Simptomi, dijagnoza i lečenje metaboličkog sindroma

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Metabolički sindrom

- Višestruki faktor rizika uslovljen rezistencijom na insulin, a praćen patloškim naslagama i funkcijom masnog tkiva.

- Obuhva faktore rizika odgovorne za koronarno oboljenje srca, dijabetes i pojedine karcinome.

- U **Evropi** se i dalje, najčešće upotrebljava termin metabolički sindrom - MetS, dok se

- U **Severnoj Americi**, uglavnom koristi termin sindrom X ili sindrom insulinske rezistencije.

Metabolički sindrom (MeTS)

- Naziv za skup faktora rizika koji se javljaju zajedno i visok su rizik za pojavu kardiovaskularnih oboljenja, moždanog udara i dijabetesa tip2.

- **Prevalenca** u populaciji odraslih je 34%

- **2X** viši rizik za smrtni ishod usled kardijalnih komplikacia,
- **3X** veća verovatnoća za nastanak srčanog ili moždanog udara.
- **5x** viši rizik za razvoj dijabetesa.

Multiple Cardiometabolic Risk

AKA: Insulin Resistance Syndrome X; Dysmetabolic Syndrome; Multiple Metabolic Syndrome; Cardiometabolic Syndrome; The Deadly Quartet

1923: Kylin describes clustering of hypertension, gout, and hyperglycemia

1988: Reaven describes "Syndrome X" – hypertension, hyperglycemia, glucose intolerance, elevated triglycerides, and low HDL cholesterol

1998: WHO defines "metabolic syndrome" as clustering of hypertension, low HDL, hypertriglyceridemia, insulin resistance, glucose intolerance or type 2 diabetes, high waist-to-hip ratio, and microalbuminuria

2001: NCEP ATP III provides clinical definition of "metabolic syndrome"

Isomaa B, et al. *Diabetes Care.* 2001;24:683-689.
Grundy SM, et al. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation.* 2002;106:3143-3421.

Kriterijumi **Evropskog udruženja za istraživanje i smernice insulinske rezistencije (*European Group for the Study of Insulin Resistance Guidelines) za*** MetS podrazumevaju hiperinsulinemiju našte i dva ili više od ponuđenih kriterijuma:

- Glukoza našte ≥ 6,1 mmol/l ali ne osobe obolele od dijabetes melitusa
- Krvni pritisak ≥ 140/90 mmHg ili korišćenje antihipertenzivne terapije
- Trigliceridi > 2 mmol/l ili HDL holesterol < 1 mmol/l ili korišćenje hipolipemika
- Obim struk/kuk > 94 cm kod muškaraca ili > 80 cm kod žena

Prema definiciji **Međunarodnog udruženja za dijabetes (***International Diabetes Federation), MetS predstavlja centralnu gojaznost (obim struka) udruženu sa* još dva od navedenih kriterijuma:

- povišene vrednosti triglicerida u krvi (vrednosti veće od 1,7 mmol/l)
- snižen HDL holesterol (vrednosti manje od 1,03 mmol/l za populaciju muškaraca i vrednosti manje od 1,29 mmol/l za populaciju žena)
- povišene vrednsoti krvnog pritiska (sistolni > 130 mmHg, dijastolni > 85 mmHg)
- povišene vrednosti glikemije u krvi (vrednosti veće od 5,6 mmol/l) ili predhodno dijagnostifikovan dijabetes melitus tip 2.

U slučaju vrednosti glikemija iznad 5,6 mmol/l savetuje se test oralnog opterećenja glukozom (OGTT) ali nije neophodan za definisanje prisustva MS. Prema ovoj definiciji ukoliko je vrednost indeksa telesne mase (BMI) preko 30 kg/m² nije potrebno ni meriti obim struka.

Kriterijumi Američkog koledža za endokrinologiju (*American College of Endocrinology – ACE) za definiciju i dijagnozu MetS podrazumevaju:*

- Prisustvo ≥ 1 od ponuđenih kriterijuma:
  - dijagnoza kardiovaskularnih bolesti (KVB), hipertenzija, sindrom policističnih jajnika ili *acanthosis nigricans*
  - porodična anamneza za dijabetes melitus tip 2, hipertenziju ili KVB
  - anamnestički podaci o gestacionom dijabetesu ili intoleranciji na glukozu
  - pripadnici drugih rasa
  - sedelački način života
  - BMI > 25 kg/m² i/ili obim struka > 40 inča kod muškaraca, > 35 inča kod žena
  - starost > 40 godina
- Prisustvo ≥ 2 od ponuđenih kriterijuma:
  - trigliceridi > 150 mg/dl
  - HDL holesterol: muškarci < 40 mg/dl, žene < 50 mg/dl
  - krvni pritisak > 130/85 mmHg
  - glukoza našte 110 – 125 mg/dl ili OGTT 140 – 200 mg/dl

(dijabetes je isključen iz ACE kriterijuma za sindrom insulinske rezistencije (IRS)).

Nacionalni program za edukaciju o holesterolu Američkog udruženja kardiologa (*National Cholesterol Education Program) (NCEP) MetS* se definiše u okolnostima kada su prisutna najmanje **tri od pet** predloženih kriterijuma:

- **centralna gojaznost (obim struka ≥ 102 cm u populaciji muškaraca i ≥ 88cm u populaciji žena)**
- **dislipidemija (trigliceridi ≥ 1,7 mmol/l**
- **dislipidemija (HDL < 1,03 mmol/l kod muškaraca i < 1,29 mmol/l kod žena)**
- **vrednosti sistolnog krvnog pritiska veće od 130 mm Hg i/ili dijastolnog krvnog pritiska veće od 85 mmHg**
- **vrednosti glikemija našte više od 6,1 mmol/l,**

Definitions of the Metabolic Syndrome

Components	NCEP ATP III ≥3	IDF WC + ≥2	AHA-NHLBI ≥3
WC, cm	>102 (m) >88 (f)	Europid ≥94 (m) ≥80 (f) S. Asian* ≥90 (m) ≥80 (f) Japanese ≥85 (m) ≥90 (f)	>102 (m) >88 (f)‡
TG, mg/dL	≥150	≥150†	≥150†
HDL-C, mg/dL	<40 (m) <50 (f)	<40 (m) <50 (f)†	<40 (m) <50 (f)†
BP, mm/Hg	≥130/≥85	≥130 OR ≥85†	≥130 OR ≥85†
FPG, mg/dL	≥110	≥110†	≥110†

