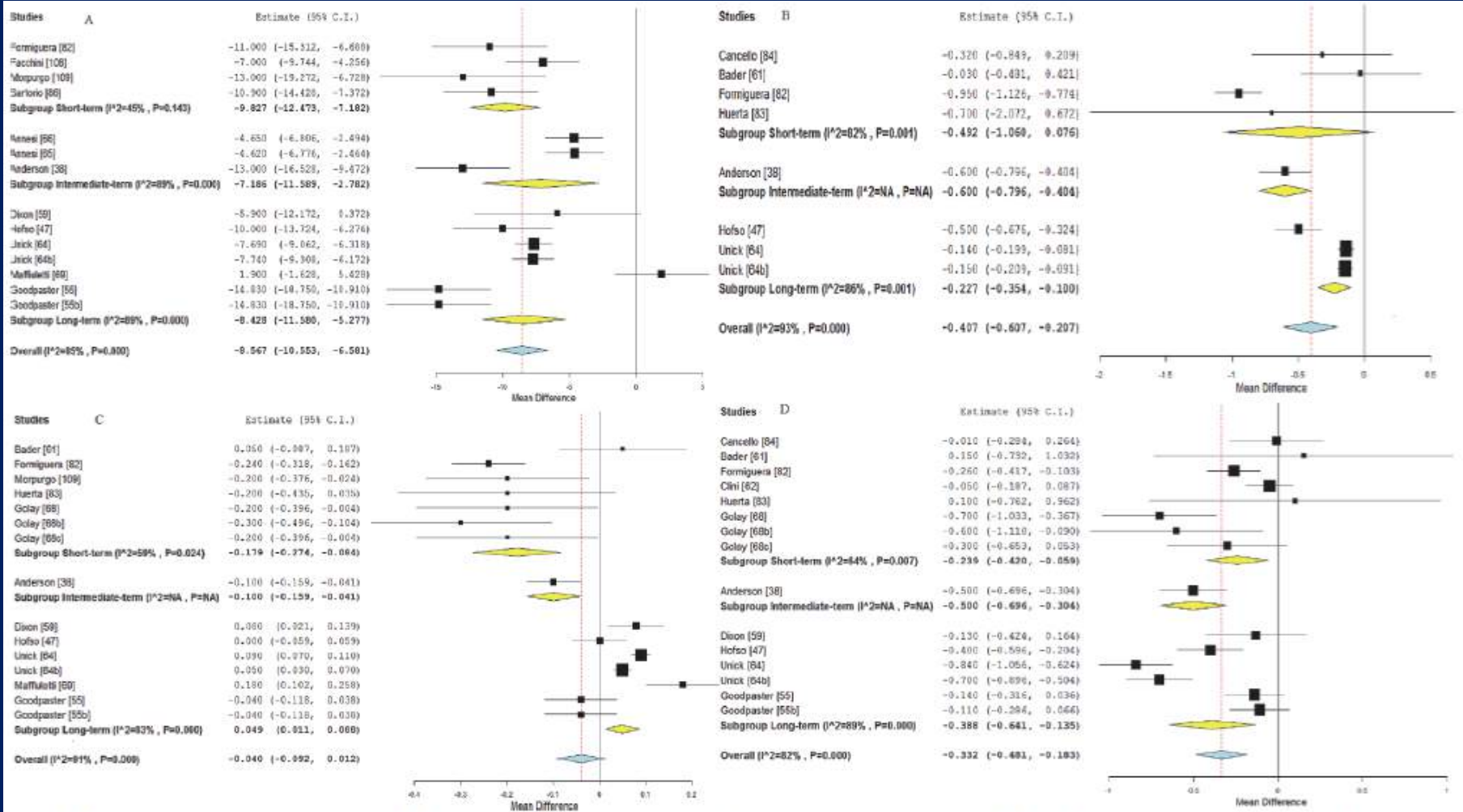
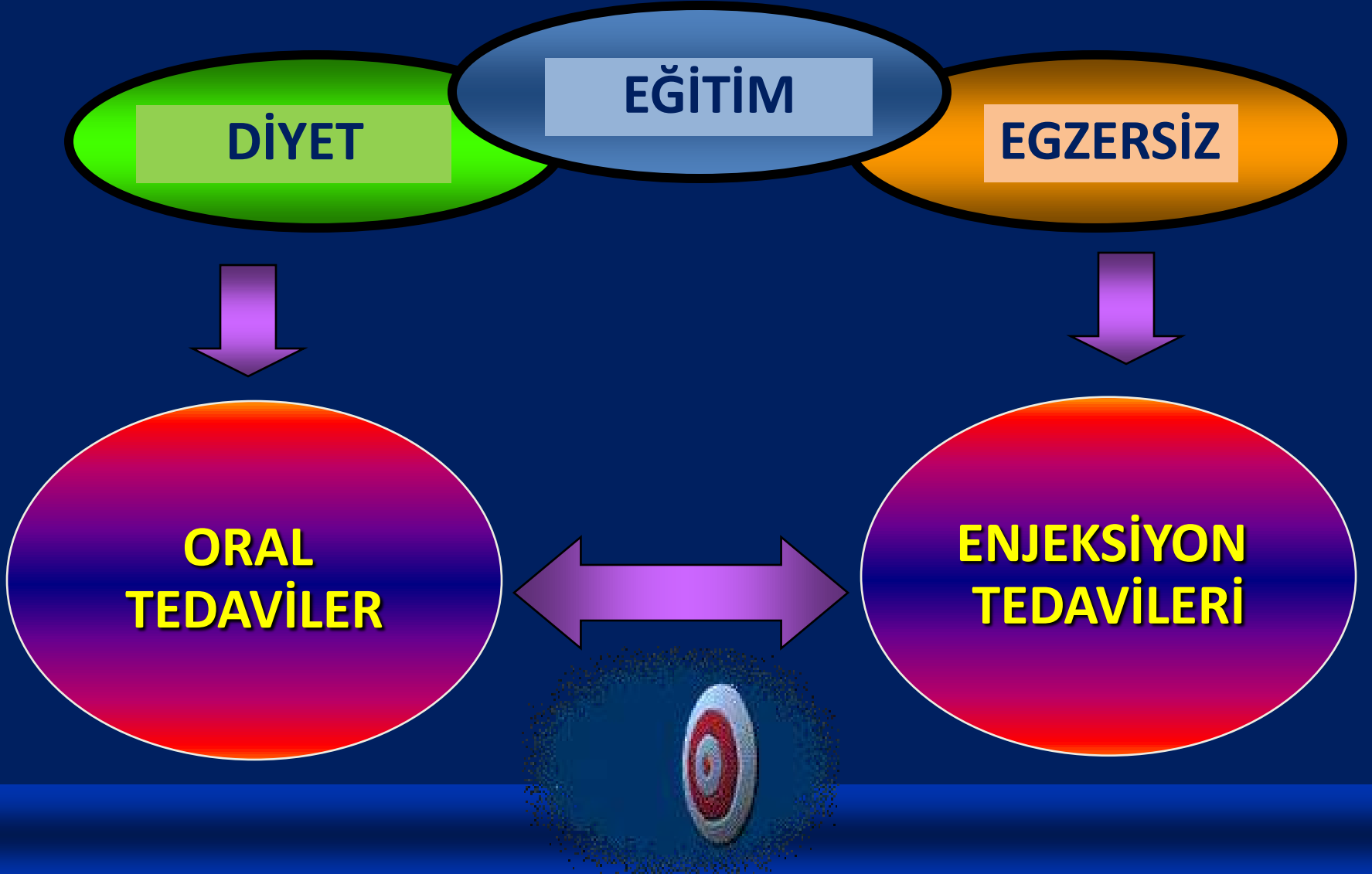


Fig 4. Forest plot of mean systolic blood pressure, LDL cholesterol, HDL cholesterol and triglycerides differences according to the intervention length in class II and III obese individuals. Notes: A (upper corner left): systolic blood pressure; B (upper corner right): LDL cholesterol; C: HDL cholesterol; D: Triglycerides. Letters inserted with the references (b, c, d) represent the different arms of intervention from the same study. A description of each intervention is given in [Table 1](#)



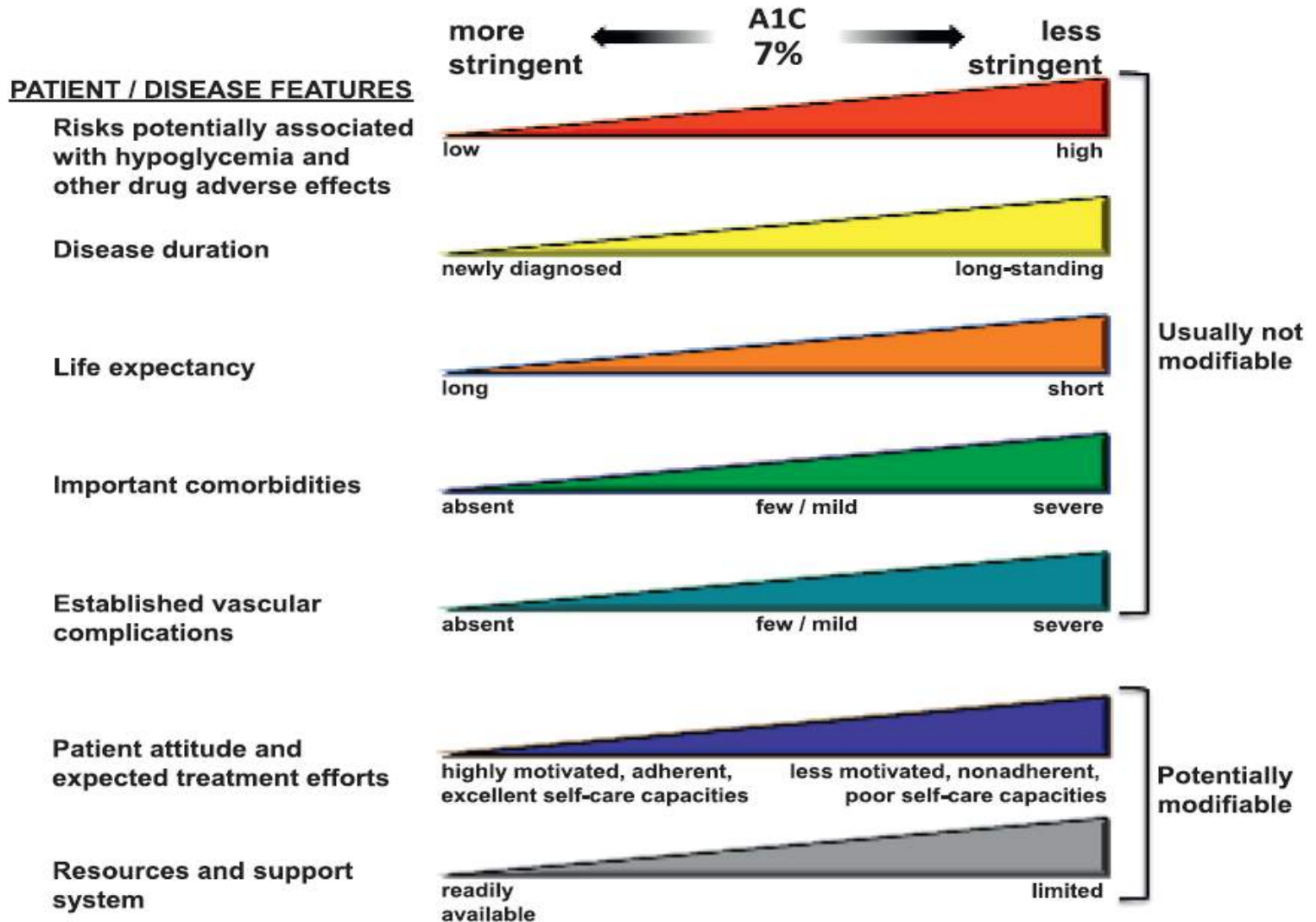
DİYABET TEDAVİSİ



TEDAVİ HEDEFLERİ

	ADA/EASD	TEMĐ
A1C (%)	<7.0	<6.5
AKŞ (mg/dl)	80-130	70-120
TKŞ (mg/dl)	<180	<140

Approach to the management of hyperglycemia



Mono-therapy
 Efficacy*
 Hypo risk
 Weight
 Side effects
 Costs*

Dual therapy†
 Efficacy*
 Hypo risk
 Weight
 Side effects
 Costs*

Triple therapy

Combination injectable therapy‡

Healthy eating, weight control, increased physical activity, and diabetes education

Metformin

high
 low risk
 neutral / loss
 GI / lactic acidosis
 low

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
high efficacy moderate risk weight gain hypoglycemia low costs	high efficacy low risk weight gain edema, HF, fxs low costs	intermediate efficacy low risk neutral weight rare side effects high costs	intermediate efficacy low risk weight loss GI, dehydration high costs	high efficacy low risk weight loss GI side effects high costs	highest efficacy high risk weight gain hypoglycemia variable costs

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
+ TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin^s	+ SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin^s	+ SU or TZD or SGLT2-i or Insulin^s	+ SU or TZD or DPP-4-i or Insulin^s	+ SU or TZD or Insulin^s	+ TZD or DPP-4-i or SGLT2-i or GLP-1-RA

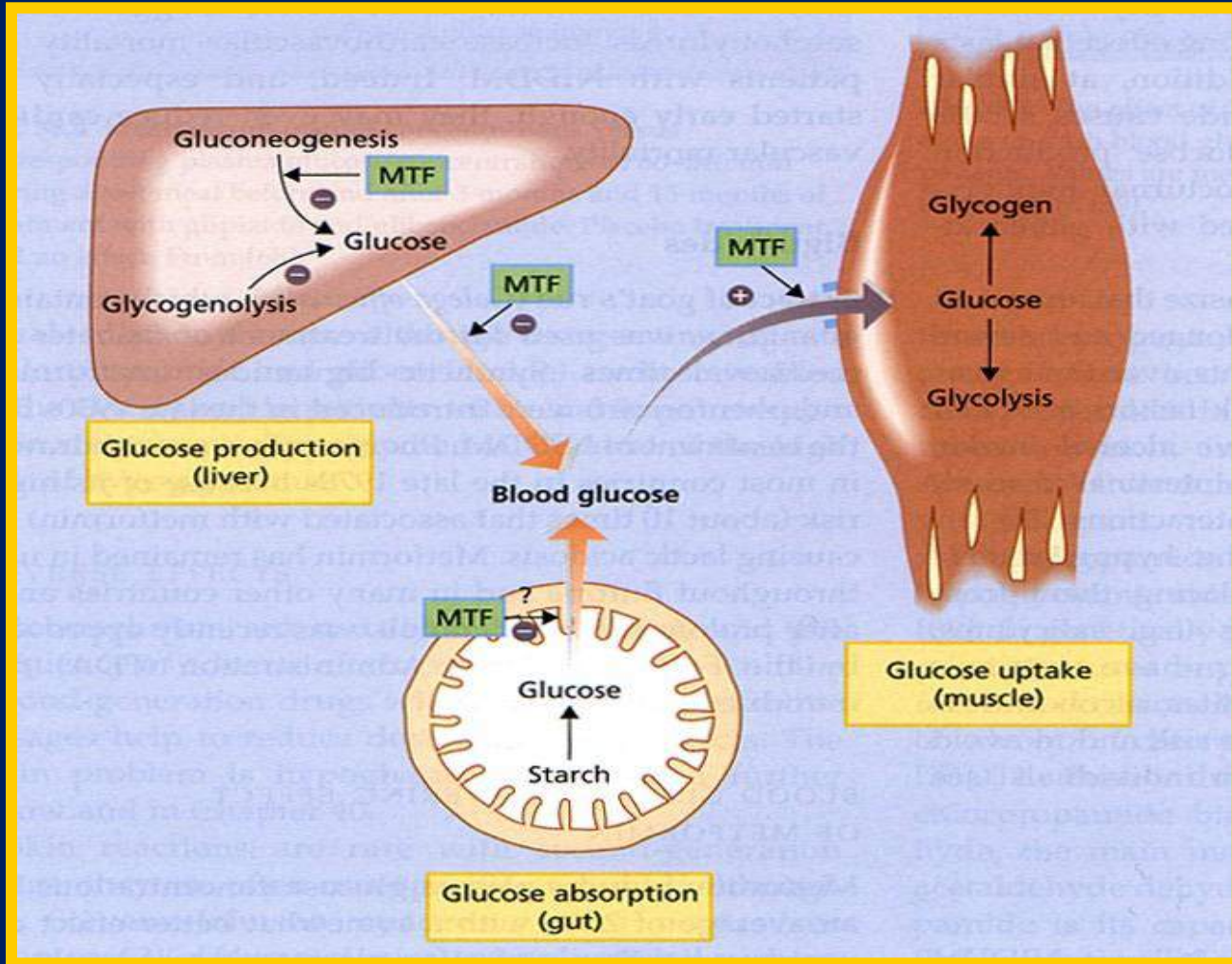
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

METFORMİN

- *Galega officinalis* (Fransız leylağı/Sedef otu) bitkisinden elde edilmiştir.
- Bu bitkinin içerdiği guanidin maddesi, insülin direncini azaltarak kan glukozunu dengeler.

METFORMIN



METFORMİN

➤ Yan etkiler:

- Gastrointestinal semptomlar
 - Bulantı, kusma, karın ağrısı
 - Abdominal dolgunluk
 - Kramplar
 - Diyare
 - Ağızda metalik tat
- Vitamin B₁₂ eksikliği
- Laktik asidoz (<1/100.000 hasta)*

METFORMIN

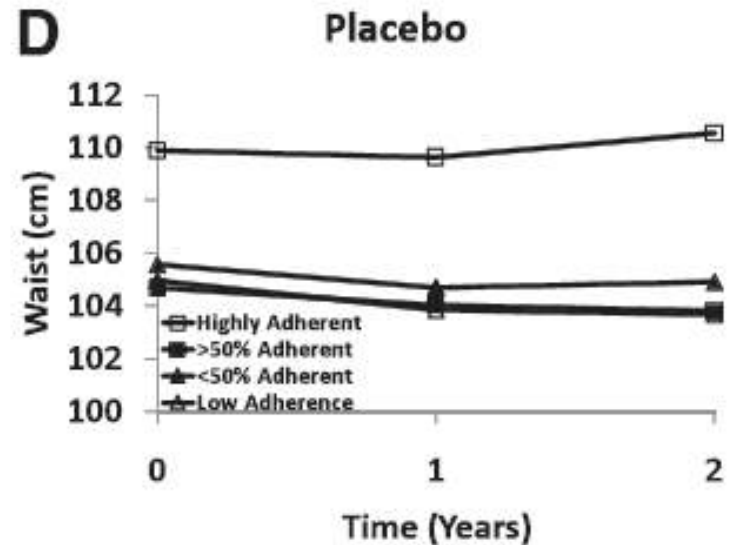
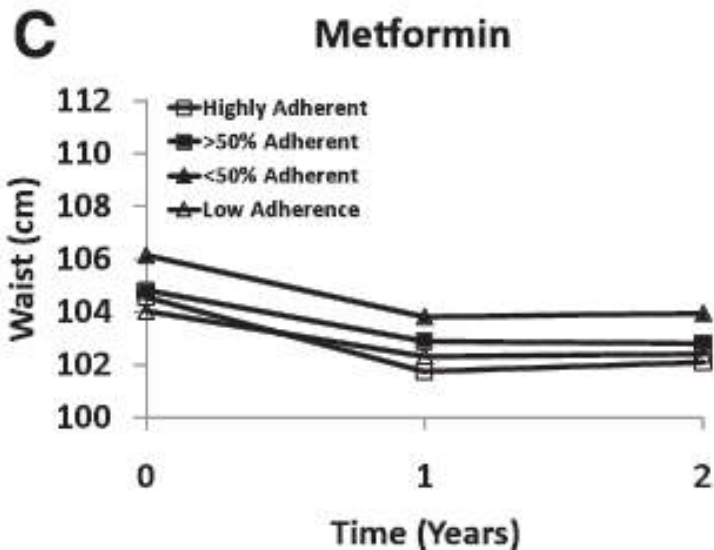
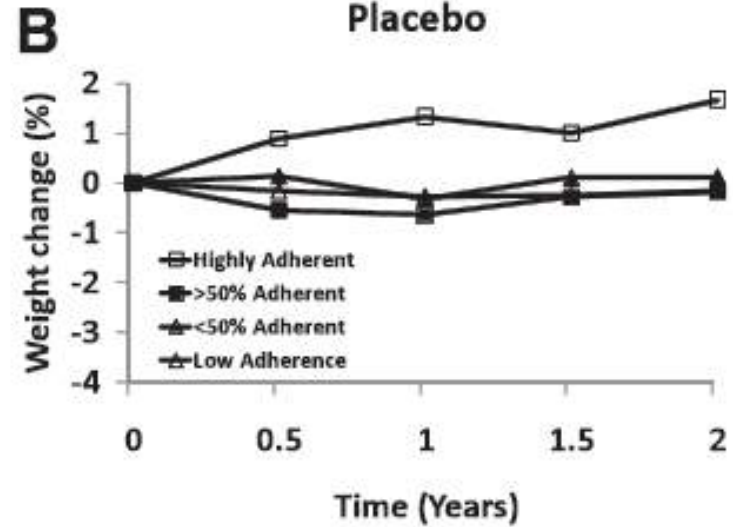
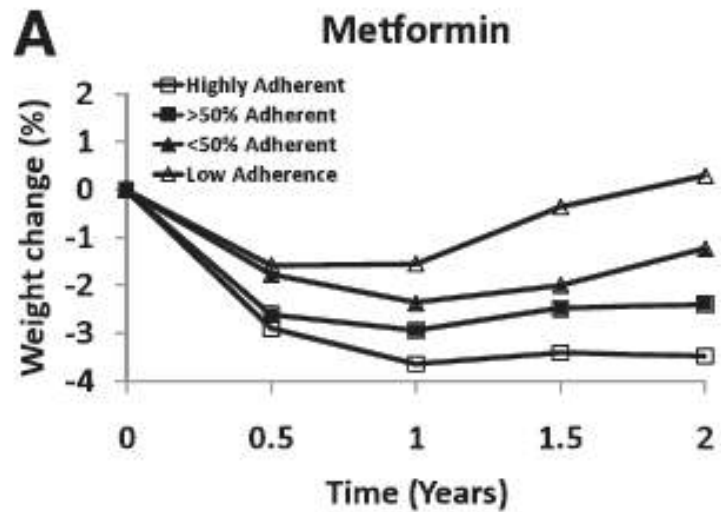
ORIGINAL ARTICLE

Long-Term Safety, Tolerability, and Weight Loss Associated With Metformin in the Diabetes Prevention Program Outcomes Study

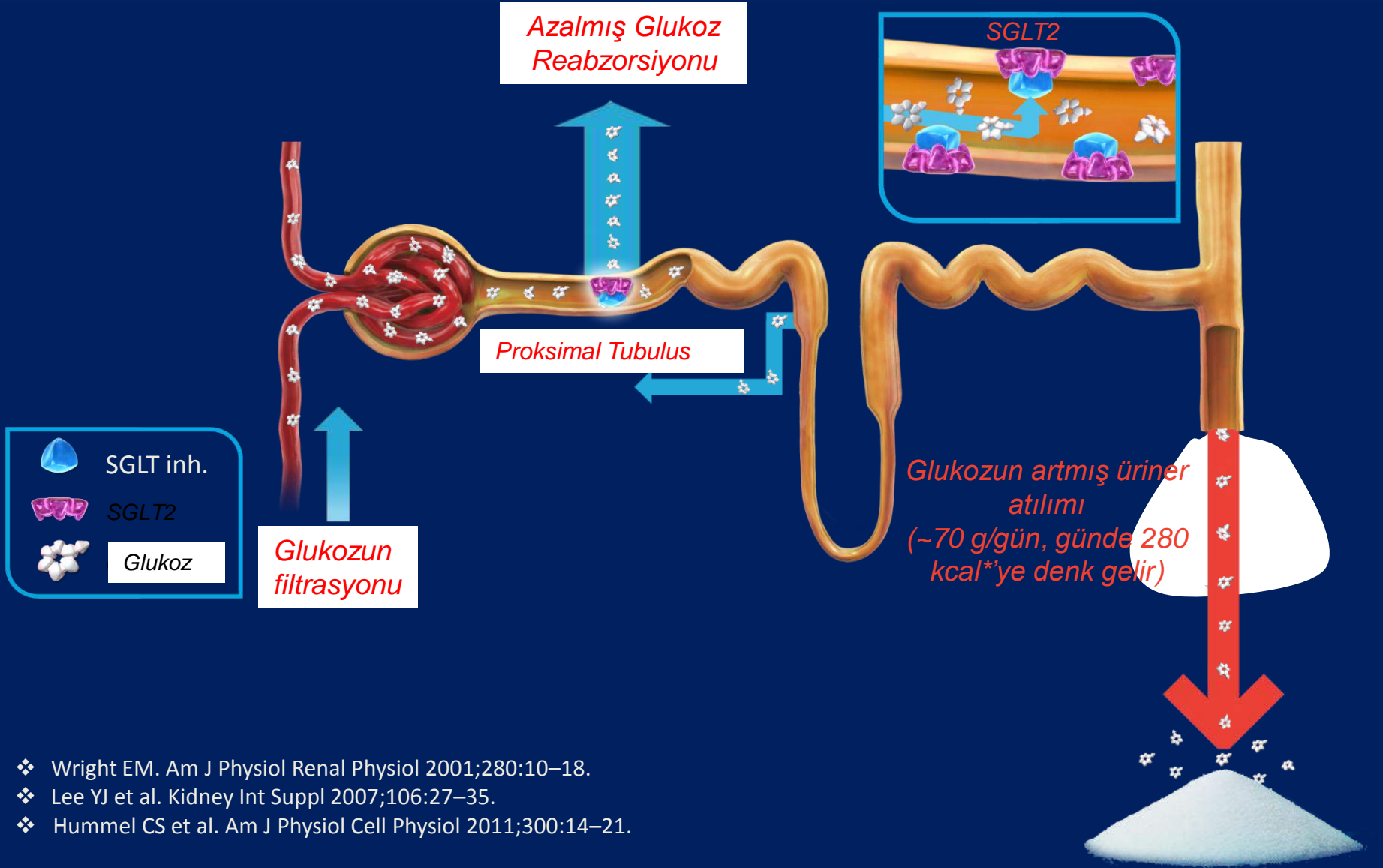
THE DIABETES PREVENTION PROGRAM
RESEARCH GROUP*

Diabetes Care 35:731–737, 2012

METFORMIN

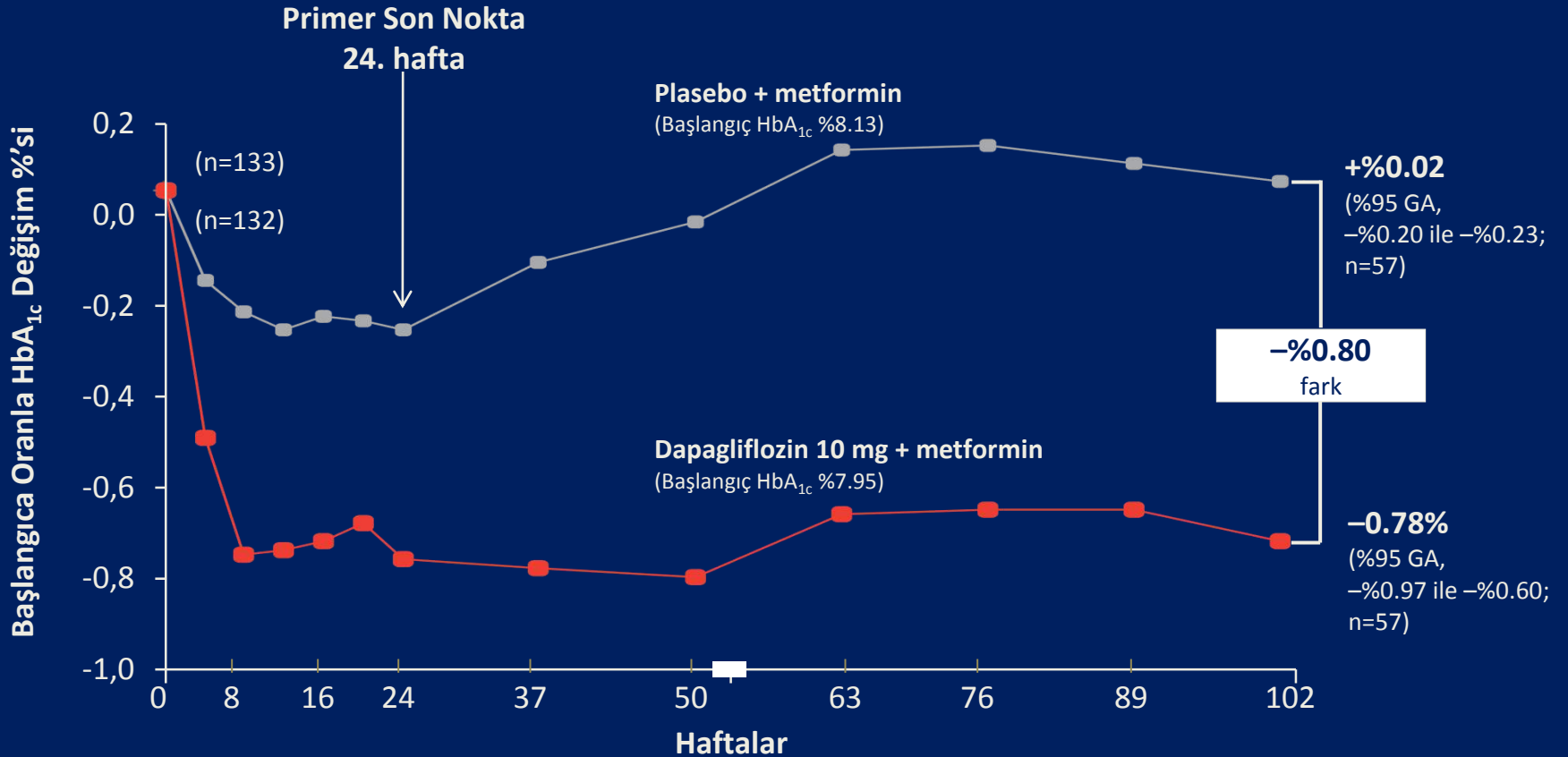


SGLT2 İNHİBİTÖRLERİ

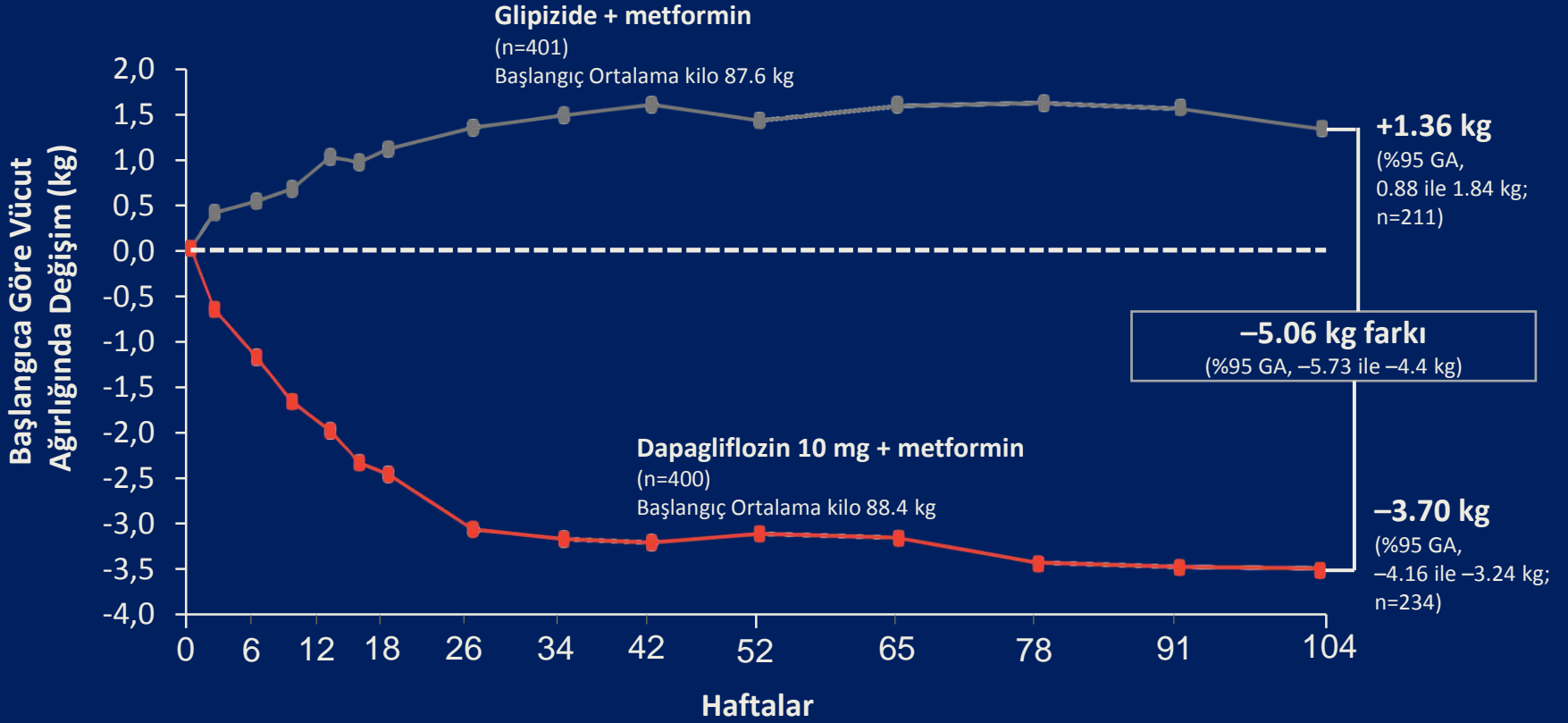


- ❖ Wright EM. Am J Physiol Renal Physiol 2001;280:10–18.
- ❖ Lee YJ et al. Kidney Int Suppl 2007;106:27–35.
- ❖ Hummel CS et al. Am J Physiol Cell Physiol 2011;300:14–21.

SGLT2 İNHİBİTÖRLERİ



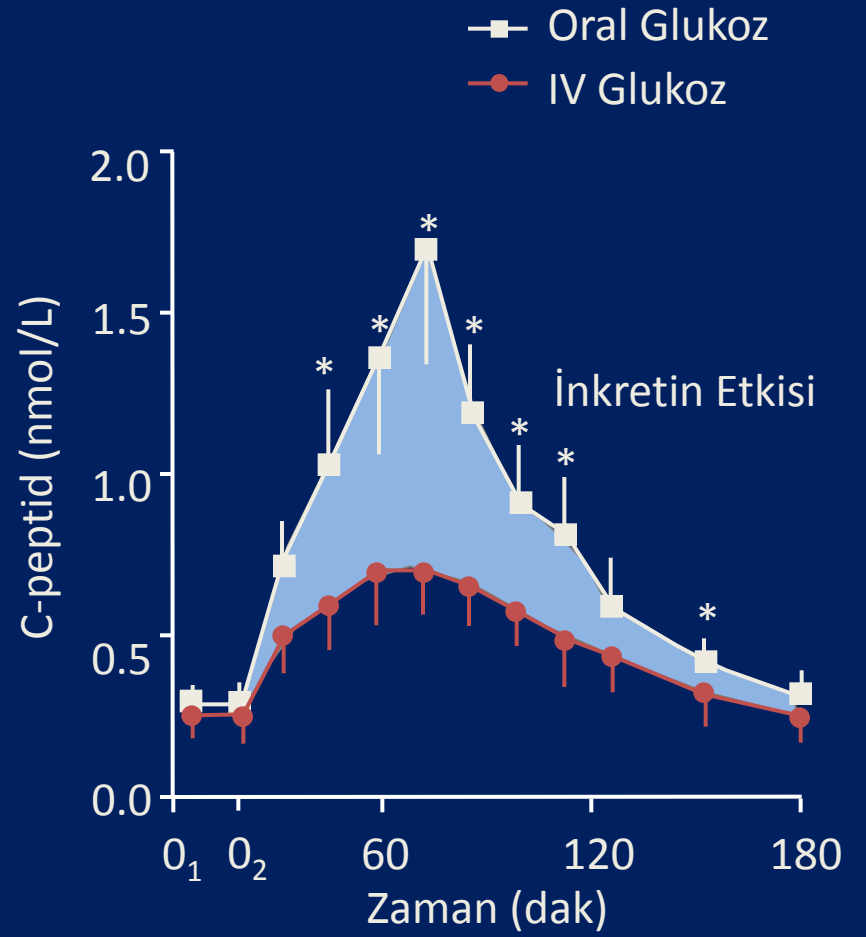
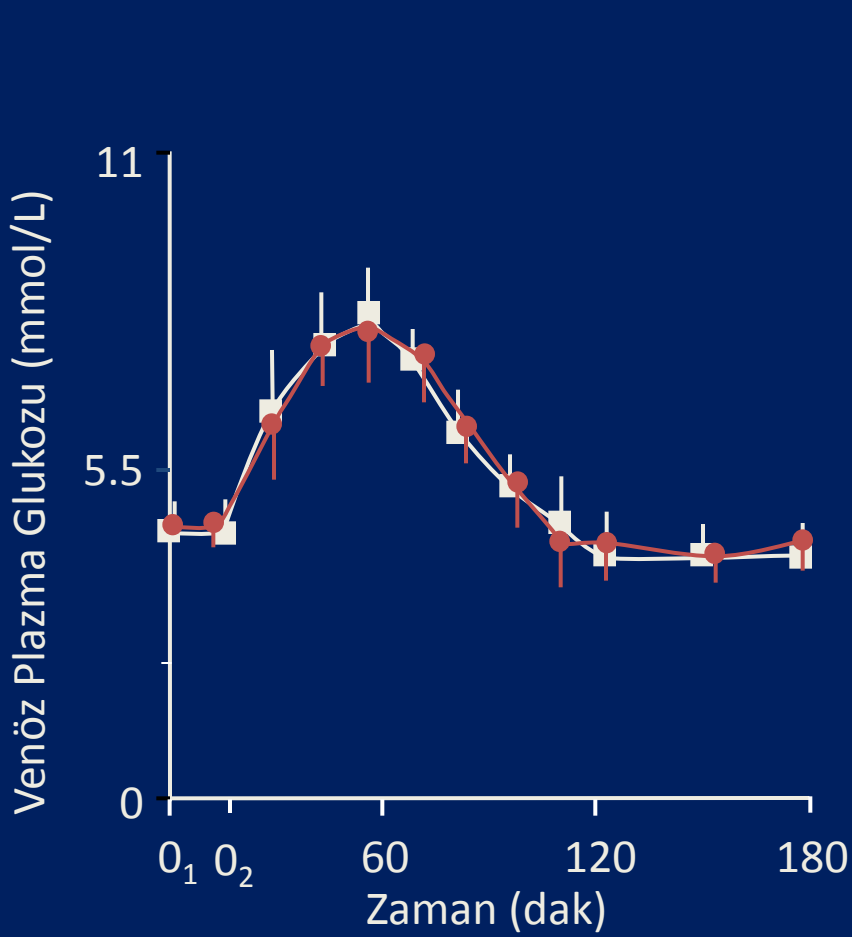
SGLT2 İNHİBİTÖRLERİ