* Based on a Chinese, Malay and Asian-Indian population

† Or on drug treatment

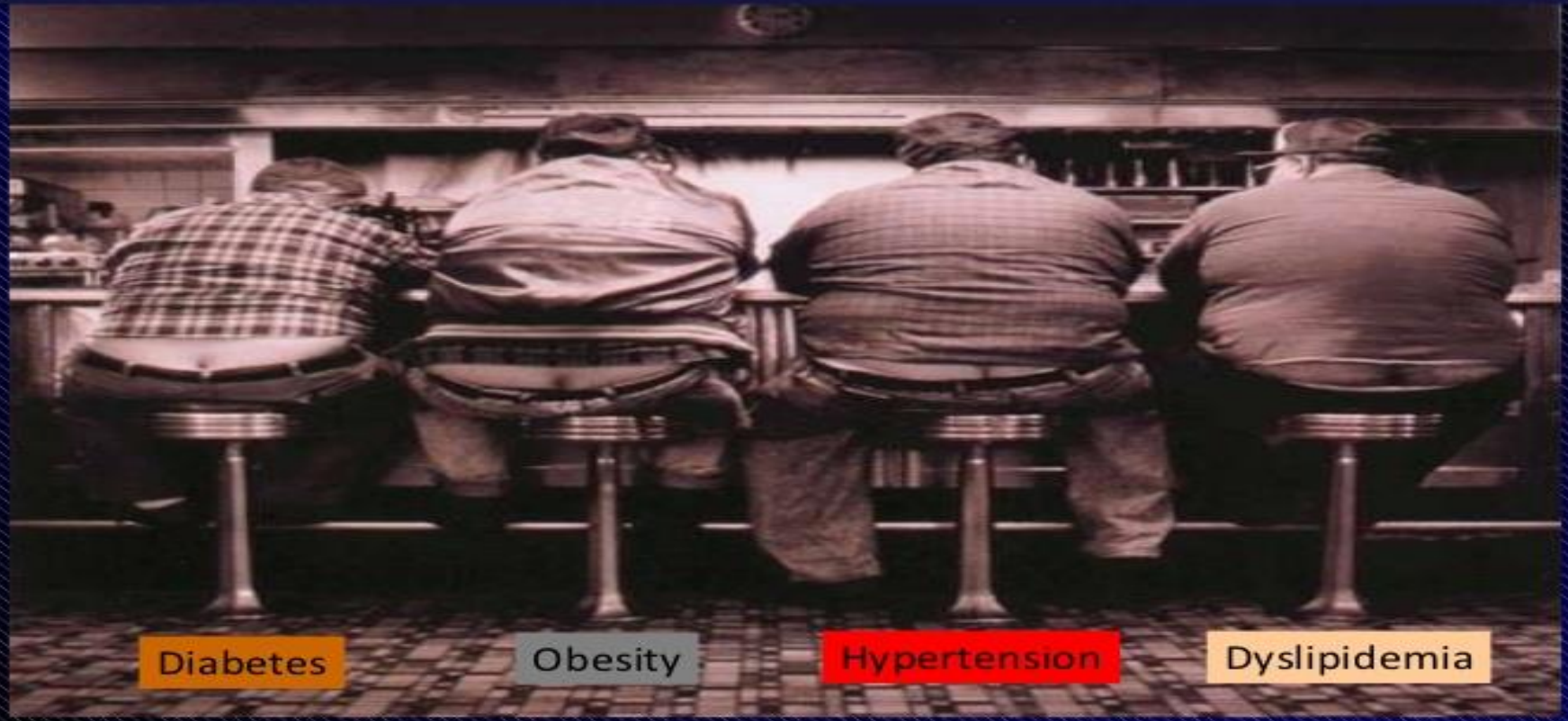
‡ ≥90cm (m) ≥80cm (f) for Asian Americans

Metabolic syndrome ICD-9-CM code: 277.7

National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). Circulation. 2002;106:3143-3421.
International Diabetes Federation 2005.
Grundy SM, et al. Circulation. 2005;112:2735-2752.

Šta uzrokuje MeTS?

ED: BAROMETER OF MEN'S HEALTH:
The Deadly Quartet

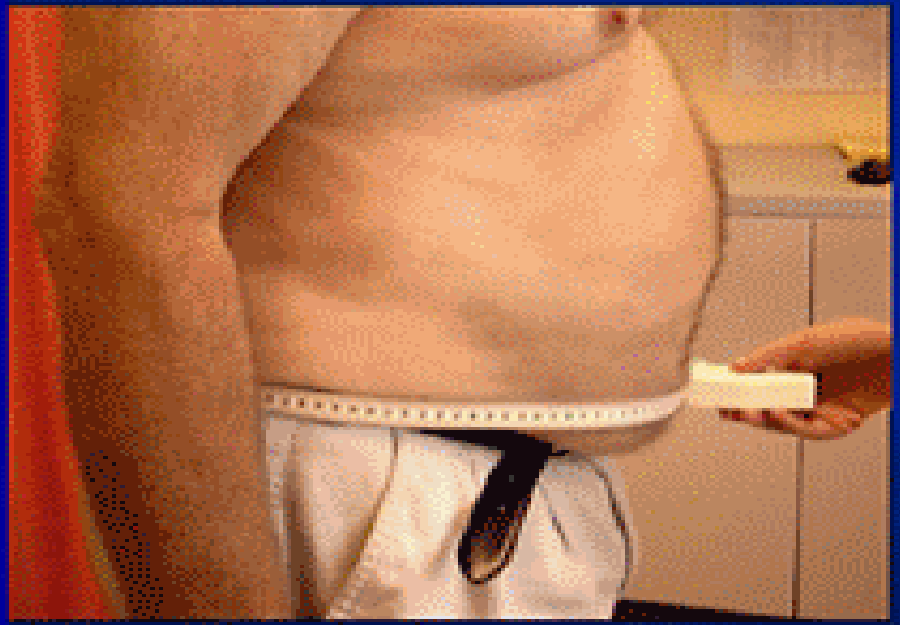


The Deadly Quartet

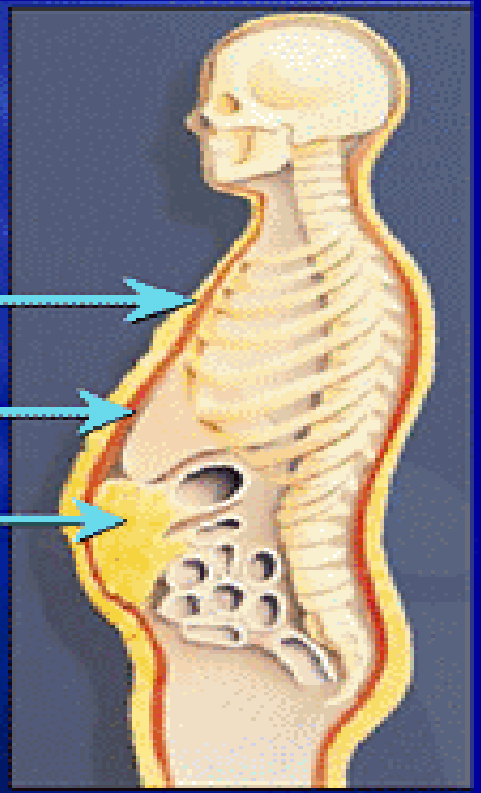
Opara JU. *South Med J*. 1997;30:1162–1168.


© Wadsworth – Thomson Learning

Abdominal Adiposity: The Critical Adipose Depot



Is this where you measure?