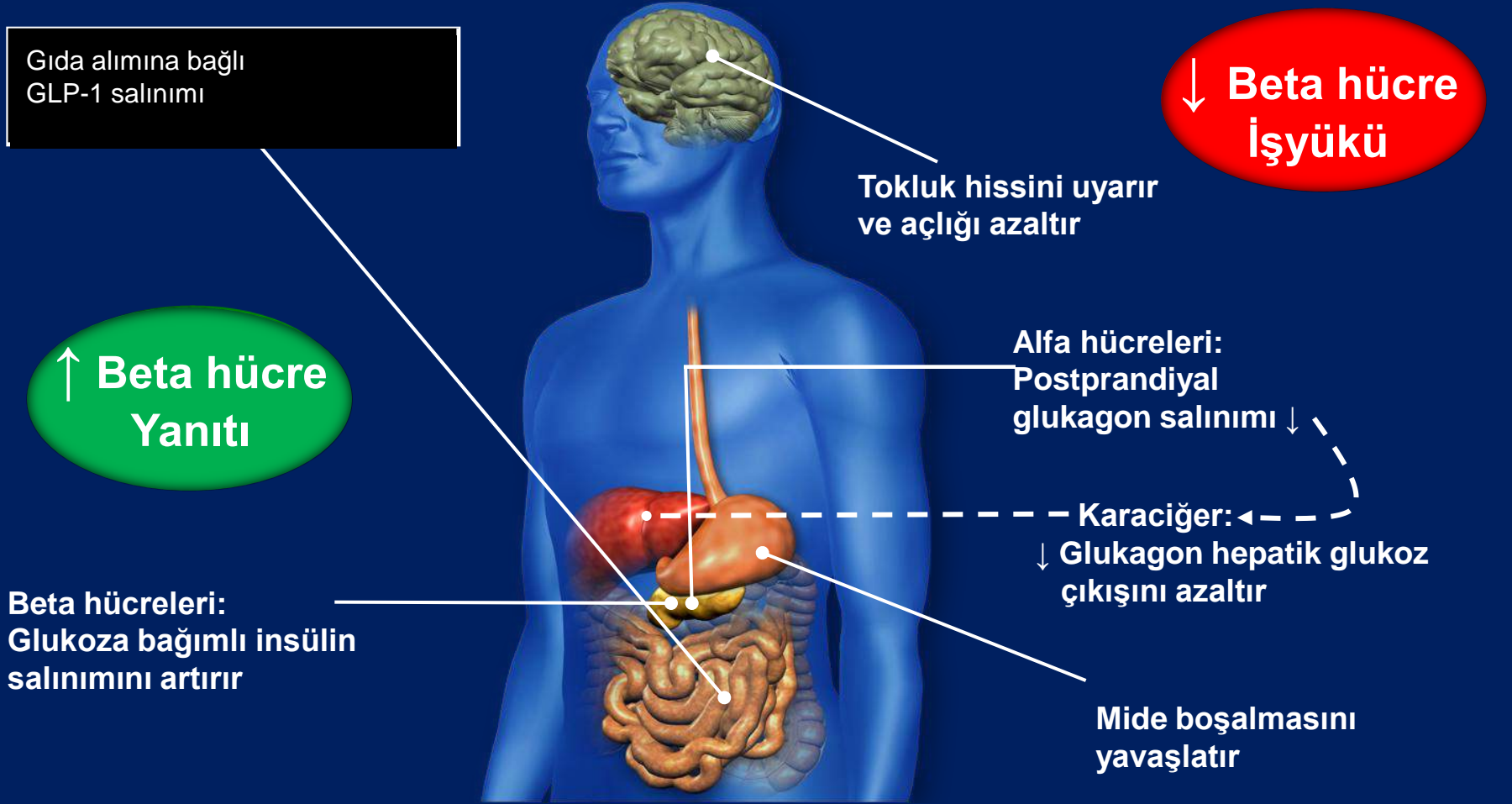
SGLT2 İNHİBİTÖRLERİ

YAN ETKİLER	Oldukça Sık (≥%10)	Sık* (≥%1 ile <%10)	Nadir† (≥%0.1 ile <%1)
Enfeksiyonlar		Vulvovajinit, balanit ve diğer genital enfeksiyonlar	Vulvovajinal kaşıntı
Metabolizma & beslenme bozuklukları	Hipoglisemi (SU yada insulinle)		Sıvı açığı Susama
Gastrointestinal bozukluklar			Kabızlık
Deri ve subkutan doku bozuklukları			Hiperhidroz
Kas iskelet ve bağ dokusu hastalıkları		Sırt ağrısı	
Renal & üriner hastalıklar		Disüri Poliüri	Nokturi
İncelemeler		Dislipidemi Hematokrit artışı	Kanda kreatinin ve üre artışı

İNKRETİN ETKİSİ



GLP-1'İN ETKİLERİ



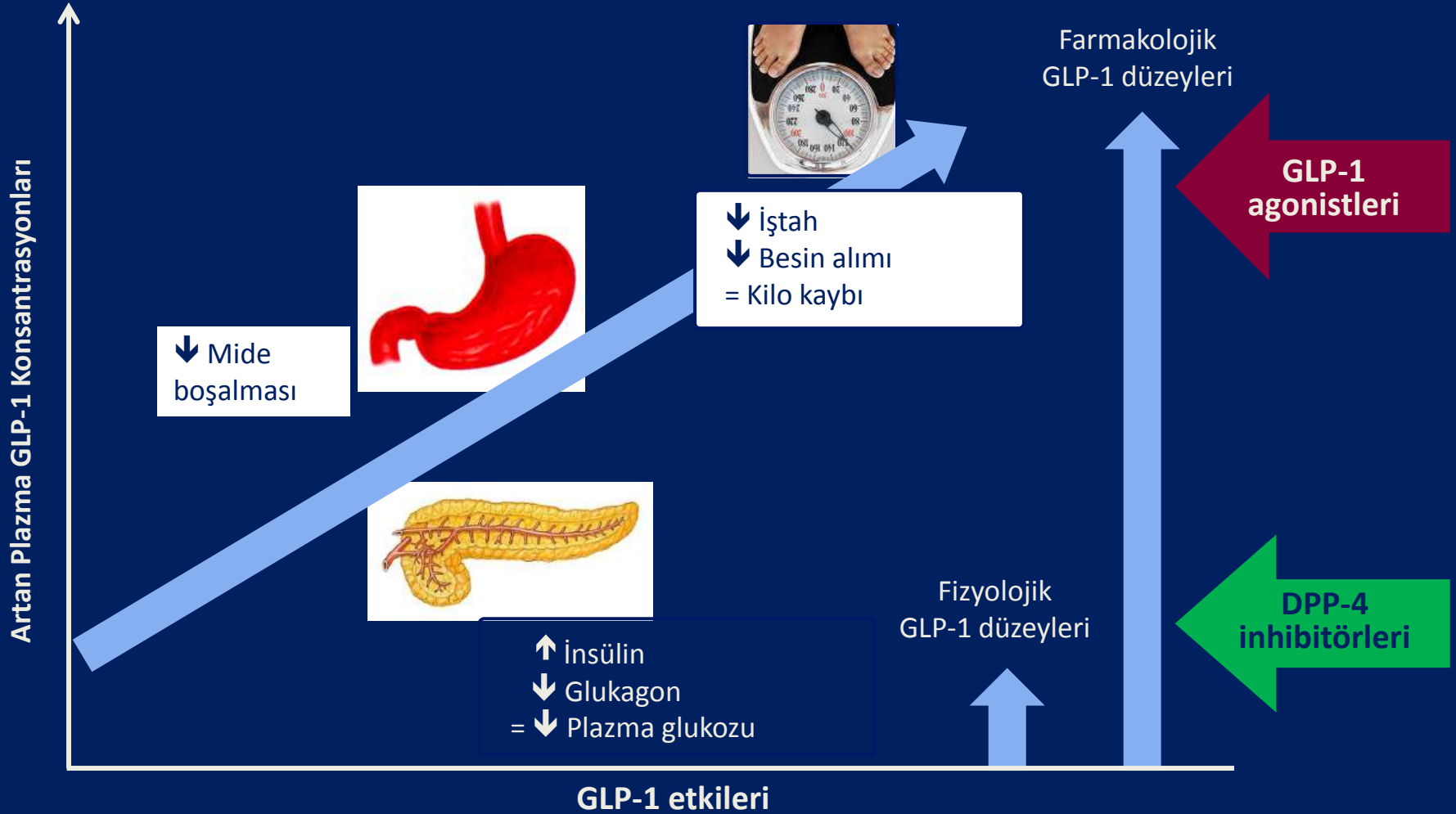
Flint A et al. J Clin Invest 1998;101:515-520.

Larsson H et al. Acta Physiol Scand 1997;160:413-422.

Nauck MA et al. Diabetologia 1996;39:1546-1553.

Drucker DJ. Diabetes 1998;47:159-169.

GLP-1 İLE İLİŞKİLİ TEDAVİLER





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Bioorganic & Medicinal Chemistry Letters

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

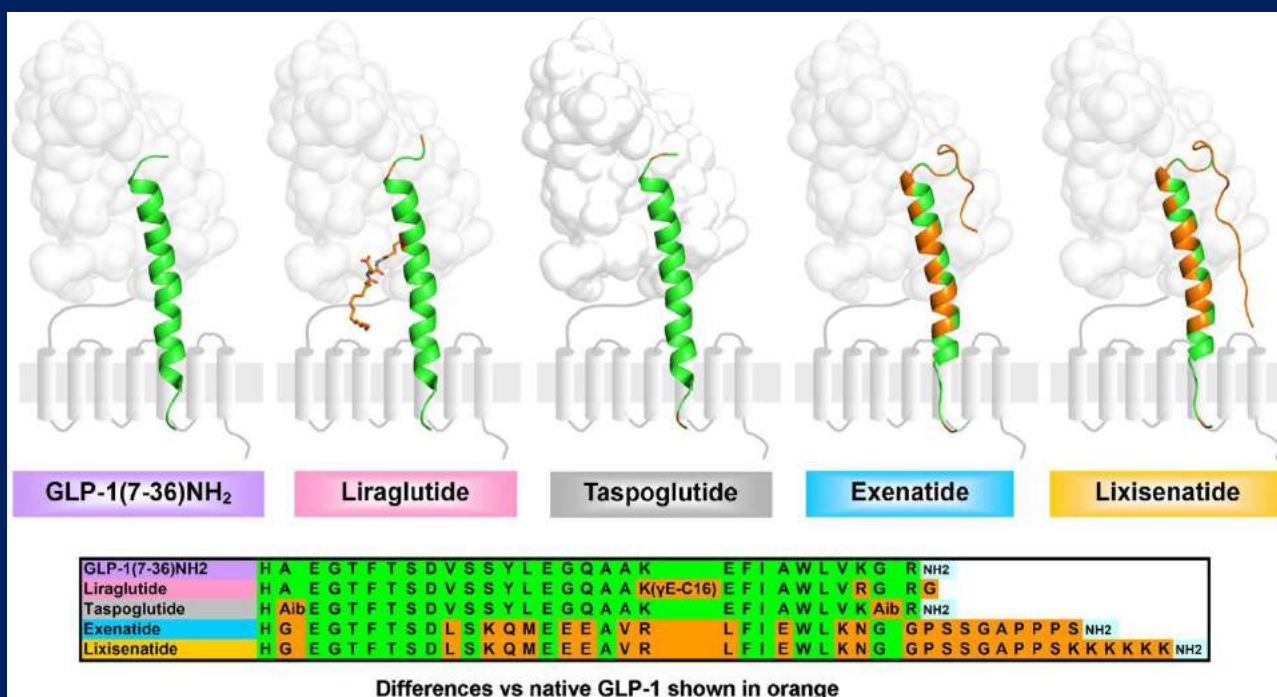
BMCL Digest

Recent progress and future options in the development of GLP-1 receptor agonists for the treatment of diabetes

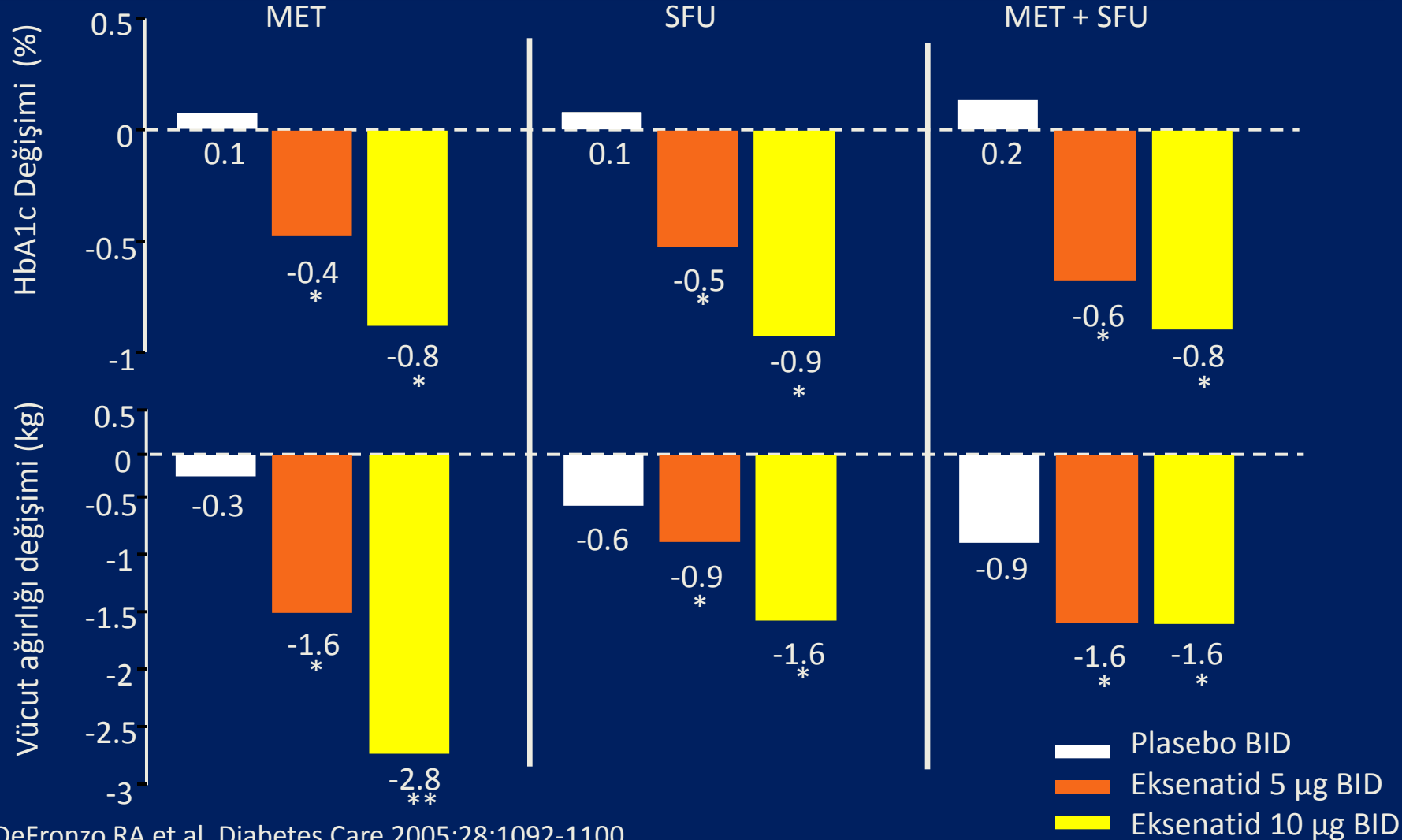
Martin Lorenz^{a,*}, Andreas Evers^b, Michael Wagner^{a,*}

^aDiabetes Division/Res. & Transl. Med, Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, 65926 Frankfurt am Main, Germany

^bLGCR/Struct., Design & Informatics, Sanofi Deutschland GmbH, 65926 Frankfurt am Main, Germany



EKSENATİD



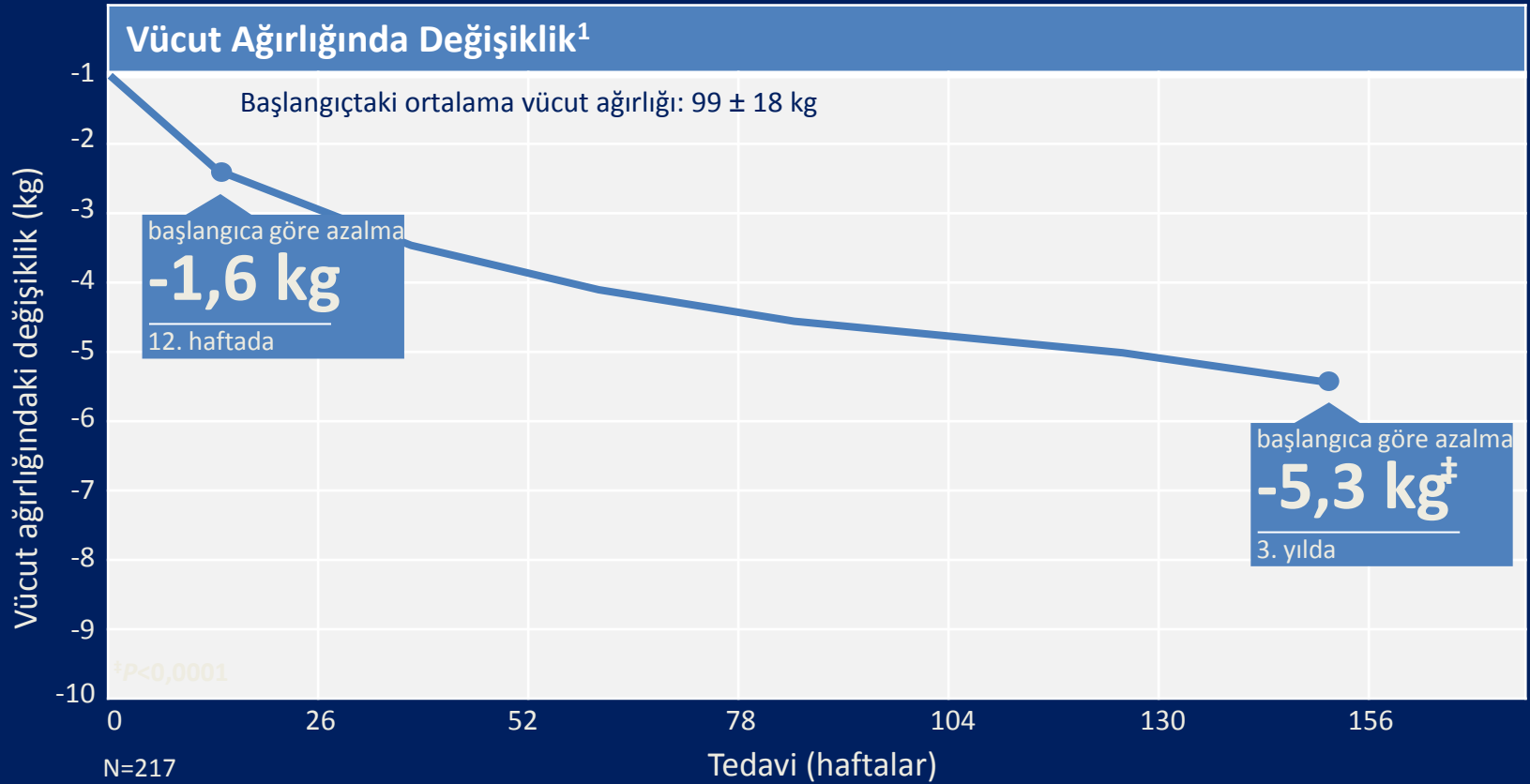
❖ DeFronzo RA et al. Diabetes Care 2005;28:1092-1100.

❖ Buse JB et al. Diabetes Care 2004;27:2628-2635.

❖ Kendall DM et al. Diabetes Care 2005;28:1083-1091.

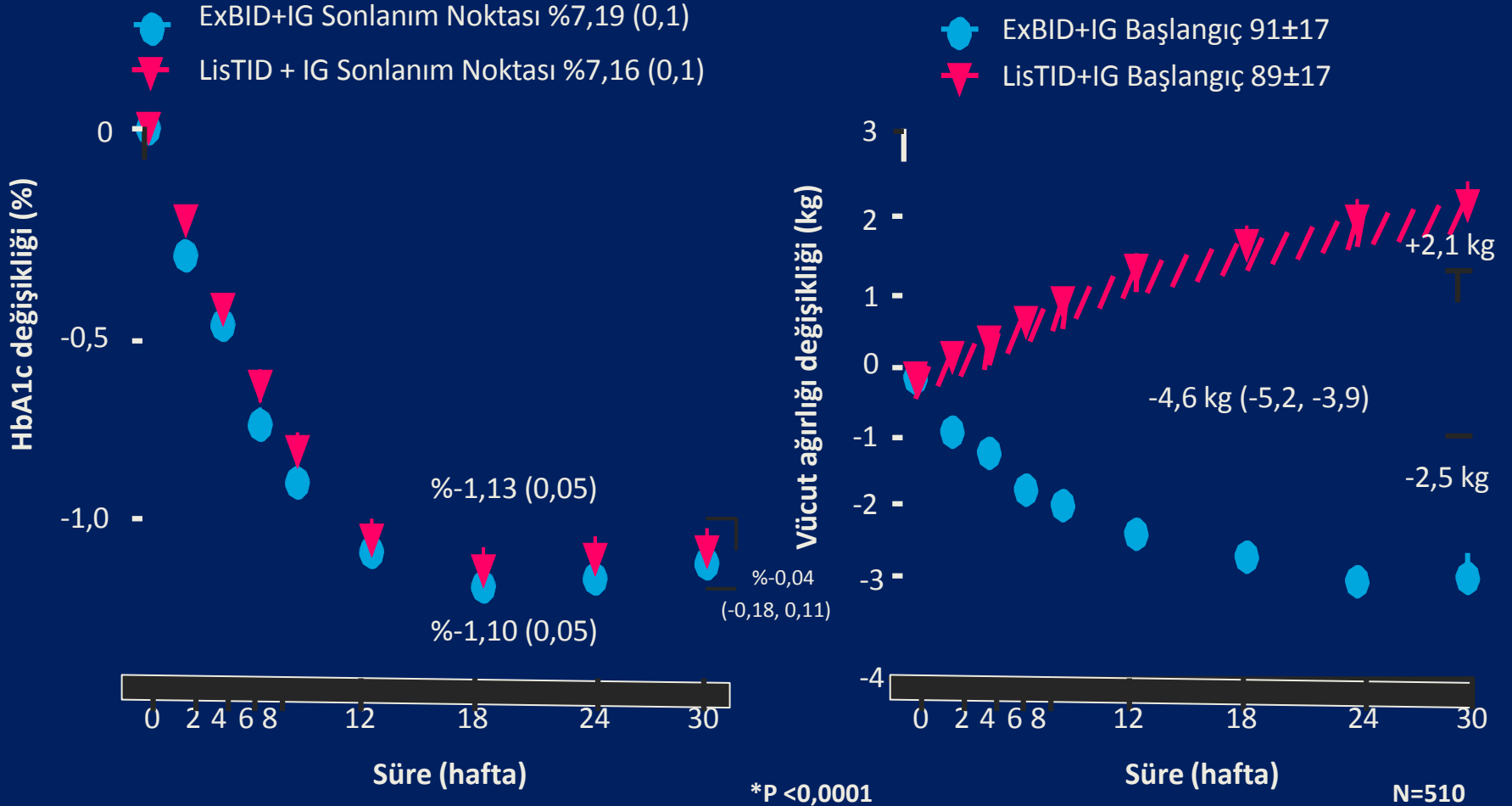
EKSENATİD

Eksenatidin vücut ağırlığını azaltıcı etkisi
156 haftalık uzatma çalışması boyunca sürmüştür

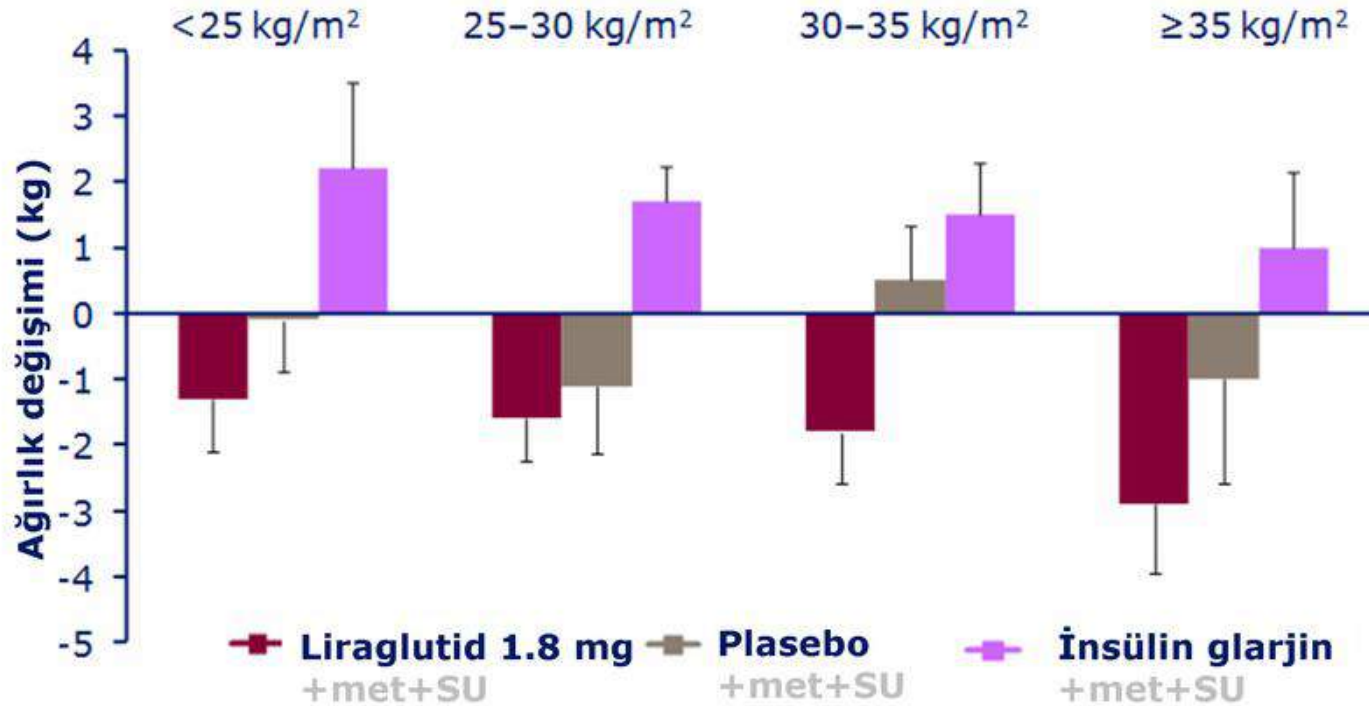


EKSENATİD

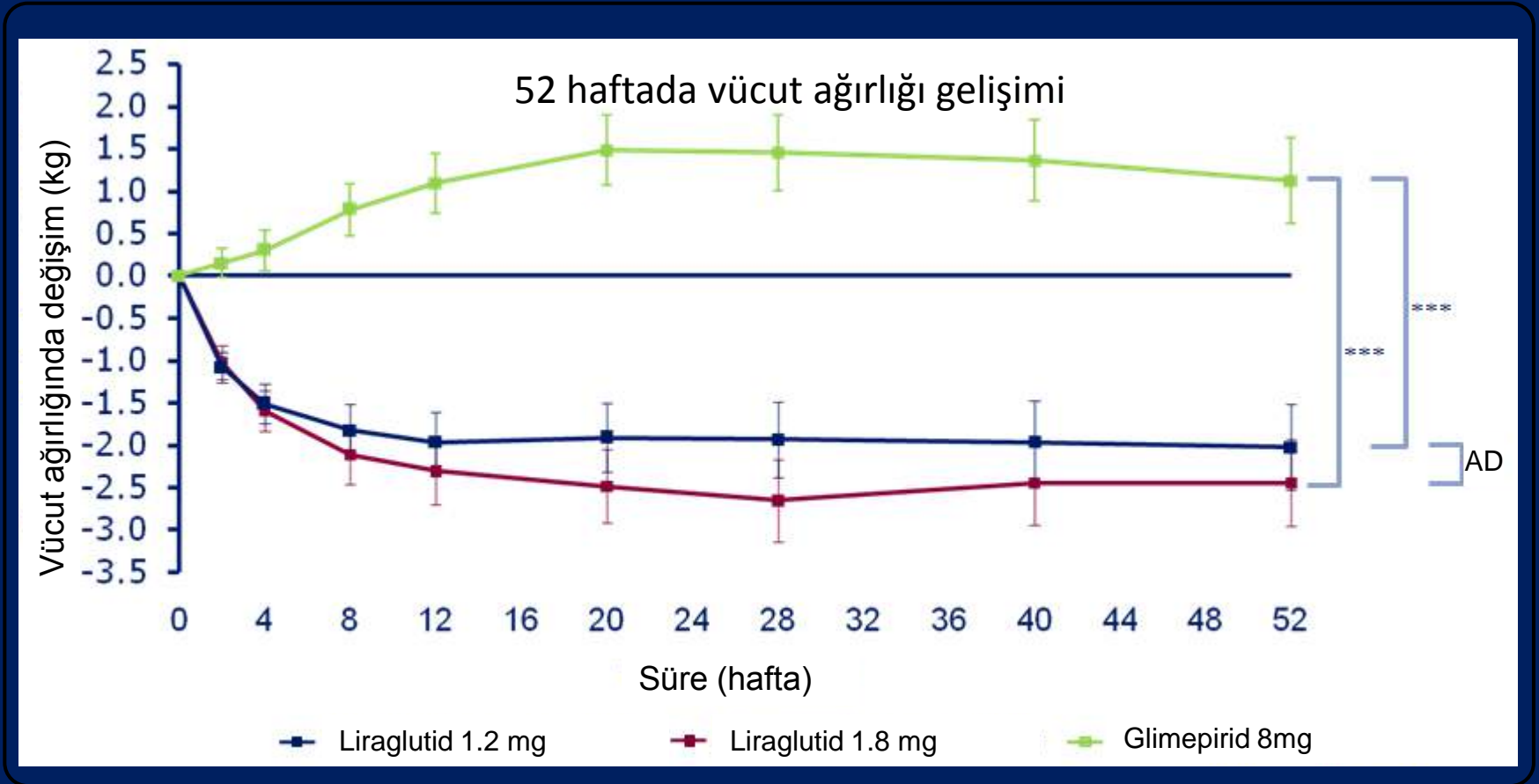
30. Haftada HbA1c ve Vücut Ağırlığı



LİRAGLUTİD



LİRAGLUTİD

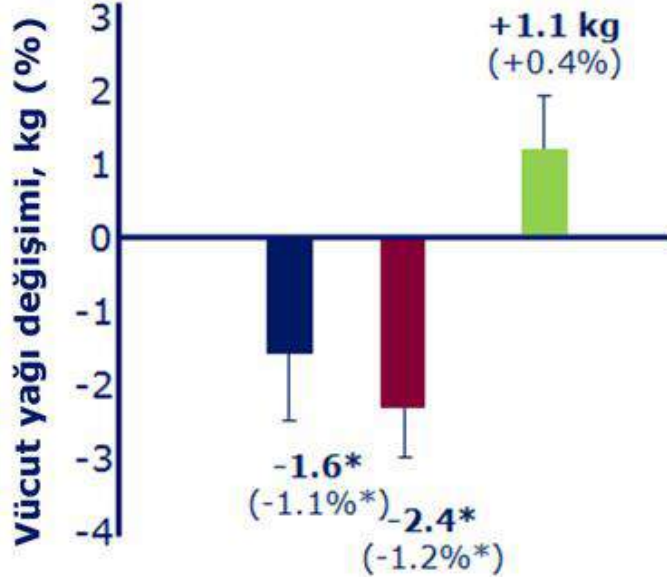


***Başlangıca göre değişim için $p < 0.0001$

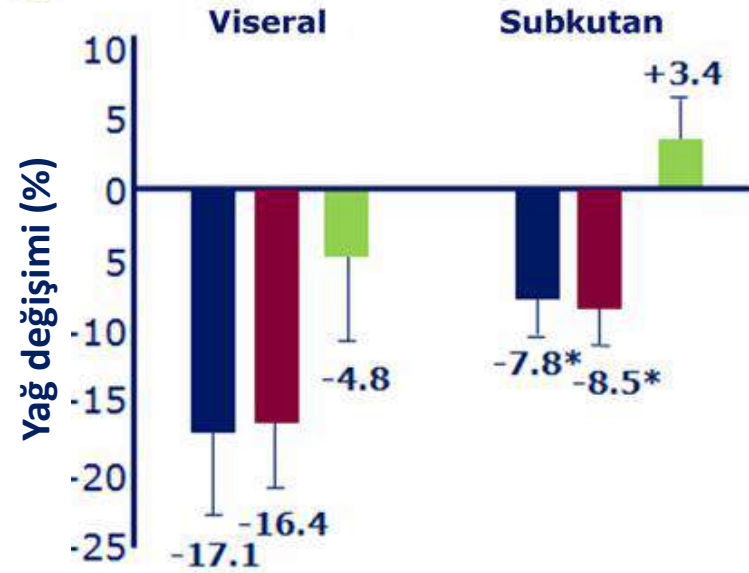
LİRAGLUTİD

Liraglutidin viseral vücut yağına etkisi

Vücut yağındaki değişim
DEXA taraması



Subkutan yağa karşı viseral yağ
CT tarama



■ Liraglutid 1.2 mg + met

■ Liraglutid 1.8 mg + met

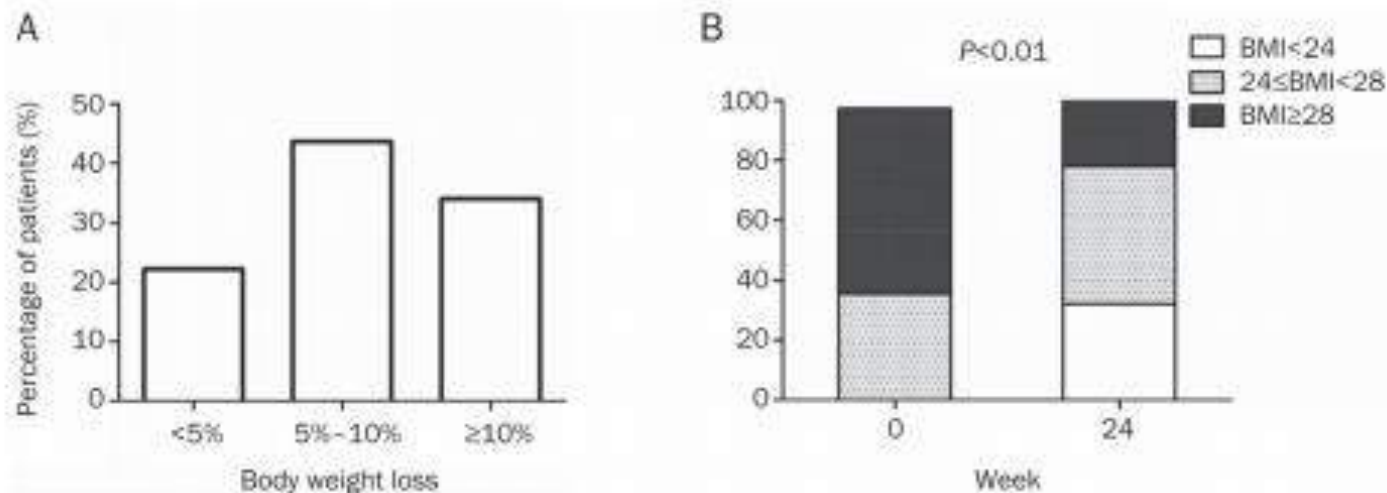
■ Glimepirid + met

LEAD-2

Original Article

Liraglutide reduces the body weight and waist circumference in Chinese overweight and obese type 2 diabetic patients

Ping FENG¹, De-min YU², Li-ming CHEN², Bao-cheng CHANG², Qiu-di JI¹, Shu-ying LI¹, Mei ZHU¹, Sheng-hua DING³, Bao-zhen ZHANG³, Su-li WANG⁴, Hong-tao LI⁵, Jing-na LIN⁶, Mao-jun WANG⁷, Jian-chao GUO⁸, Jie LIU⁹, Zhong-dong LIU⁹, Shen-tao WU¹⁰, Ju-hong YANG^{2,*}, Clinical Cooperation Group of Liraglutide in Chinese Type 2 Diabetes



ORIGINAL INVESTIGATION

Open Access

Association among weight change, glycemic control, and markers of cardiovascular risk with exenatide once weekly: a pooled analysis of patients with type 2 diabetes

Lawrence Blonde^{1*}, Richard Pencek² and Leigh MacConell²

Table 1 Characteristics of exenatide once weekly studies

Author	N	Study duration (weeks)	Baseline A1C (%) ^a	Change in A1C (%) ^{a,b}	Baseline body weight (kg) ^a	Change in body weight (kg) ^{a,b}
Drucker et al. 2008 [14] (DURATION-1)	148	30	8.3	-1.9	102	-3.7
Bergental et al. 2010 [9] (DURATION-2)	160	26	8.6	-1.5	89	-2.3
Diamant et al. 2010 [13] (DURATION-3)	233	26	8.3	-1.5	91.2	-2.6
Russell-Jones et al. 2012 [16] (DURATION-4)	248	26	8.5	-1.5	87.5	-2.0
Blevins et al. 2011 [10] (DURATION-5)	129	24	8.5	-1.6	97.0	-2.3
Buse et al. 2013 [11] (DURATION-6)	461	26	8.5	-1.3	90.9	-2.7
Davies et al. 2013 [12]	111	26	8.4	-1.3	96.7	-2.7
Ji et al. 2013 [15]	340	26	8.7	-1.4	69.6	-1.6

A1C: glycated hemoglobin; ^aAll mean or least-squares mean values; ^bAt study end point.