Courtesy of M. Davidson, MD

Abdominal Obesity Criteria for among Specific Populations

Population	Men	Women
Europid	≥94cm	≥80 cm
Caucasian	≥94 cm (increased risk) ≥102 (still higher risk)	≥80 (increased risk) ≥88 (still higher risk)
Europe and North America	≥102 cm	≥88 cm
Middle east, Mediterranean, Sub-Saharan Africa	≥94 cm	≥80 cm
South Asians and other Asians Ethnic central and South Americans	≥90 cm	≥80 cm
Japanese	≥ 85cm	≥90 cm
Chinese	≥ 85 cm	≥80 cm

Alberi KGMM. Circulation 2009;120:1640-45

Metabilički sindrom - Da li nam je potreban još jedan termin?

- Faktor rizika za:
  - *Diabetes melitus* tip II
  - Kardiovaskularna oboljenja

Terapijski ciljevi

- Korekcija aterogenih lipidemija
- Korekcija hipertenzije
- Primena aspirina za sniženje protrombogene aktivnosti
- Korekcija insulinske rezistencije
  - Redukcija TM
  - Povećana fizička aktivnost
- Kontrola DM2 ako je prisutan

Guidelines

USA

- **ACC** - American College of Cardiology
- **AH**A - American Heart Association
- **NLA** - National Lipid Association

EU

- **ESC** – European Society of Cardiology
- **EAS** – European Atherosclerosis Society

What's changed ? Yet another new ESC lipid guidelines

European Heart Journal (2016) 37, 2999–3058
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Evolution of Lipid Guidelines (cont)

2013 ACC/AHA Guidelines[a]

Category	Recommendation
Clinical ASCVD	High-intensity statin
Primary LDL-C≥190 mg/dL	High-intensity statin Combination therapy if 50% LDL-C lowering not reached
Diabetes (type 1 or 2) without clinical ASCVD, but LDL-C = 70 to 189 mg/dL	Low risk: moderate-intensity statin High risk: high-intensity statin
None of the above, but estimated 10-y risk ≥7.5%	Moderate- to high-intensity statin

2016 ESC/EAS Guidelines[b]

Category	Recommendation
CVD	Very high CV risk: LDL-C<70 mg/dL or 50% reduction High CV risk: <100 mg/dL or 50% reduction Low or moderate risk: <115 mg/dL
Familial dyslipidemia (FH, FCH)	LDL-C<100 mg/dL (<70 mg/dL in presence of CVD) or maximal LDL-C reduction with drug combination and LDL apheresis
T2D or type 1 with target organ damage	LDL-C<70 mg/dL or 50% reduction in LDL-C LDL-C<100 mg/dL in absence of additional risk factors
None of the above but estimate 10-y risk (SCORE)	Very high risk (SCORE>10%) LDL-C<70 mg/dL or 50% reduction; High risk (SCORE 5% to 10%) LDL-C<100 mg/dL or 50% reduction; Moderate risk (SCORE 1% to 5%) LDL-C<155 mg/dL

a. Stone N, et al. *J Am Coll Cardiol.* 2014;63:2889-2934; b. Catapano A, et al. *Eur Heart J.* 2016;37:2999-3058.

Evolution of Lipid Guidelines (cont)

2015 NLA Guidelines[a]

Category	Recommendation
Very High Risk Clinical ASCVD Diabetes with ≥2 major ASCVD risk factors or end-organ damage*	Moderate- or high-intensity statin, irrespective of baseline atherogenic cholesterol levels
High Risk Primary LDL-C≥190 mg/dL Diabetes with 0 to 1 major ASCVD risk factors CKD stage 3B or 4 ≥3 major ASCVD risk factors	Lifestyle therapy + drug therapy in those whose atherogenic cholesterol levels are higher than goal: Non-HDL-C<130 mg/dL and LDL-C<100 mg/dL

2016 & 2017 ACC/AHA Guidelines[b,c]

Category	Recommendation
Clinical ASCVD (≥21 years old)	≤75 years old: high-intensity statin† >75 years old: moderate-intensity statin
Primary LDL-C≥190 mg/dL (≥21 years old)	High-intensity statin† to achieve ≥50% reduction; consider combination with non-statin for further LDL-C reduction Screen relatives to identify a need for treatment
LDL-C 70-189 mg/dL without ASCVD, but with diabetes (40 to 75 years old)	Moderate-intensity statin; consider high-intensity statin if 10-year ASCVD risk ≥7.5%
LDL-C 70-189 mg/dL without diabetes, with estimated 10-year risk for ASCVD of ≥7.5% (40 to 75 years old)	10-year ASCVD risk: ≥7.5%: moderate- or high-intensity statin ≥5 to <7.5%: moderate-intensity statin <5% (or <40 to >75 years old): based on presence of other high-risk features. Before statin initiation for primary prevention, discuss options with patient

*End-organ damage indicated by increased albumin-to-creatinine ratio (≥30 mg/g), CKD (eGFR < 60 mL/min/1.73 m^2), or retinopathy.
†Or moderate-intensity statin if not a candidate for high-intensity statin due to safety concerns).
a. Jacobson T, et al. *J Clin Lipidol.* 2015;9:129-169; b. Lloyd-Jones D, et al. *JACC.* 2016;68:92-125; c. Lloyd-Jones D, et al. *JACC.* 2017;70:1785-1822.

Evolution of Lipid Guidelines (cont)

2017 ESC/EAS Recommendations in Patients with Acute MI

Risk category	Recommendation
High-intensity statin treatment	• Recommended in all patients with AMI* • Start as early as possible after discharge, for adherence and early and sustained clinical benefits • Use highest tolerated dose
Low-intensity statin treatment	Patients with increased risk of AEs from statins (eg, elderly, hepatic or renal impairment, previous AE, or potential DDI with essential concomitant therapy
Statin intolerance	Consider treatment with ezetimibe
Non-statin treatment (PCSK9 inhibitors)	Consider for selected high-risk patients who do not reach treatment targets after STEMI despite the maximum tolerated dose of statin

*Irrespective of cholesterol concentration at presentation.
Ibanez B, et al. *Eur Heart J.* 2017;00:1-66.

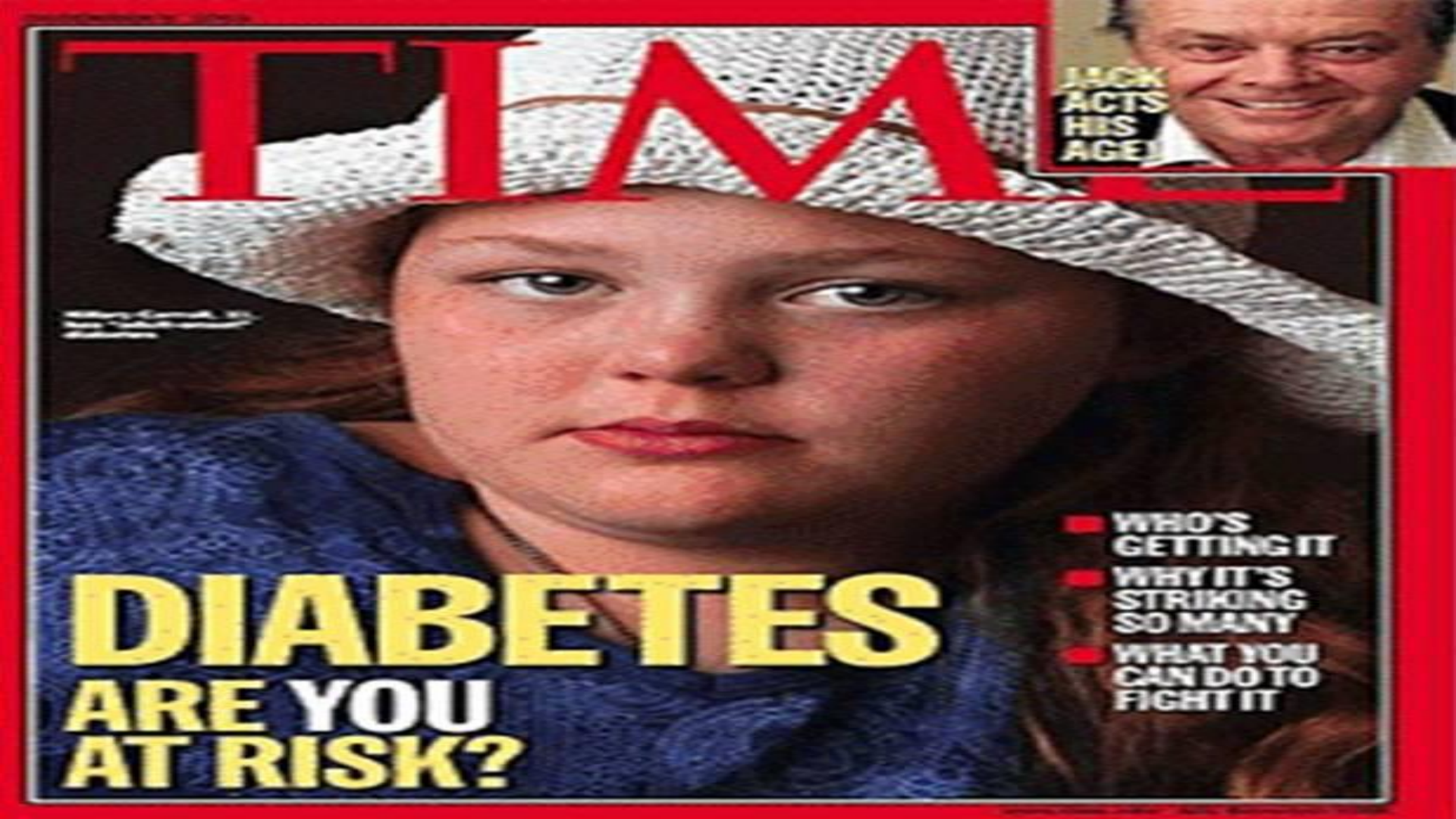
Evolution of Lipid Guidelines (cont)

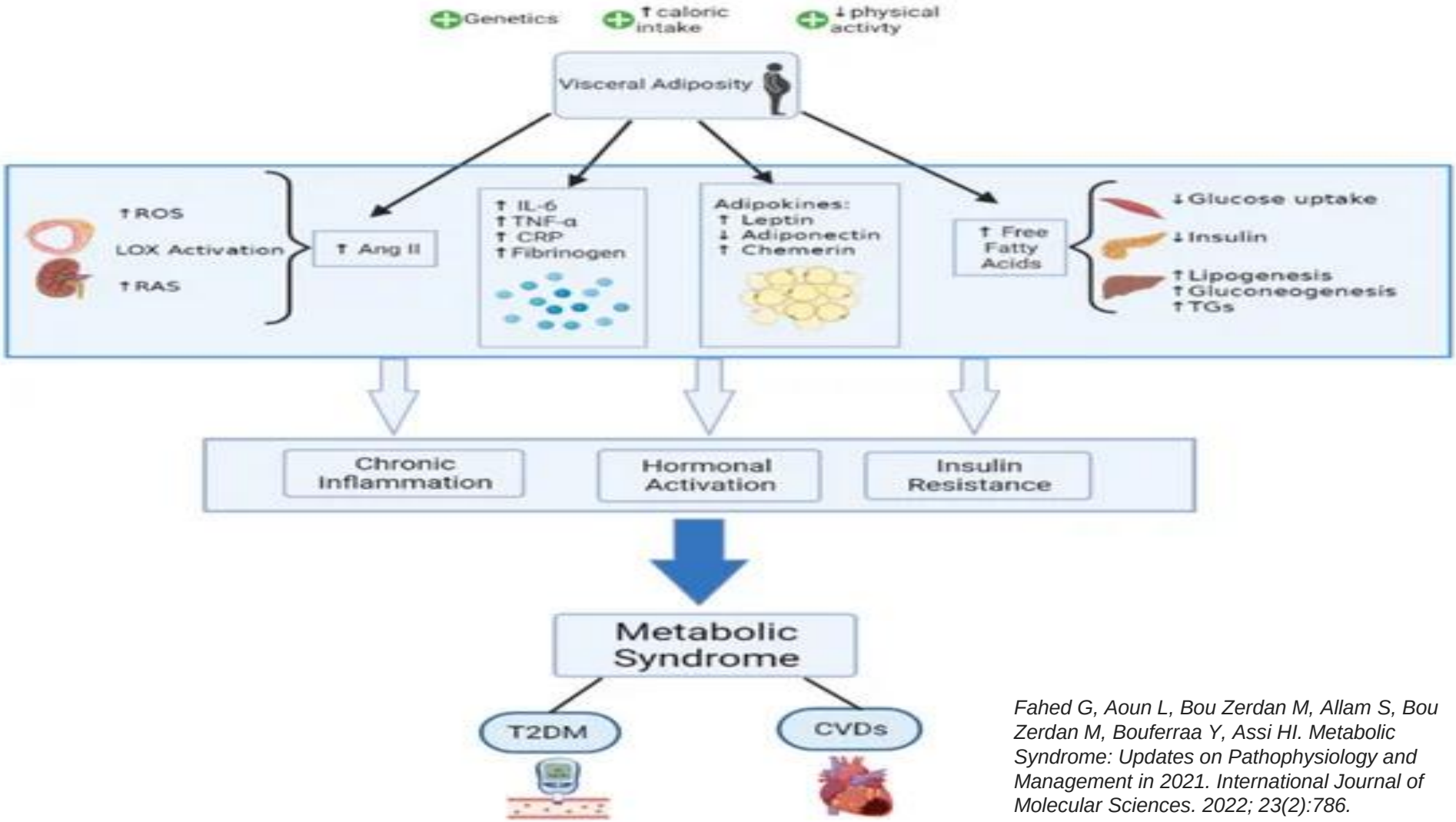
2017 AACE/ACE Guidelines: ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10 y risk (Framingham)	Treatment Goals (mg/dL)		
		LDL-C	Non-HDL-C	ApoB
Extreme risk	• Progressive ASCVD including unstable angina in patients after achieving an LDL-C<70 mg/dL • Established clinical CVD in patients with DM, CKD 3/4, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10 y risk >20% • Diabetes or CKD 3/4 with 1 or more risk factor(s) • HeFH	<70	<100	<80
High risk	• ≥2 risk factors and 10 y risk 10% to 20% • Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	• ≤2 risk factors and 10-y risk <10%	<100	<130	<90
Low risk	• 0 risk factors	<130	<160	NR

Risk factors: high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family Hx CAD (in male, first-degree relative <55 years; in female, first-degree relative <65 years), CKD stage 3/4, evidence of coronary artery calcification, age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

Jellinger P, et al. *Endocr Pract* 2017;23:479-497. Garber A, et al. *Endocr Pract* 2017;23:207-238.