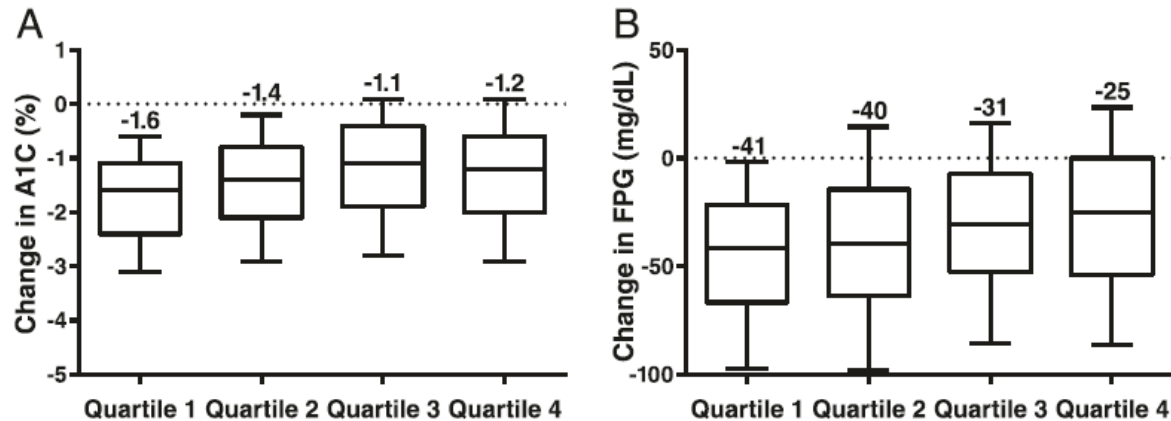


Figure 2 Median changes in A1C and FPG, by end-point body weight change quartiles. (A) A1C. (B) FPG. A1C, hemoglobin A1C; FPG, fasting plasma glucose. The central line represents the median (also labelled above the plot), the box encloses the 25th to 75th percentiles of the distribution, and the outer bars are drawn to the 10th and 90th percentiles.

Table 3 Mean changes in parameters from baseline to end point

Parameter, mean (SE) [95% CI]	Quartile 1 (n = 455)	Quartile 2 (n = 458)	Quartile 3 (n = 450)	Quartile 4 (n = 455)	All Patients (N = 1830)
Weight (kg)	-7.0 (0.15) [-7.3, -6.7]	-3.0 (0.03) [-3.0, -2.9]	-1.0 (0.03) [-1.1, -1.0]	1.5 (0.09) [1.4, 1.7]	-2.4 (0.09) [-2.5, -2.2]
A1C (%)	-1.7 (0.05) [-1.8, -1.6]	-1.4 (0.05) [-1.5, -1.3]	-1.2 (0.06) [-1.3, -1.1]	-1.3 (0.05) [-1.4, -1.2]	-1.4 (0.03) [-1.5, -1.3]
FPG (mg/dL)	-43.5 (2.30) [-48.0, -39.0]	-38.3 (2.29) [-42.8, -33.8]	-31.7 (2.13) [-35.9, -27.6]	-29.1 (2.50) [-34.1, -24.2]	-35.7 (1.16) [-38.0, -33.5]

OLGU - 2

- Yakınma: Karında şişkinlik
- Boy: 170 cm VA: 118 kg
- VKİ: 40.8 kg/m²
- Bel çevresi: 128 cm
- A1C: %6.9

Sabah açlık	S abah tokluk	Öğle tokluk	Akşam tokluk
121	144	163	133
135	150	138	145

OLGU - 2

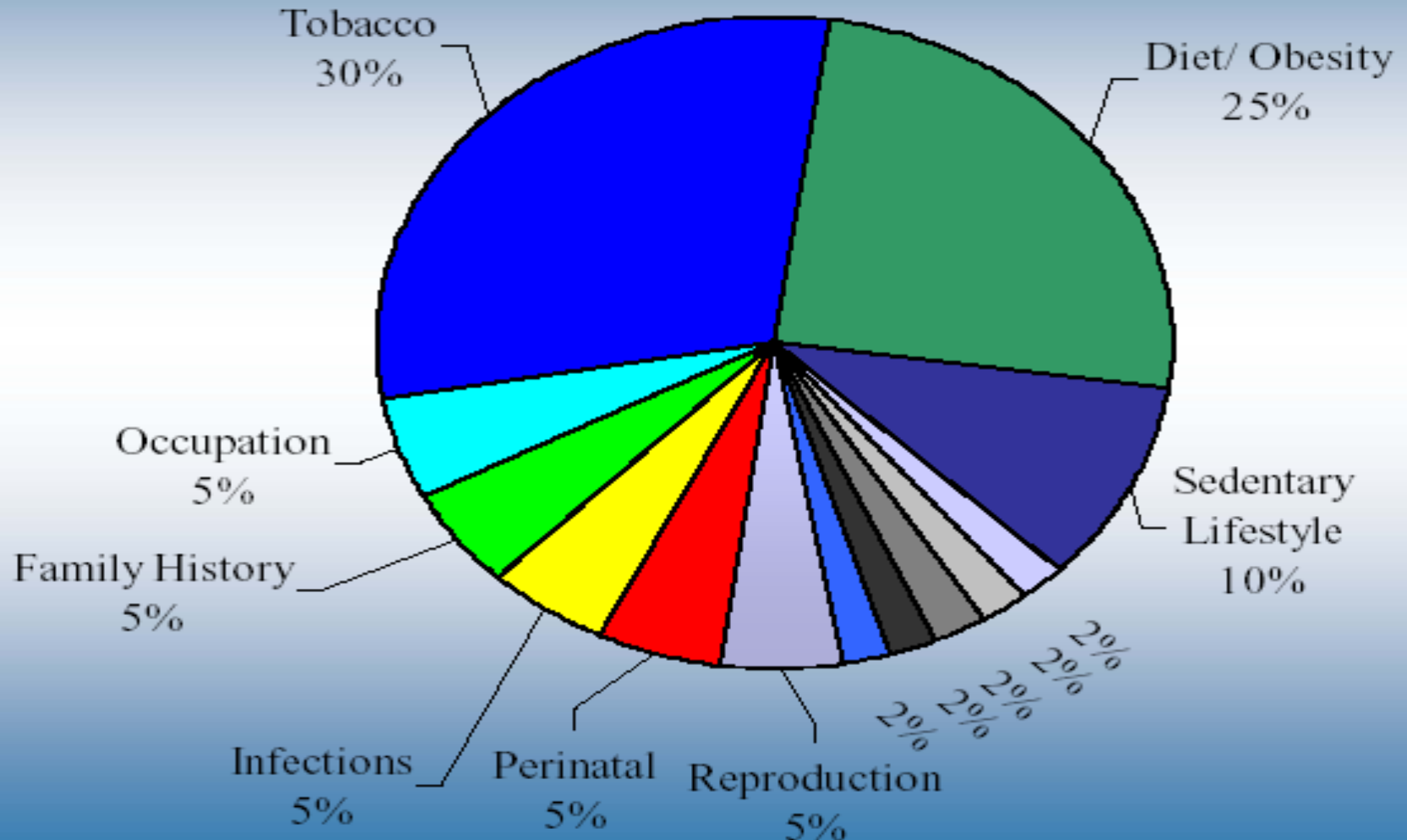
❖ Kullandığı ilaçlar:

Byetta 2x10 µg Levemir 20 U Glifor 1000 mg 2x1
Crestor 10 mg 1x1 Coveram 10/5 mg 1x1
Coraspin 100 mg 1x1

❖ Tiroid USG:

Sağ lob:35-38-70 mm Sol lob:27-27-45 mm.
Parenkim heterojen. Sağ lobda 34 mm sınırları
düzensiz, milimetrik kalsifikasyon içeren
hipoekoik nodül, sol lobda 12 mm düzgün sınırlı
izoekoik nodül

OBEZİTE VE KANSER



OBEZİTE VE KANSER

Purpose

Analyze the relationship between obesity and type-2 diabetes mellitus (DM) and the development of differentiated thyroid cancer (DTC).

Materials and methods

A randomized case-controlled retrospective chart review of outpatient clinic patients at an academic medical center between January 2005 and December 2012. DTC patients were compared to two control groups: primary hyperparathyroidism (PHPTH) patients with euthyroid state and Internal Medicine (IM) patients. Exposure variables included historical body-mass-index (BMI), most recent BMI within 6 months and DM. Multivariate logistic regressions adjusting for gender, age, and year of BMI assessed the adjusted Odds Ratio (OR) of DTC with both BMI and DM.

Results

Comparison of means showed a statistically significant higher BMI in DTC (BMI = 37.83) than PHPTH, IM, and pooled controls, BMI = 30.36 $p = <0.0001$, BMI = 28.96 $p = <0.0001$, BMI = 29.53 $p = <0.0001$, respectively. When compared to PHPTH, DM was more frequent in DTC (29% vs. 16%) and prevalence trended towards significance ($p = 0.0829$, 95% CI = 0.902–5.407). BMI adjusted OR was significant when compared to PHPTH, IM and pooled controls: 1.125 ($p = 0.0001$), 1.154 ($p = <0.0001$), and 1.113 ($p = <0.0001$), respectively. DM adjusted OR was significant when compared to PHPTH and pooled controls at 3.178 (95% 1.202, 8.404, $p = 0.0198$) and 2.237 (95% 1.033, 4.844, $p = 0.0410$), respectively.

Conclusion

Our results show that obesity and, to a lesser degree, DM are significantly associated with DTC. BMI in particular was a strong predictive variable for DTC (C = 0.82 bivariate, C = 0.84 multivariate).

- ❖ Oberman B et al. Relationship between obesity, diabetes and the risk of thyroid cancer. Am J Otolaryngol. 2015 Mar 3. pii: S0196-0709(15)00064-2. [Epub ahead of print]

OLGU - 3

- ❖ F.G. 49 K, Öğretmen, Aydın
- ❖ Yakınma: Kilo verememe
- ❖ Öykü: Çocukluğundan beri fazla kilo sorunu olan hasta gebelik dönemlerinde aldığı kiloları veremediğini, ayrıca son yıllarda kilo almaya devam ettiğini ifade ediyor. Sürekli diyet uygulamasına rağmen kilo veremiyormuş.
- ❖ 6 yıldır diyabetik olan hastaya 1 yıl önceki kontrolde GLP-1 analogu başlanmış. 4-5 kg kadar vermiş ama 6 ay önce sigarayı bıraktınca geri almış.

OLGU - 3

- ❖ Hipertansiyon ve talasemi minör var
- ❖ Ailede DM öyküsü yok
- ❖ Sigara:6 ay önce bırakmış Alkol:Sosyal içici
- ❖ Fizik muayene:
 - TA: 140/90 mm Hg.
 - Obez
 - Boy: 158 cm VA: 118 kg
 - VKİ: 44.9 kg/m² Bel çevresi: 130 cm
- ❖ Vücut yağ oranı: %46.6

OLGU - 3

❖ Kullandığı ilaçlar:

Byetta 10 2x1 Matofin XR 500 1x2 Hyperium 1x1
Coraspin 100 mg 1x1

❖ Laboratuvar:

AKŞ:111 mg/dl TKŞ:157 mg/dl A1C:%6.6

LDL:114 mg/dl Trigliserid:174 mg/dl

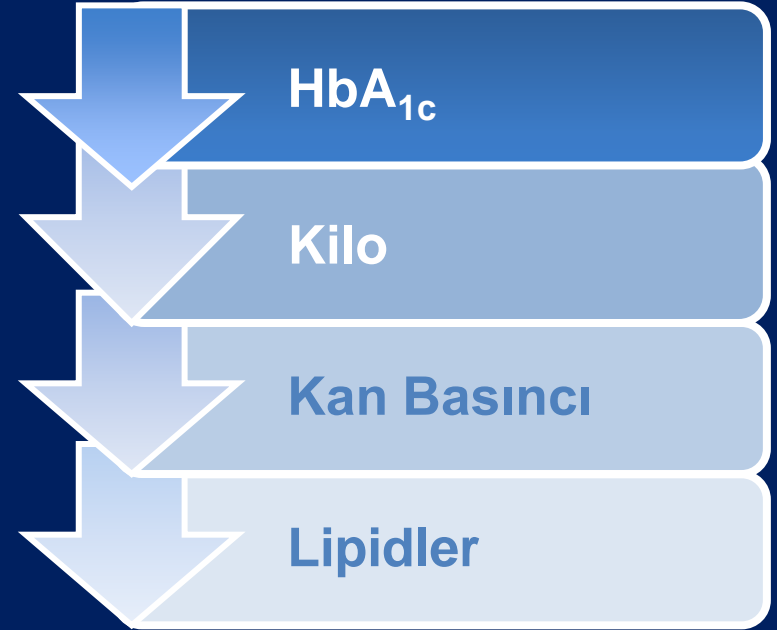
Kreatinin:0.6 mg/dl ALT: 22 U/L

Mikroalbüminüri:55 mg/gün

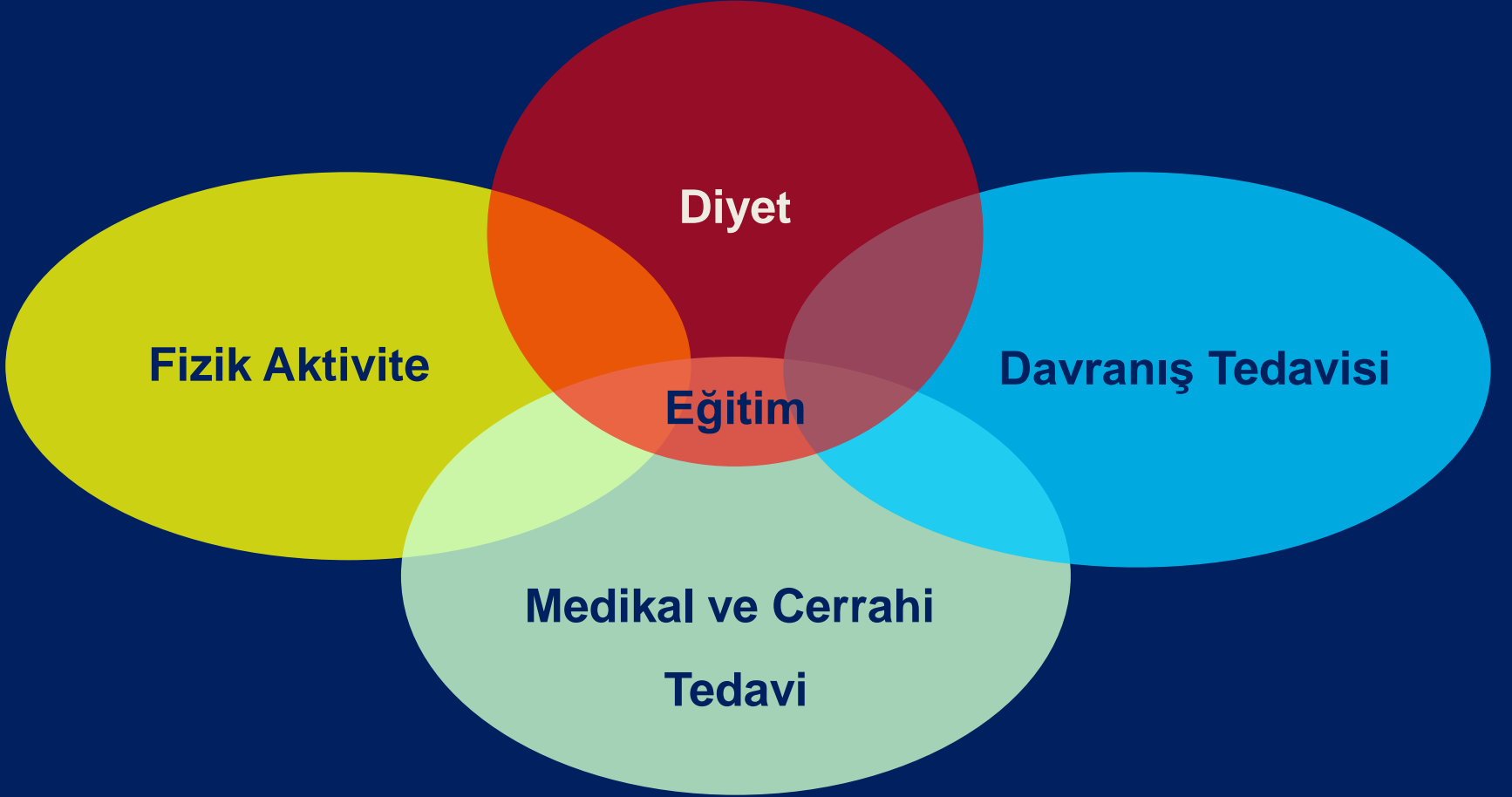
OLGU - 3

❖ Bu hastaya yaklaşımda ilk olarak aşağıdakilerden hangisini yapmayı düşünürsünüz?

- Kan şekeri regülasyonu
- Obeziteye yönelik tedavi
- Kan basıncı ve lipidlerin düzenlenmesi
- Hepsi
- Hiçbiri



OBEZİTE TEDAVİSİ



DAVRANIŞ TEDAVİSİ

Open Access

Research

BMJ Open
Diabetes
Research
& Care

The effect of slow spaced eating on hunger and satiety in overweight and obese patients with type 2 diabetes mellitus

Theodoros Angelopoulos,¹ Alexander Kokkinos,¹ Christos Liaskos,¹ Nicholas Tentolouris,¹ Kleopatra Alexiadou,¹ Alexander Dimitri Miras,² Iordanis Mourouzis,³ Despoina Perrea,⁴ Constantinos Pantos,³ Nicholas Katsilambros,¹ Stephen R Bloom,² Carel Wynard le Roux²

DAVRANIŞ TEDAVİSİ

- 300 ml dondurma
- 675 kcal
- %59 yağ
- %33 karbonhidrat
- %9 protein
- 2 eşit parça 5 dk arayla toplam süre 5 dk
- 7 eşit parça 5 dk arayla toplam süre 30 dk

DAVRANIŞ TEDAVİSİ

Table 2 Postprandial responses of the study participants (mean±SEM)

	5 min Meal	30 min Meal	Difference*	df	t	p Value
Glucose AUC (mg/dL × min)	28 687.7±1490.9	28 566.8±1557.9	120.9±496.4	19	0.24	0.81
Insulin AUC (IU/L × min)	6793.7±940.1	6752.4±1015.2	41.3±321.1	19	0.13	0.90
Triglycerides AUC (mg/dL × min)	24 203.8±2392.2	24 468.7±2085.1	-264.9±860.0	19	-0.31	0.76
Ghrelin AUC (pg/mL × min)	39 275.9±4359.1	40 733.8±5191.7	-1457.9±1395.0	19	-1.05	0.31
PYY AUC (pmol/L × min)	10 570.9±1550.2	9740.0±974.8	830.9±831.4	19	0.99	0.34
GLP-1 AUC (pmol/L × min)	7414.0±948.9	7159.4±827.6	254.6±356.7	19	0.71	0.49
Fullness AUC (mm × min)	10 901.0±568.8	11 943.7±541.2	-1042.7±301.9	19	-3.45	0.003
Hunger AUC (mm × min)	4966.7±347.5	4442.9±328.0	523.8±188.2	19	2.78	0.012

*Difference between the 5 and 30 min meal.