TIME
JACK ACTS HIS AGE!
DIABETES
ARE YOU AT RISK?
WHO'S GETTING IT
WHY IT'S STRIKING SO MANY
WHAT YOU CAN DO TO FIGHT IT



Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, Assi HI. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. International Journal of Molecular Sciences. 2022; 23(2):786.

Metabolic Risk Factors

CVD

Obesity

↑Calories

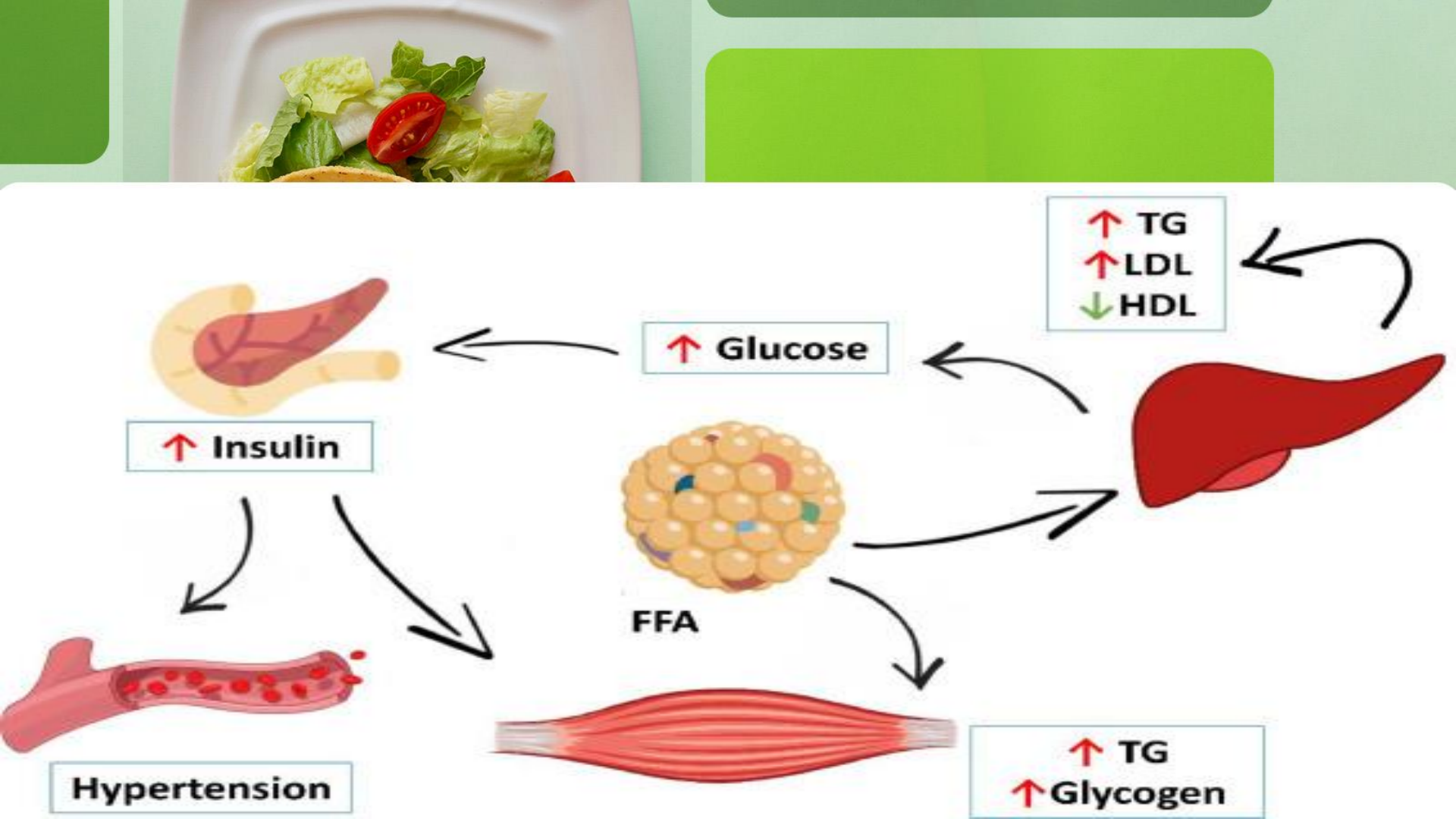
Smoking

↓Activity

↓Sleep

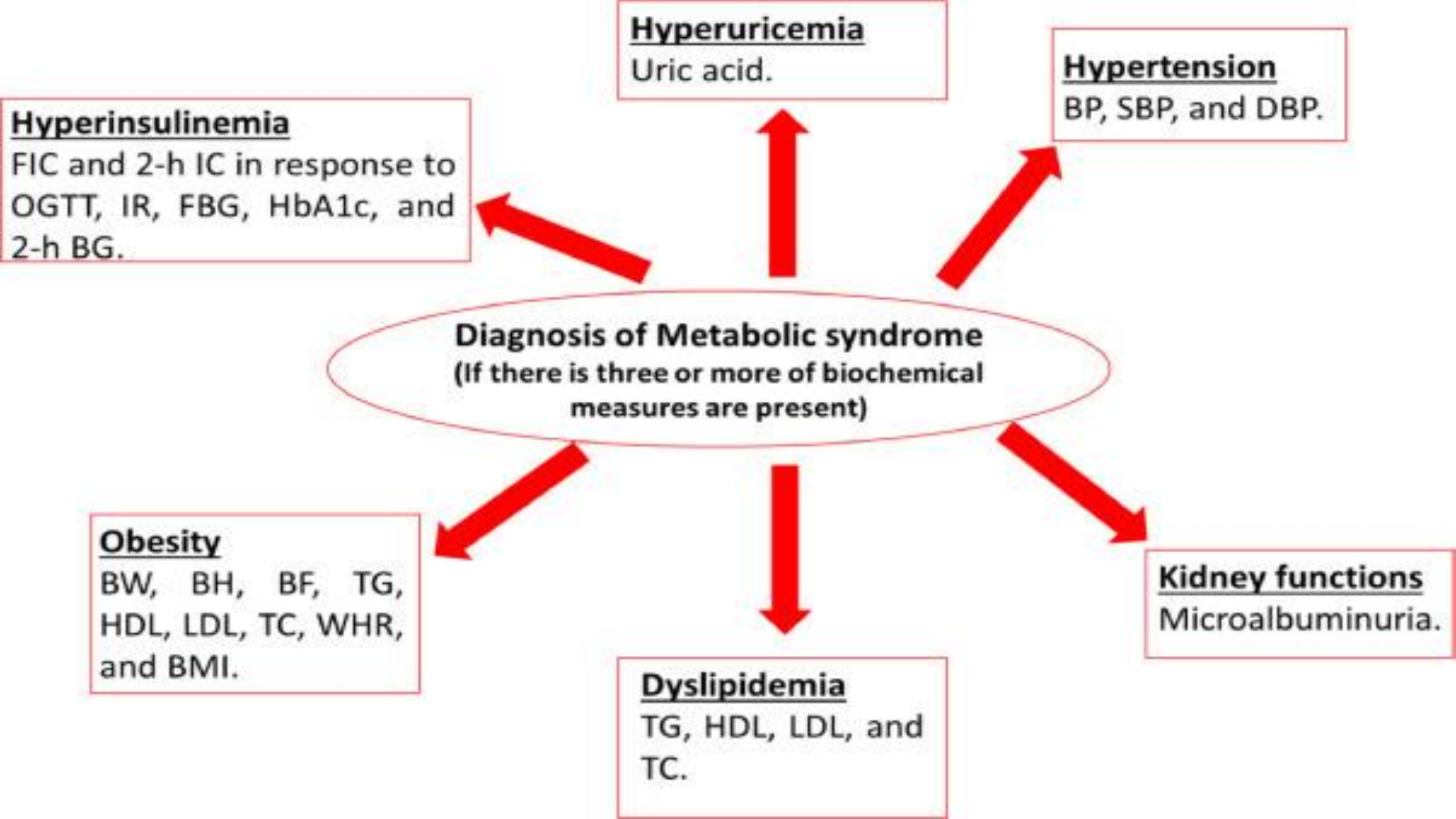
Stress

Diabetes


↑ TG
↑ LDL
↓ HDL
↑ Glucose
↑ Insulin
FFA
Hypertension
↑ TG
↑ Glycogen

Causes of Metabolic Syndrome

- Genetic mutations
- Inflammation
- Insulin resistance
- Obesity and lack of physical activity
- Hypertension


Hyperuricemia
Uric acid.
Hypertension
BP, SBP, and DBP.
Hyperinsulinemia
FIC and 2-h IC in response to OGTT, IR, FBG, HbA1c, and 2-h BG.
Diagnosis of Metabolic syndrome
(If there is three or more of biochemical measures are present)
Obesity
BW, BH, BF, TG, HDL, LDL, TC, WHR, and BMI.
Dyslipidemia
TG, HDL, LDL, and TC.
Kidney functions
Microalbuminuria.

ORIGINAL ARTICLE

Diabetes Care. 2004 May 1; 27(5):1047-1053.

Global Prevalence of Diabetes

Estimates for the year 2000 and projections for 2030

SARAH WILD, MB BCHIR, PHD[1]
GOJKA ROGLIC, MD[2]
ANDERS GREEN, MD, PHD, DR MED SCI[3]
RICHARD SICREE, MBBS, MPH[4]
HILARY KING, MD, DSC[3]

OBJECTIVE — The goal of this study was to estimate the prevalence of diabetes and the number of people of all ages with diabetes for years 2000 and 2030.

RESEARCH DESIGN AND METHODS — Data on diabetes prevalence by age and sex from a limited number of countries were extrapolated to all 191 World Health Organization member states and applied to United Nations' population estimates for 2000 and 2030. Urban and rural populations were considered separately for developing countries.

RESULTS — The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age.

CONCLUSIONS — These findings indicate that the "diabetes epidemic" will continue even if levels of obesity remain constant. Given the increasing prevalence of obesity, it is likely that these figures provide an underestimate of future diabetes prevalence.

in 1990 (2) using newer data and different methods for estimating age-specific prevalence. As before, the estimates are based on demographic changes alone with the conservative assumption that other risk factor levels such as obesity and physical activity remain constant (in developed countries) or are accounted for by urbanization (in less developed countries). The current estimates include all age-groups, and age-specific data are presented (online appendix [available at http://care.diabetesjournals.org]) to allow comparison with previous estimates that were for adults only (2). As most data sources do not distinguish between type 1 and type 2 diabetes in adults, it is not possible to present data separately for subtypes of diabetes.

RESEARCH DESIGN AND METHODS

— Diabetes prevalence data for adults (≥20 years of age) were

NEDOSTACI U TIP 2 DM

TEORIJA JEDNOG HORMONA

NEDOSTATAK INSULINA

TEORIJA DVA HORMONA

NEDOSTATAK INSULINA + **VIŠAK GLUKAGONA**

TEORIJA TRI HORMONA

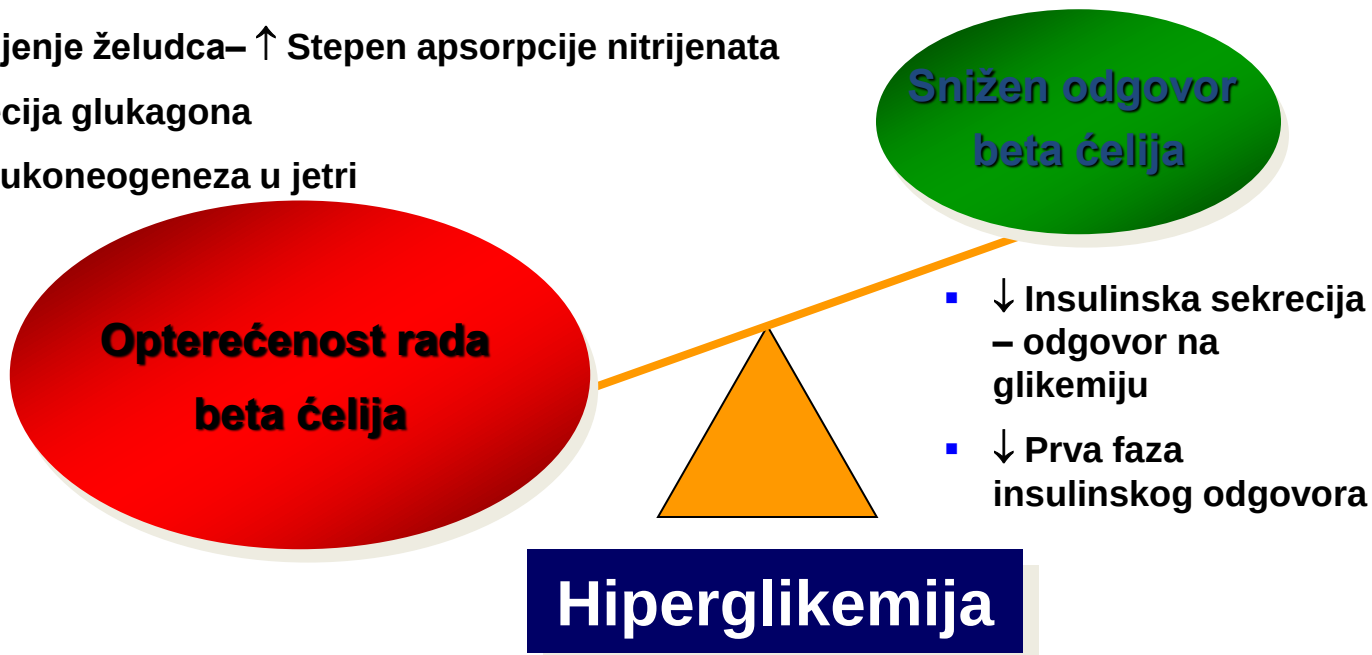
NEDOSTATAK INSULINA + **VIŠAK GLUKAGONA** + **SNIŽENI INKRETINI**

“ZLOSUTNI OKTET”