AUC, area under the curve; df, degrees of freedom; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

DAVRANIŞ TEDAVİSİ

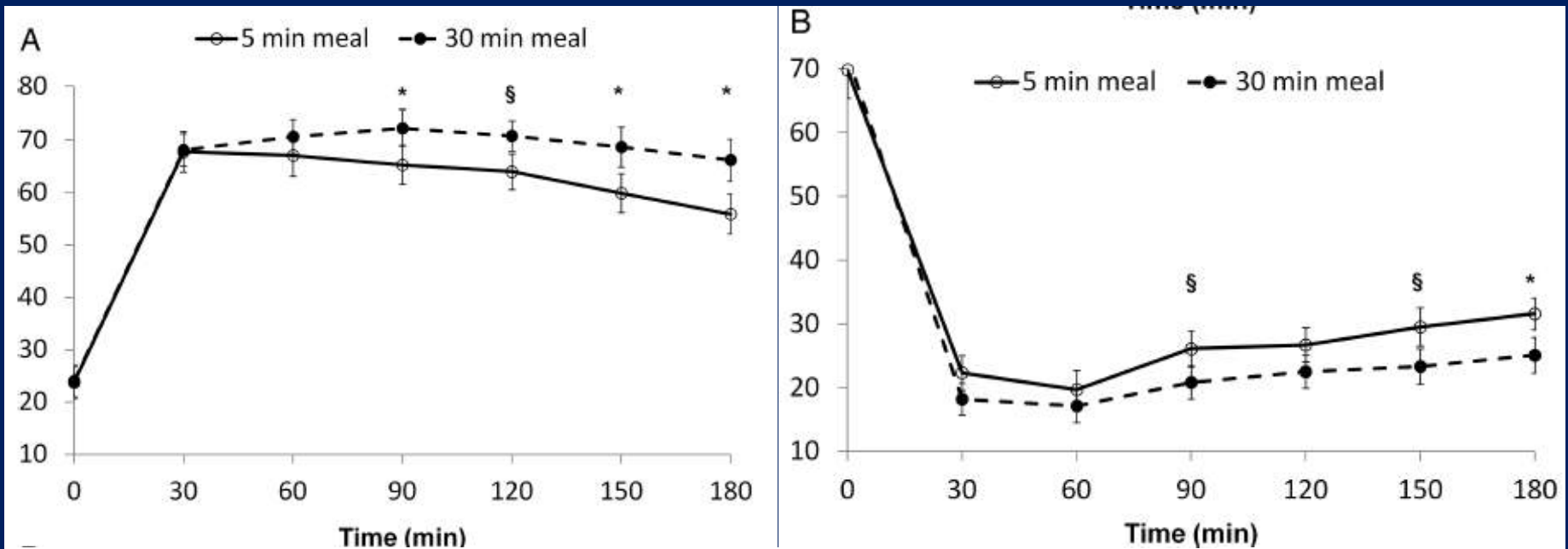
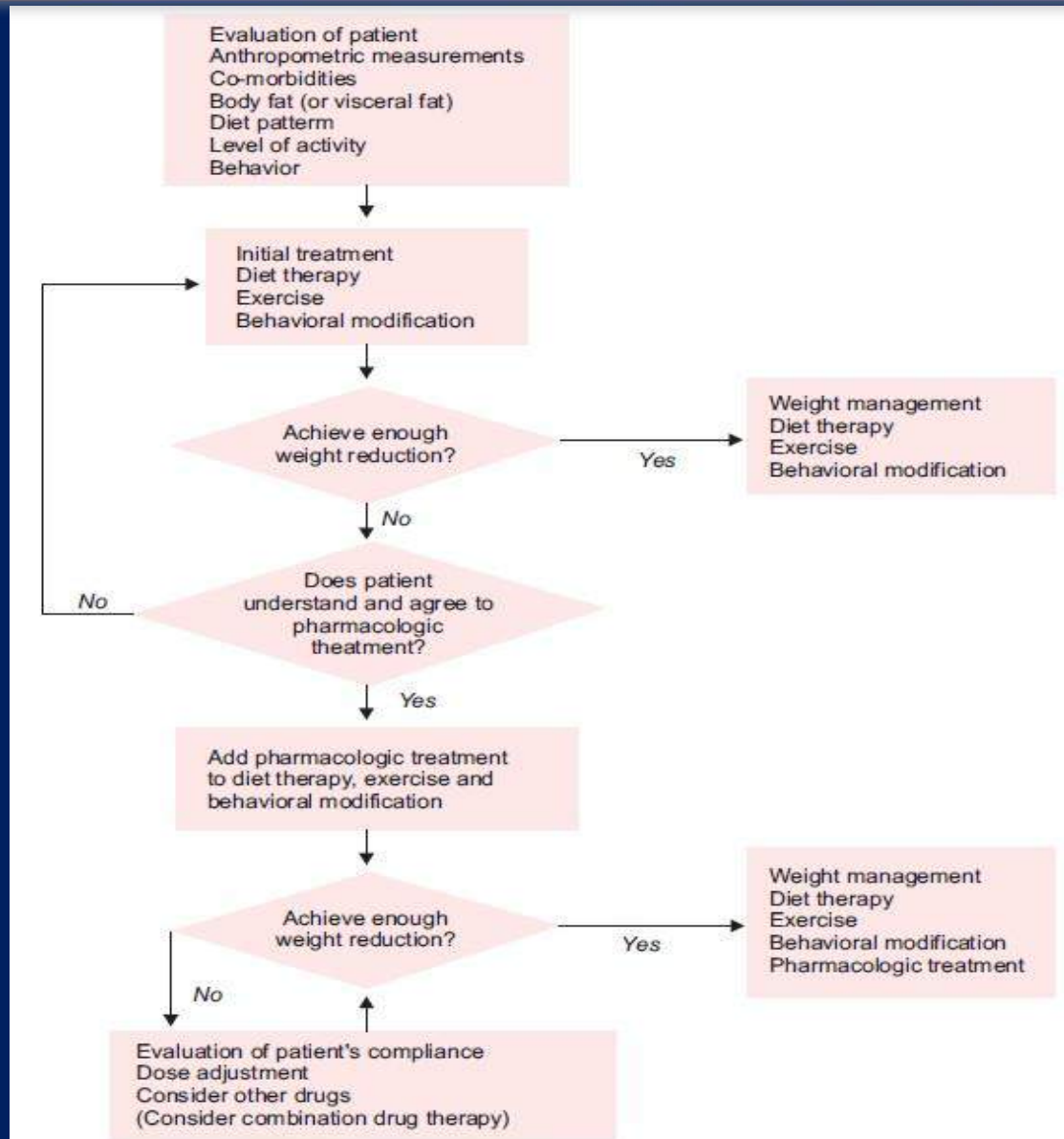


Figure 1 Visual analog scale (VAS) ratings for fullness (A) and hunger (B) after a 5 and 30 min meal (*p<0.01, §p<0.05).

MEDİKAL TEDAVİ




MEDİKAL TEDAVİ

Drug Design, Development and Therapy

Dovepress

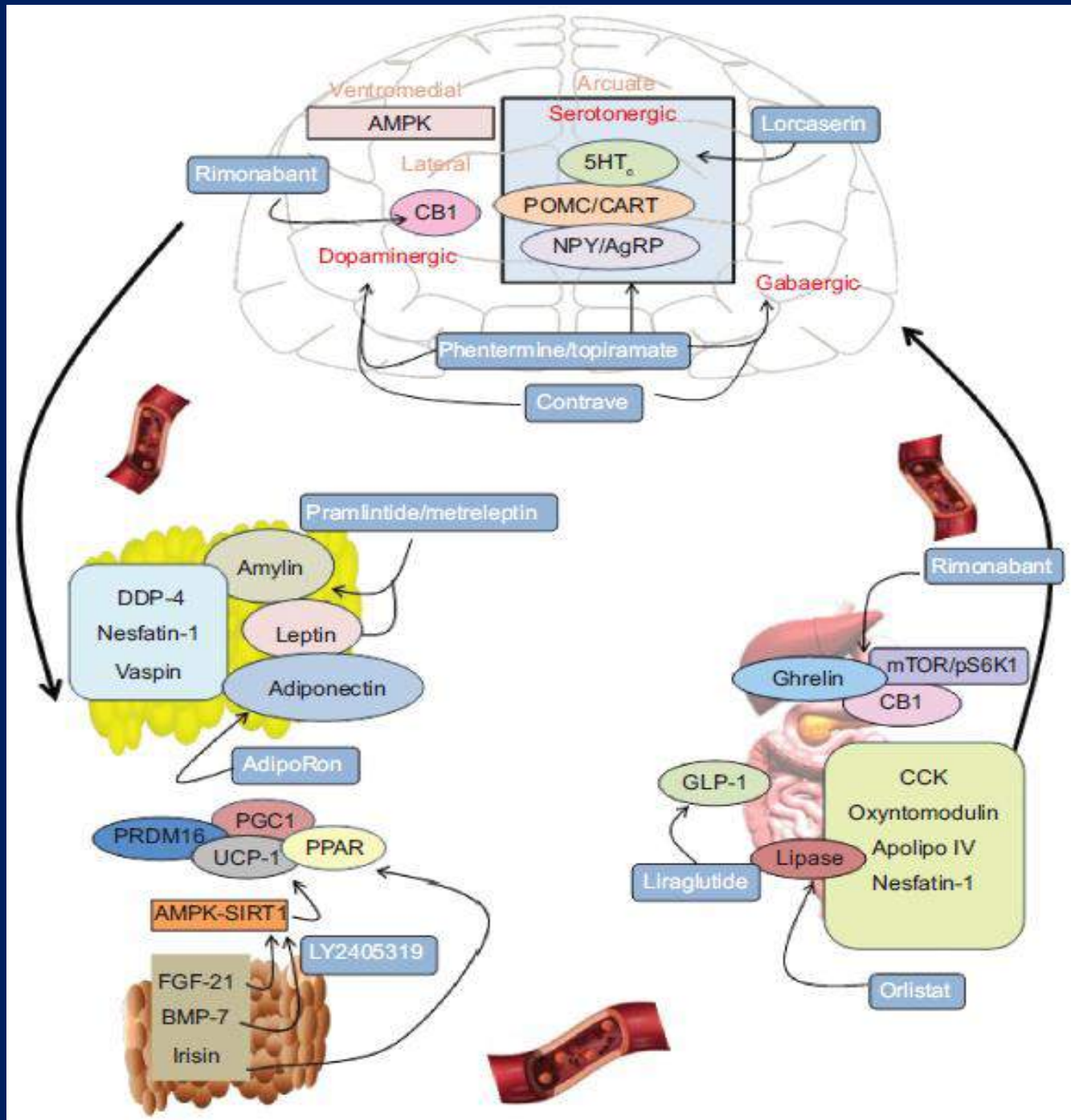
open access to scientific and medical research

 Open Access Full Text Article

REVIEW

Drug development strategies for the treatment of obesity: how to ensure efficacy, safety, and sustainable weight loss

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
1 December 2014



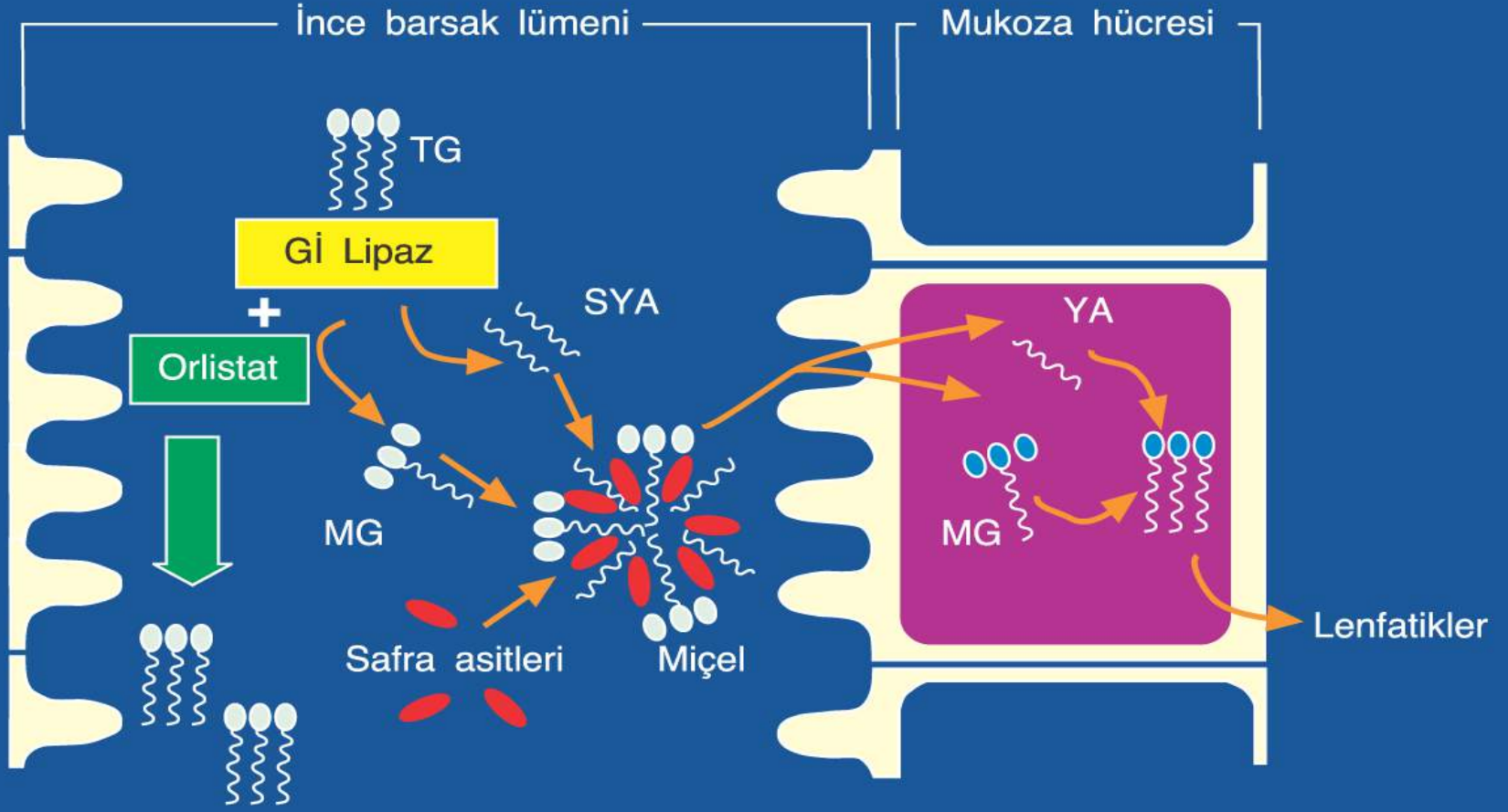
MEDİKAL TEDAVİ

- Obezite farmakoterapisi, birçok umut verici ilacın çıkışı ve kabul edilemeyecek güvenlik sorunları nedeniyle kullanımdan kaldırılması nedeniyle çok sayıda iniş-çıkışa tanıklık etmiştir.
- ❖ Kakkar AK, Dahiya N. Drug treatment of obesity: Current status and future prospects. Eur J Intern Med 2015 Mar;26(2):89-94.

MEDİKAL TEDAVİ

- Günümüzde kullanımı onaylı ilaçlar (FDA):
 - ✓ Orlistat (1999)
 - ✓ Lorcaserin (2012)
 - ✓ Phentermine/topiramate CR (2012)
 - ✓ Naltrexone/bupropion CR (2014)
- ❖ Kakkar AK, Dahiya N. Drug treatment of obesity: Current status and future prospects.
Eur J Intern Med 2015 Mar;26(2):89-94.

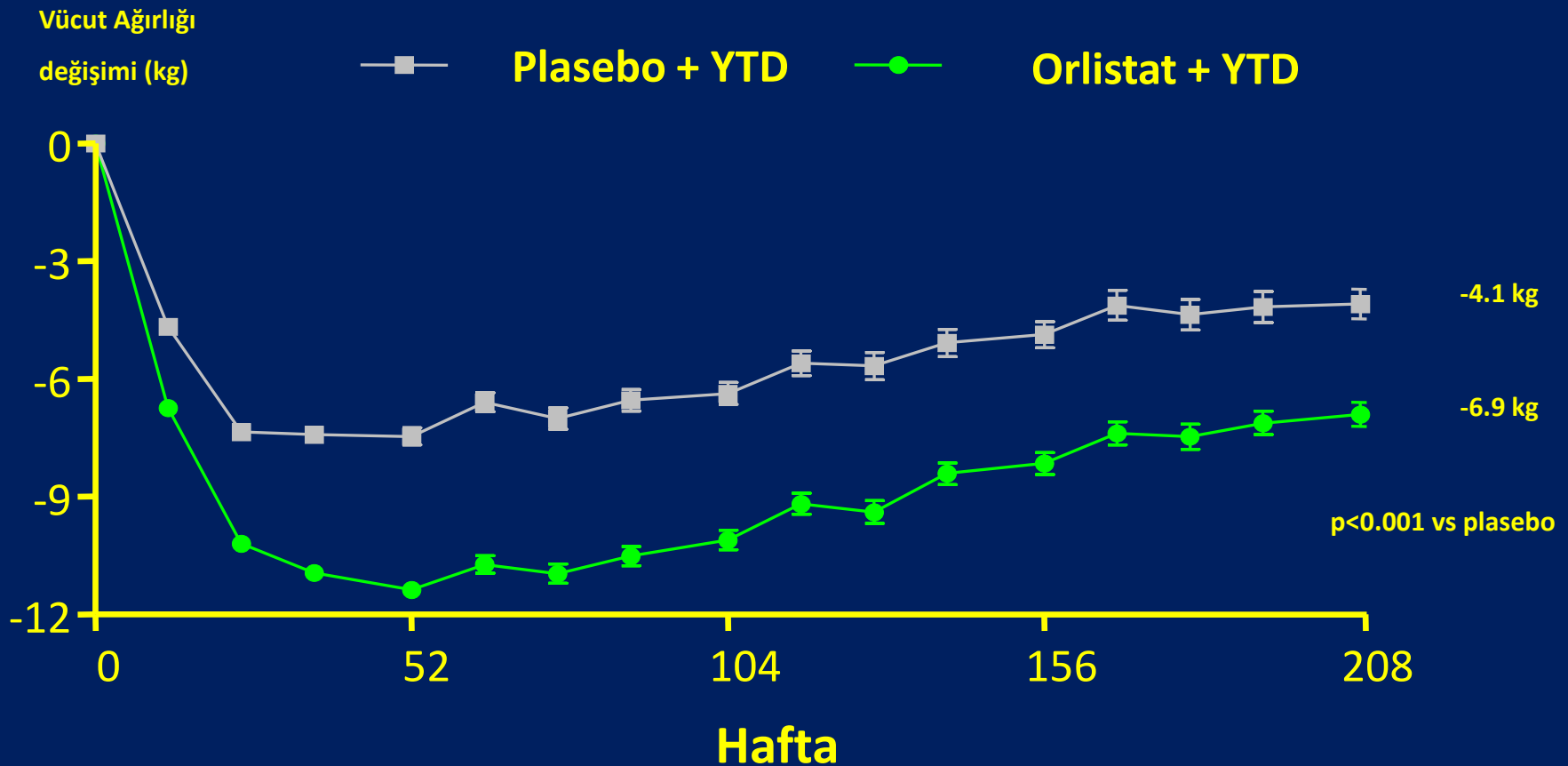
ORLISTAT



TG'lerin % 30'u emilmez

ORLISTAT

XENDOS (3304 hasta)



ORLISTAT

- ❖ UK Multimorbidity Study
 - ❖ 54 hafta izlem
 - ❖ Çift-kör, randomize plasebo kontrollü çalışma
 - ❖ Ortalama kilo kaybı:
 - Orlistat: %5.8
 - Plasebo: %2.3
- ($p < 0.0001$)

ORLISTAT

- ❖ Kardiyovasküler risk faktörlerinde azalma:
 - Sistolik kan basıncı ($p < 0.01$)
 - Diastolik kan basıncı ($p < 0.01$)
 - Total kolesterol ($p < 0.0001$)
 - LDL kolesterol ($p < 0.0001$)
 - Açlık glukoz düzeyi ($p < 0.05$)
 - Bel çevresi ($p < 0.0001$)

ORLISTAT

❖ Yan etkiler:

➤ Yağda eriyen vitaminlerde azalma

➤ Gastrointestinal yakınmalar

Diare, yağlı dışkılama, gaz...