The ominous octet

Patogeneza Tip 2 dijabetesa
Neuravnoteženost optrerećenja i odgovora beta ćelija

- ↑ Insulinska rezistencija
  - Gojaznost
- ↑ Unos hrane
- ↑ Pražnjenje želudca– ↑ Stepen apsorpcije nitrijenata
- ↑ Sekrecija glukagona
  - ↑ Glukoneogeneza u jetri



KONCETRACIJA GLUKOZE U KRVI JE ZNAČAJNO JE DEFINISANA FUNKCIJOM BETA ĆELIJA

- FUNKCIJA BETA ĆELIJA
  - Sinteza insulina
  - Sekrecija insulina
- Funkcionalni kapacitet beta ćelija
  - Masa beta ćelija*(cell turnover, neogenesis*)
  - Prva faza/druga faza oslobadjanja insulina
  - Formiranje insulina (proinsulin do insulina)
  - Senzitivnost na glukozu
- Funkcionalno opterećenje beta ćelija
  - Opterećenje glukozom (ishrana, gastrično pražnjenje)
  - Stvaranje glukoze u jetri (glikoliza, glukoneogeneza)
  - Periferno preuzimanje glukoze (senzitivnost na insulin, fizička aktivnost)

“Zlosutni oktet”

Ralph A. DeFronzo. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes 2009 Apr; 58(4): 773-795.

1. Skeletni mišići – insulinska rezistencija, sniženo preuzimanje glukoze;
2. Jetra – insulinska rezistencija, glukoneogeneza;
3. Pankreas – nedostatak insulina, oštećena I faza lučenja insulina sa progresivnim slabljenjem beta ćelija;
4. Masno tkivo – insulinska rezistencija, oslobadjanje slobodnih masnih kiselina i “lipotoksičnost;
5. Pankreas – povećano lučenje glukagona u alfa ćelijama;
6. Snižen nivo inkretina i/ili snižena senzitivnost na inkretine;
7. CNS – neadekvatan odgovor na “sitost” po unosu glukoze;
8. Bubrezi – povećana renalna reapsorpcija glukoze;

Anti-diabetic treatment options for T2DM

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose co-transporter-2; T2DM, type 2 diabetes mellitus

Current Diabetes Treatment Paradigm: Intensification of Treatment in Response to Progression of Diabetes

Inkretini

- **INCRETIN** = **IN**testinal + se**CRET**ion + of **In**sulin

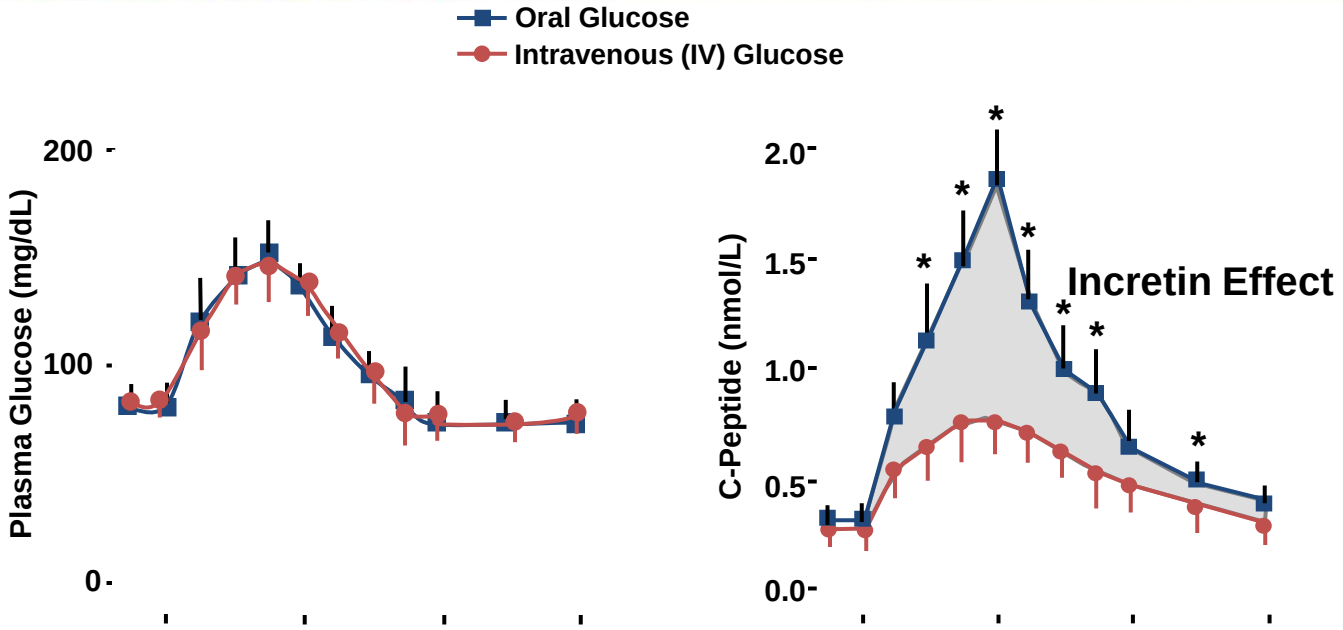
- "***INCRETIN effect***" prvi put opisan 1960. (*Bersan & Yalow*)
- **ENTERO-INSULARNA OSOVINA**, 1969. (*Unger*)

- Efekat inkretina posredovan hormonima poreklom iz creva:
  - **GIP** – (*Gastric Inhibitory Peptide,* ***Glucose-dependent Insulinotropic Peptide)*** izolovao *Brown* 1969;
  - **GLP-1** - **(*Glucagon-Like Peptide-1)*** izolovao *Goke* 1988.

Efekat inkretina

U zdravih ispitanika, oralno unesena glukoza dovodi do većeg insulinskog odgovora u odnosu na ekvivalentni intravenski unos.