➤ Bildirilen olgular

Ciddi karaciğer hasarı

Meme kanseri

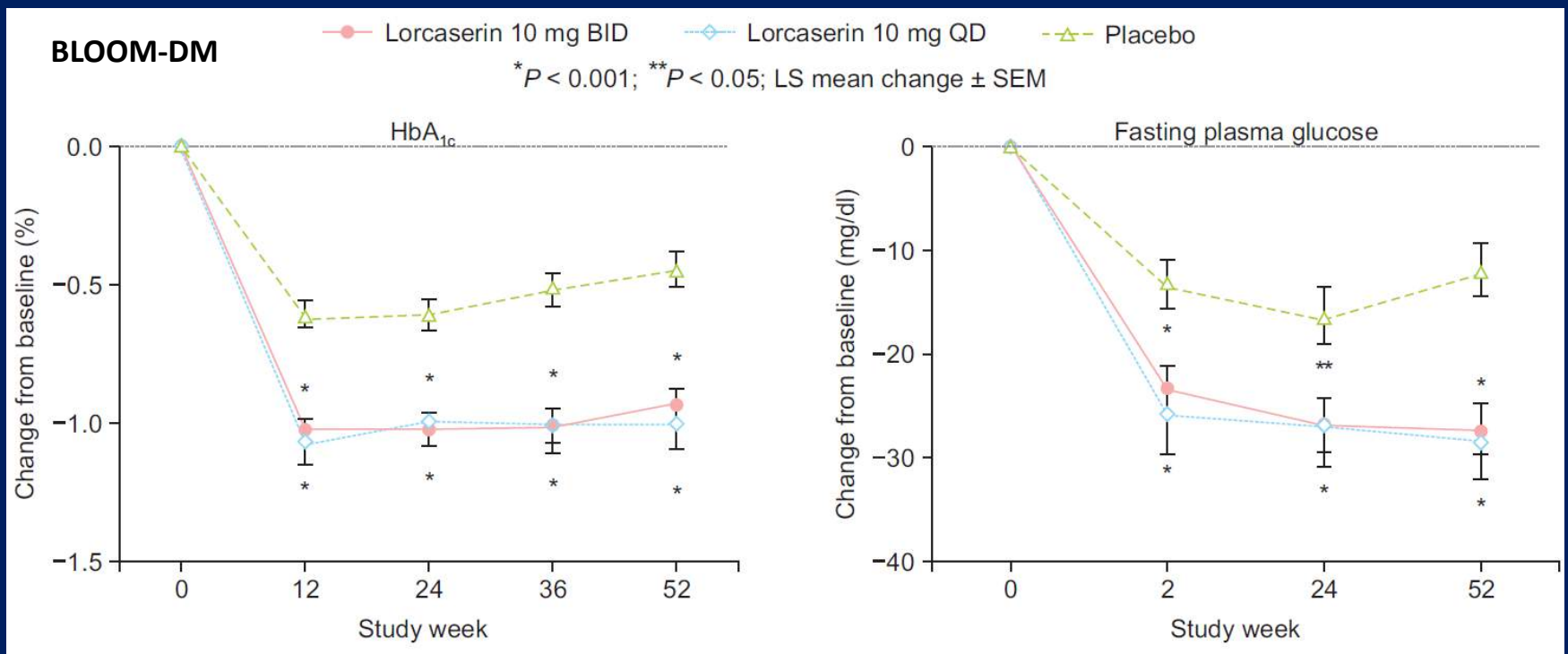
LORCASERİN

- ❖ Serotonin tip 2C reseptör agonisti
- ❖ BLOOM-DM çalışması:
- ❖ Kilo kaybı:
 - Lorcaserin: $\%4.5 \pm 0.35$
 - Plasebo: $\%1.5 \pm 0.36$
 - $P < 0.001$

LORCASERIN

❖ A1C: ($P < 0.001$)

➤ Lorcaserin: $\% 0.9 \pm 0.06$ Placebo: $\% 0.4 \pm 0.06$



LORCASERİN

❖ Yan etkiler:

➤ Baş ağrısı

➤ Bulantı

➤ Halsizlik

➤ Ağız kuruluđu

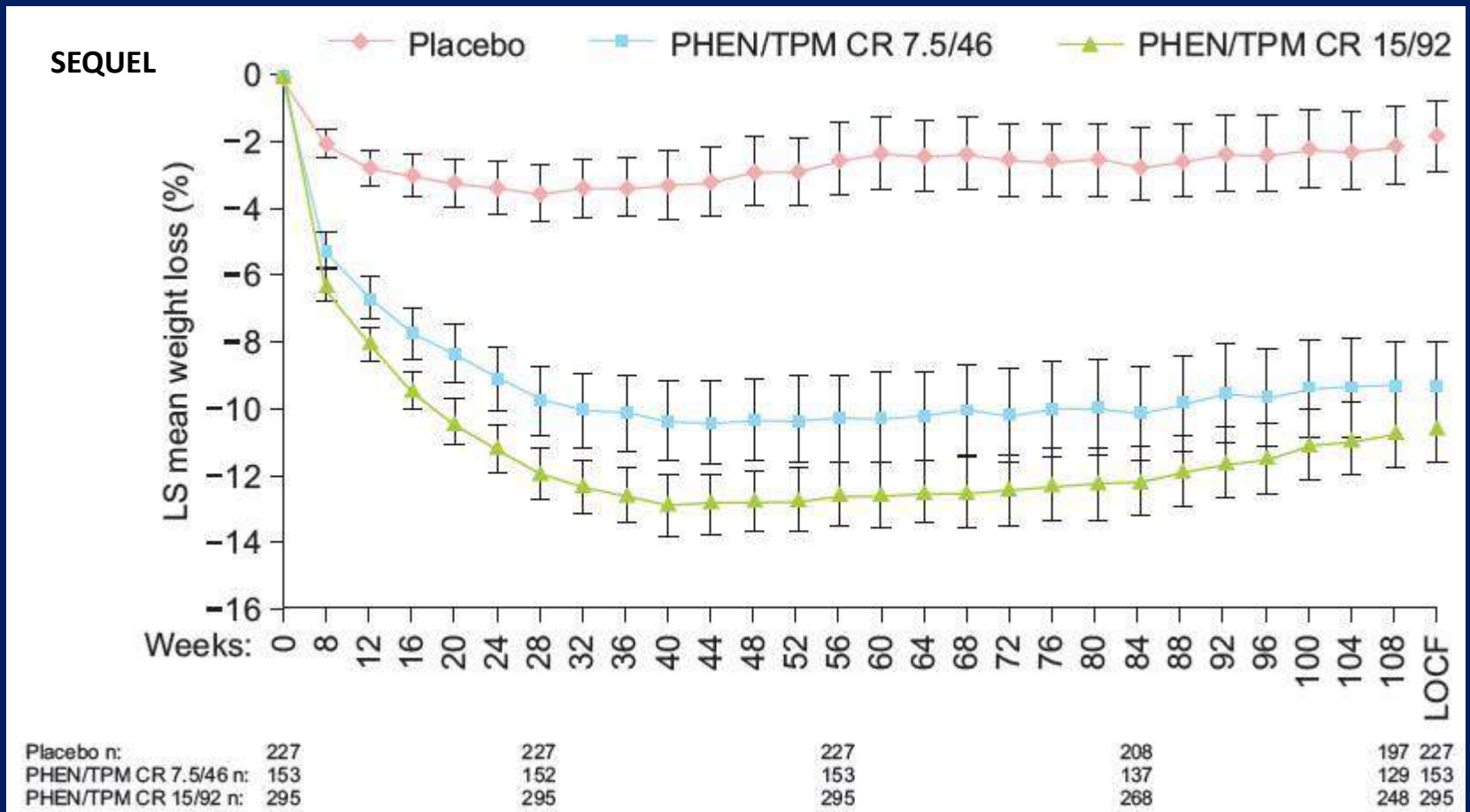
➤ Konstipasyon

✓ Valvulopati saptanmamış! (Faz 3 - 5200 hasta)

FENTERMIN/TOPIRAMAT CR

- ❖ Fentermin: Sempatomimetik
- ❖ Topiramate: Antikonvülzan
(GABA reseptörleri üzerine etki?)
- ❖ 2 yıllık izlem
- ❖ Ortalama %9.3 kilo kaybı
- ❖ Glisemik parametreler, kan basıncı,
HDL ve trigliseridler üzerine olumlu etki

FENTERMIN/TOPIRAMAT CR



FENTERMIN/TOPIRAMAT CR

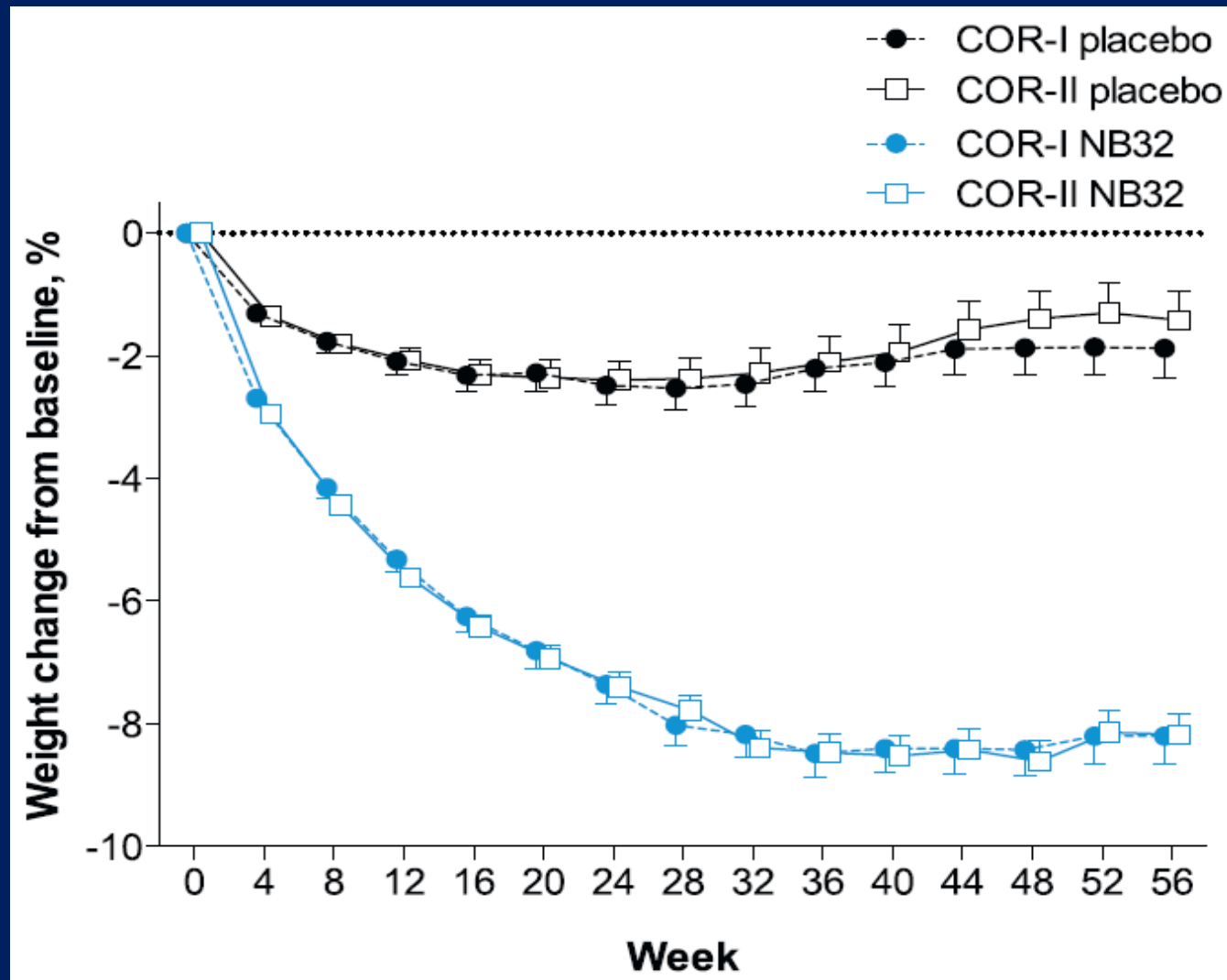
❖ Yan etkiler:

- Parestezi
- Baş dönmesi
- Uykusuzluk
- Tat değişikliği
- Ağız kuruluđu
- Konstipasyon

NALTREKSON/BUPROPION

- ❖ Naltrekson: Opioid antagonisti
- ❖ Bupropion: Antidepresan
(Dopamin ve noradrenalin geri alım inhibitörü ve nikotinik asetilkolin reseptörler antagonisti)
- ❖ Kilo kaybı (COR-1 çalışması):
 - Naltrekson/Bupropion: % 8.1
 - Plasebo: % 1.8
 - $P < 0.01$

NALTREKSON/BUPROPION

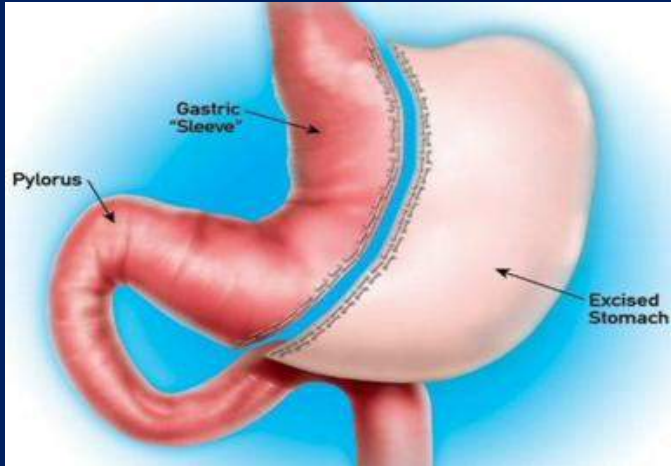


NALTREKSON/BUPROPİON

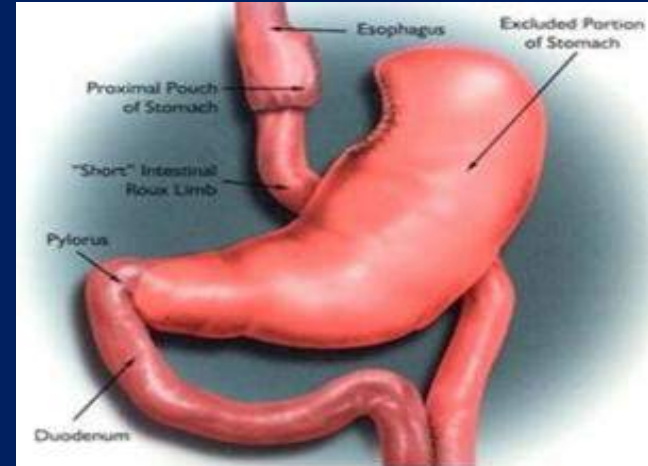
❖ Yan etkiler:

- Bulantı
- Baş ağrısı
- Konstipasyon
- Kusma
- Kan basıncında hafif artış

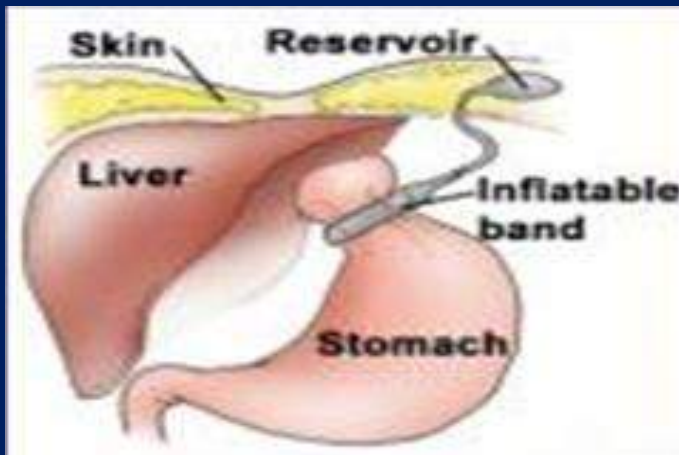
BARIATRİK CERRAHİ



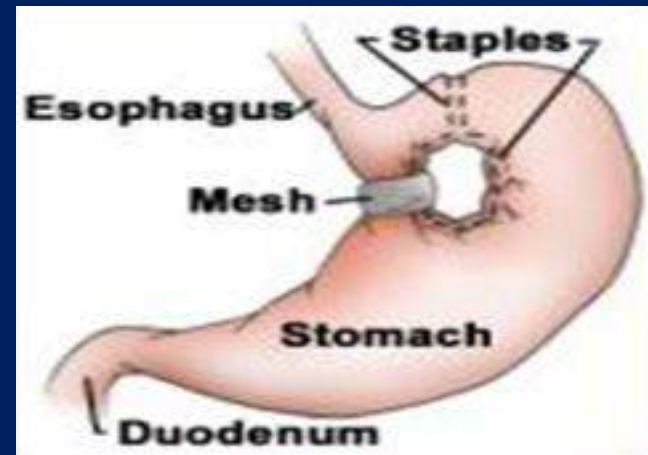
Vertikal Sleeve Gastrektomi



Roux-en-Y Gastrik Bypass



Gastrik Band



Vertikal Band Gastroplasti

BARIATRİK CERRAHİ

Lindegaard *et al. Diabetology & Metabolic Syndrome* (2015) 7:12
DOI 10.1186/s13098-015-0012-9



DIABETOLOGY &
METABOLIC SYNDROME

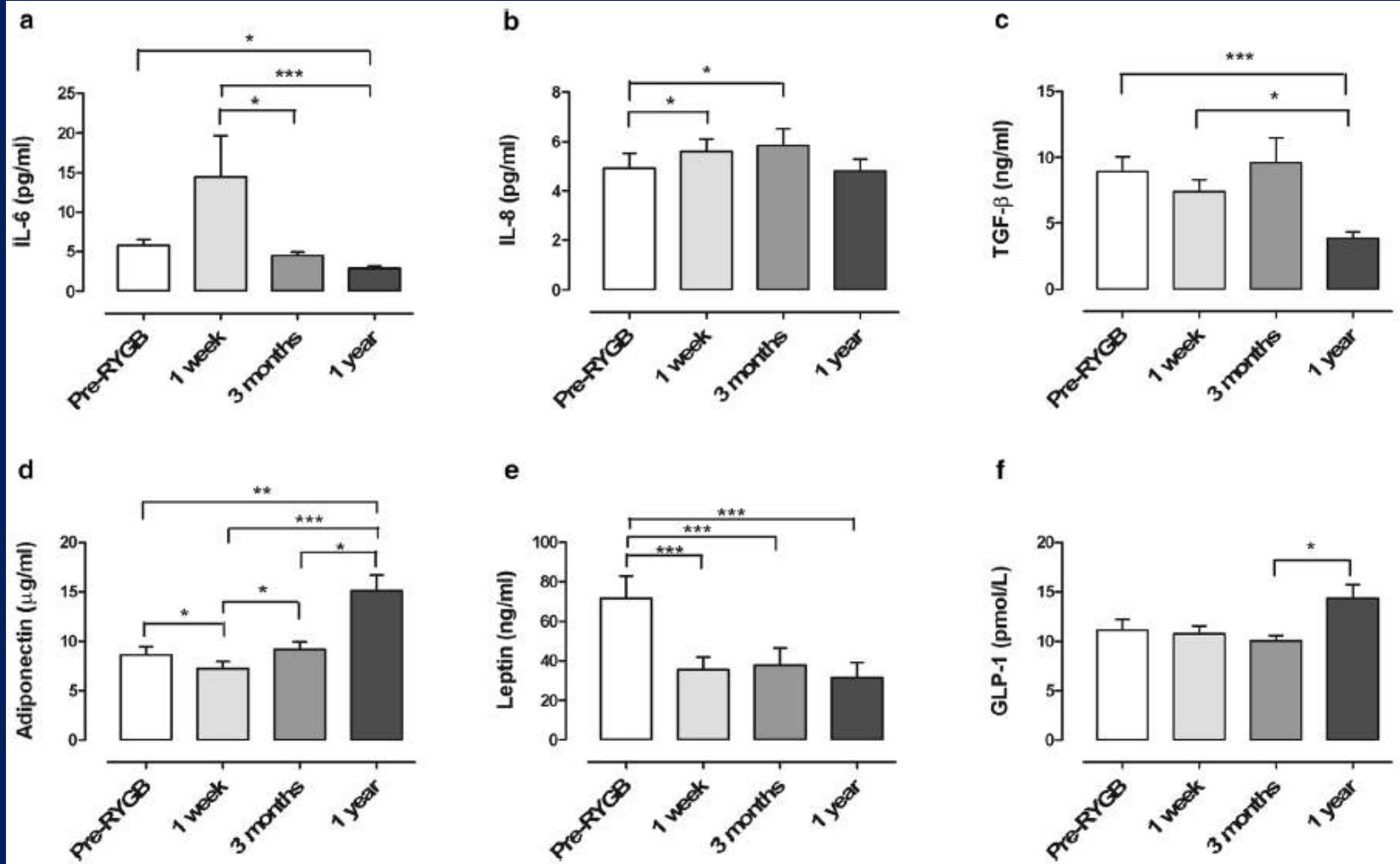
RESEARCH

Open Access

Effects of Roux-en-Y gastric bypass on fasting and postprandial inflammation-related parameters in obese subjects with normal glucose tolerance and in obese subjects with type 2 diabetes

Kirsten Katrine Lindegaard^{1,2*}, Nils Bruun Jorgensen³, Rasmus Just¹, Peter MH Heegaard² and Sten Madsbad³

BARIATRİK CERRAHİ



Sten Madsbad¹ and Jens J. Holst²

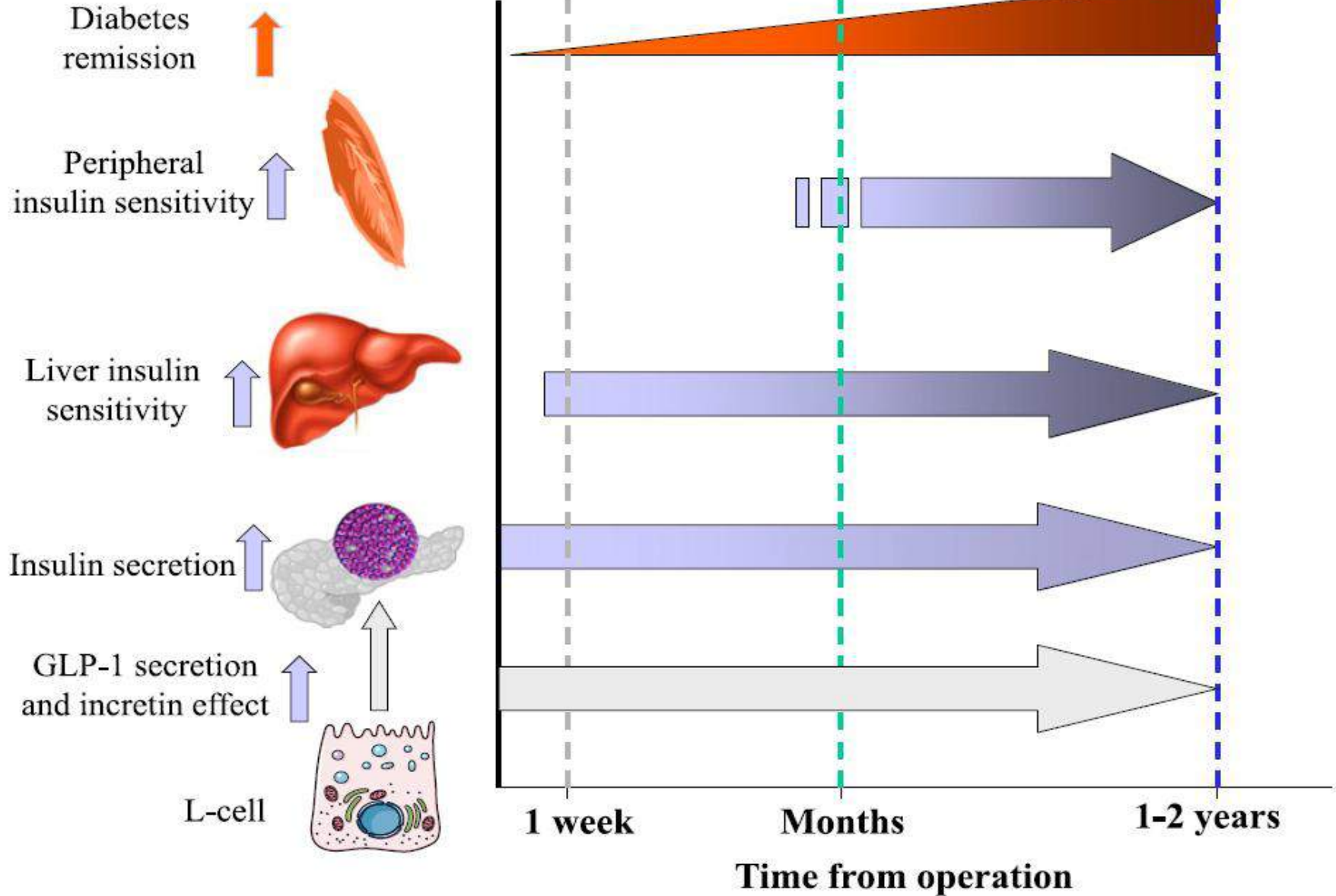


GLP-1 as a Mediator in the Remission of Type 2 Diabetes After Gastric Bypass and Sleeve Gastrectomy Surgery



Diabetes 2014;63:3172–3174 | DOI: 10.2337/db14-0935

Operation



BARIATRİK CERRAHİ



The Journal of Biomedical Research, 2015, 29(2):98-104

Review Article

JBR

Recent advances in bariatric/metabolic surgery: appraisal of clinical evidence

Wei-Jei Lee[✉], Abdullah Almulaifi

BARIATRİK CERRAHİ

Table 2 Variables and point values used for the computation of the age, body-mass index, c-peptide, duration of diabetes (ABCD) score.*

Variable	Points on ABCD index			
	Gastric bypass			
	<i>P</i> value			
	0	1	2	3
Age	≥40	< 40		
BMI (kg/m ²)	< 27	27–34.9	35–41.9	≥ 42
C-peptide (mmol/L)	< 2	2–2.9	3–4.9	≥ 5
Duration of DM (years)	> 8	4–8	1–3.9	< 1

BARIATRİK CERRAHİ

Table 3 Remission rate of T2DM according to ABCD score

ABCD score	Complete remission (HbA1C < 6%)	Partial remission (HbA1C < 6.5%)
0	5.9%	5.9%
1	5.0%	20.0%
2	26.3%	38.6%
3	31.9%	42.0%
4	52.5%	67.8%
5	55.4%	75.0%
6	61.7%	78.3%
7	77.0%	92.3%
8	85.2%	96.3%
9	87.1%	87.1%
10	93.3%	93.3%
Overall	52.2%	64.7%

BARIATRİK CERRAHİ

❖ Bariatrik cerrahi, VKİ>35 kg/m² olan tip 2 diyabetik erişkinlerde, özellikle diyabet ya da eşlik eden komorbiditelerin yaşam tarzı değişikliği ve farmakolojik tedavilerle kontrol altına alınmasında güçlük çekilen hastalarda düşünülebilir.

BARIATRIC SURGERY

Recommendations

- Bariatric surgery may be considered for adults with BMI >35 kg/m² and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. **B**
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m². **E**

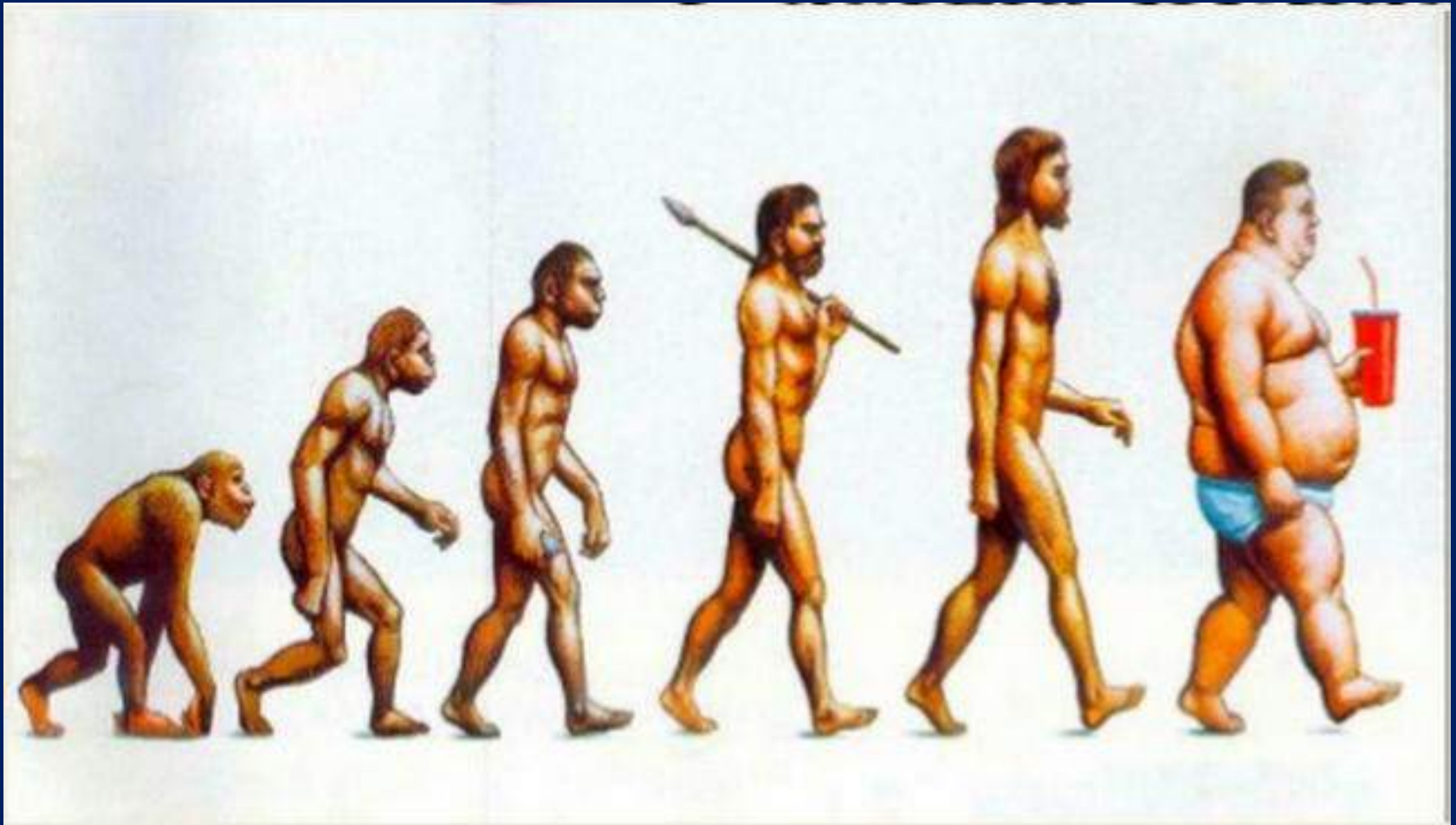
BARIATRİK CERRAHİ

- ❖ Bariatrik cerrahi uygulanan tip 2 diyabetiklerin yaşam boyu yaşam tarzı desteği ve medikal izleme gereksinimi vardır.
- ❖ Bazı çalışmalarda bariatrik cerrahinin VKİ 30-35 kg/m² olan tip 2 diyabetiklerde glisemik yararı gösterilmiş olmakla birlikte, genel olarak VKİ<35 kg/m² olan hastalarda cerrahi önerilmesi için yeterli kanıt yoktur.

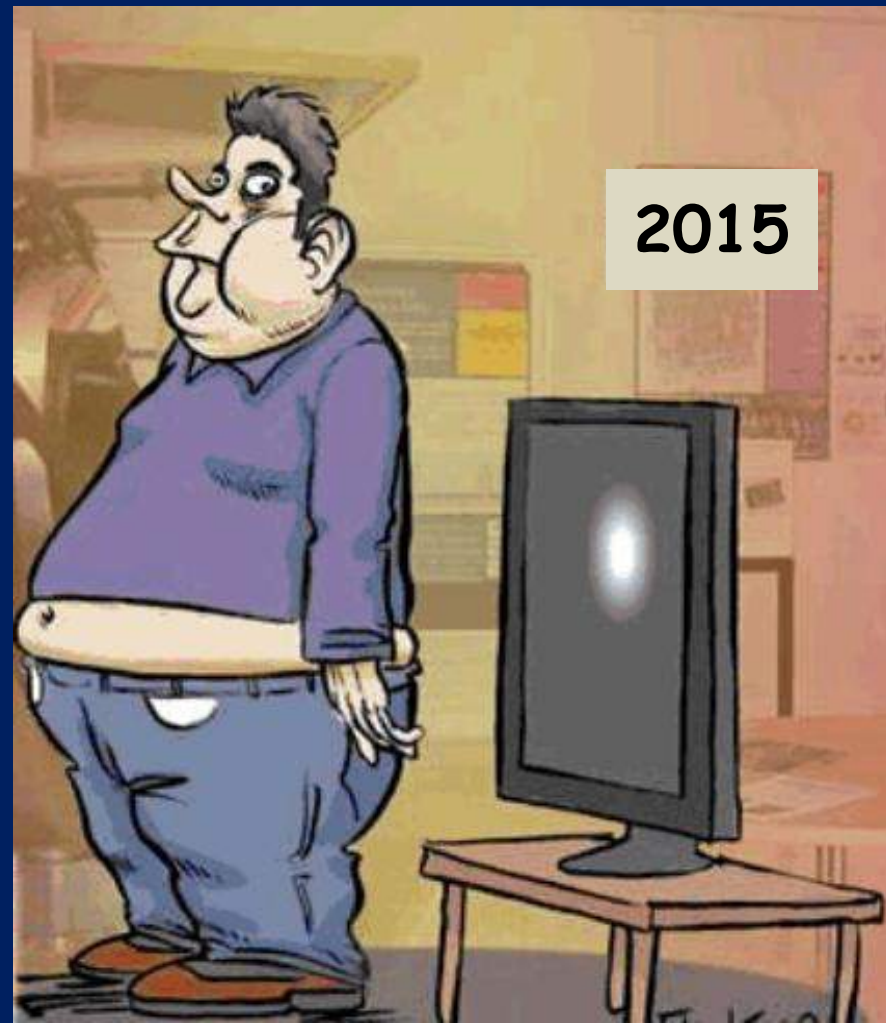
OLGU - 3

- TA: 130/80 mm Hg.
- Boy: 158 cm VA: 114 kg
- VKİ: 45.6 kg/m² Bel çevresi: 128 cm
- ❖ Vücut yağ oranı: %46.0
- ❖ Kullandığı ilaçlar:
 - Byetta 10 µg 2x1 Matofin XR 1000 mg 2x1
 - Cozaar 100 mg 1x1 Coraspin 100 mg 1x1 Thincal 3x1
- ❖ Laboratuvar:
 - AKŞ:105 mg/dl TKŞ:125 mg/dl A1C:%6.2
 - Mikroalbüminüri:35 mg/gün

ÖZET



OBEZİTE



OBEZİTENİN SONUÇLARI

FİZİKSEL

PSİKOLOJİK

SOSYAL

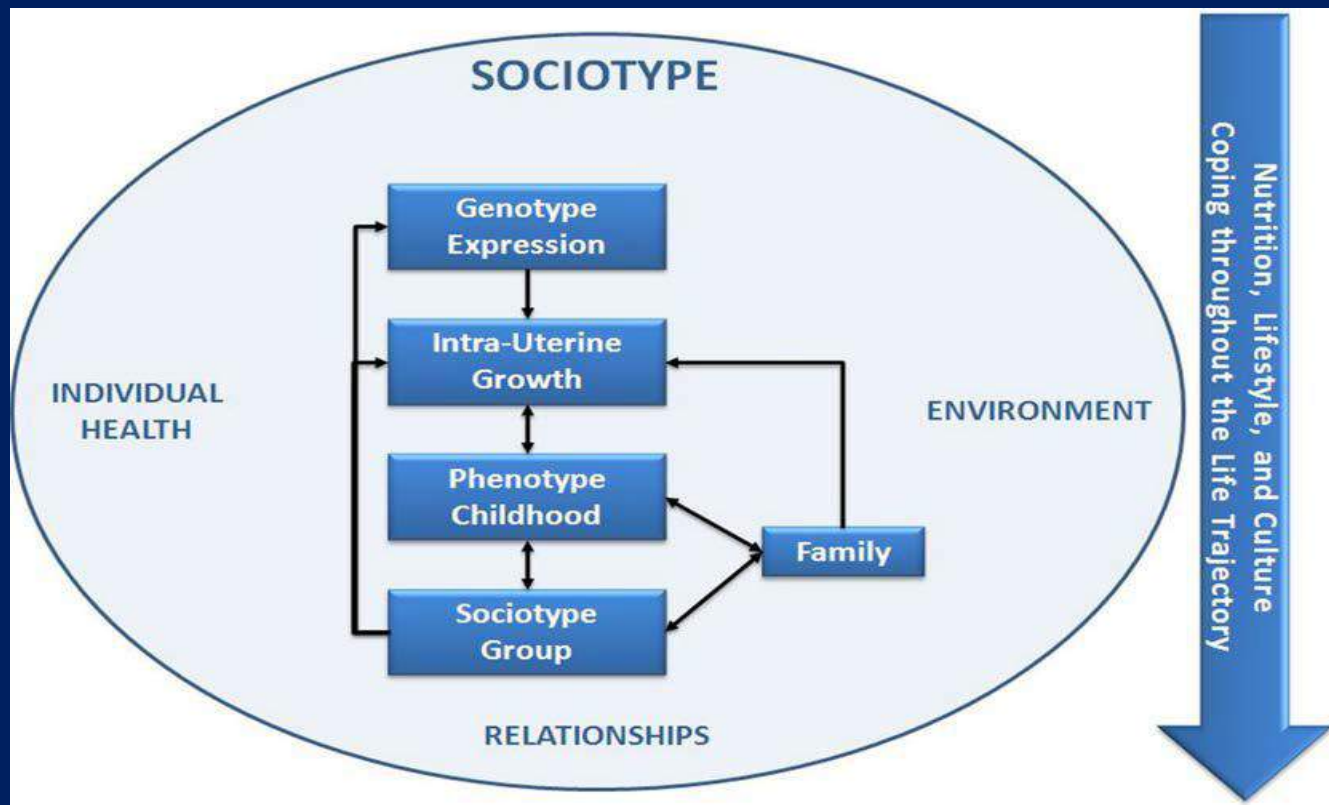
EKONOMİK



Tell Me What You Eat and I Will Tell You Your Sociotype: Coping with Diabesity

Elliot M. Berry, M.D., F.R.C.P.^{1*}, and Sabina De Geest, Ph.D., R.N., F.A.A.N., F.R.C.N.²

¹Braun School of Public Health, Faculty of Medicine, Hebrew University of Jerusalem, Israel; and
²Institute of Nursing Science, Faculty of Medicine, University of Basel, Switzerland



TEDAVİ



TEDAVİ



TEDAVİ



SONUÇ



TEŞEKKÜRLER