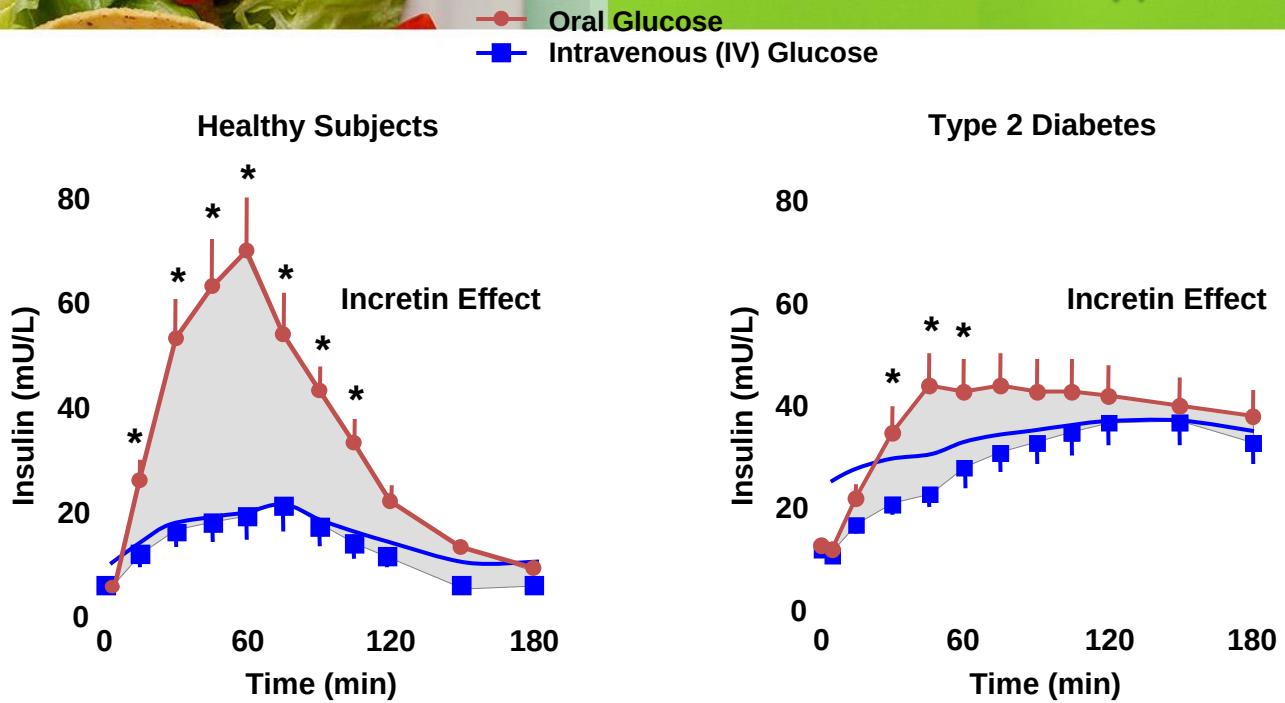
The Incretin Effect in Healthy Subjects



N = 6; Mean (SE); *$P \leq 0.05$

Data from Nauck MA, et al. J Clin Endocrinol Metab 1986;63:492-498.

The Incretin Effect Is Reduced in Type 2 Diabetes



N = 22; Mean (SE); *$P \leq 0.05$

Data from Nauck M, et al. Diabetologia 1986;29:46-52.

Primarni inkretini (*incretin hormones*)

GLP-1 - (*Glucagon-Like Peptide-1)*

Peptid = 30 amino kiselina

Sintetišu i oslobadjaju L ćelije ileuma i kolona; neuroni u hipotalamusu;

Mesto delovanja:

- GI trakt;
- CNS
- Pluća
- Srce

GIP – (*Gastric Inhibitory Peptide*, ***Glucose-dependent Insulinotropic Peptide)***

Peptid = 42 amino kiseline

Sintetišu i oslobadjaju K ćelije jejunuma i duodenuma;

Mesto delovanja:

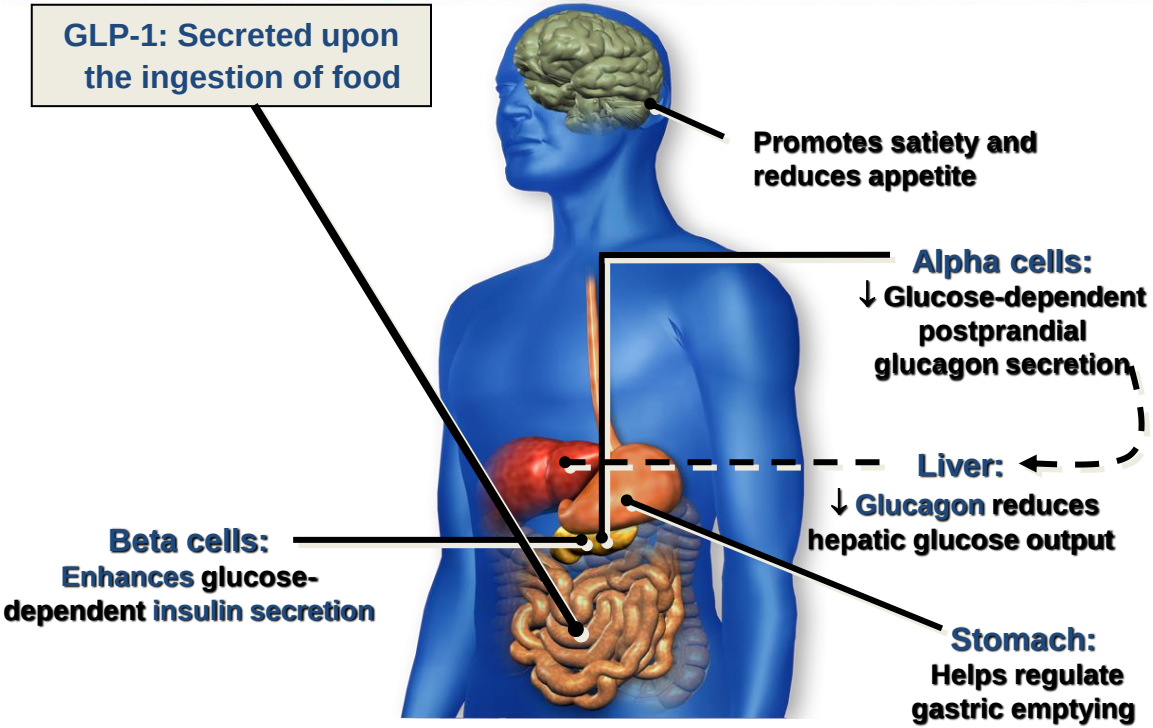
- Pankreasne beta ćelije
- Adipociti;

Uporedne karakteristike inkretina

	GLP-1	GIP
Proteolitička inaktivacija		
DPP-4 (*dipeptidyl peptidase – 4*)	**Da (1,5-2,1 min)**	**Da (5 min)**
Snižena sekrecija u T2DM	**Da**	**Ne**
Inhibicija sekrecije glukagona postprandijalno	**Da**	**Ne**
Redukuje unos hrane i porast telesne mase	**Da**	**Ne**
Usporava gastrično pražnjenje	**Da**	**Ne**
Stimuliše beta ćelije, volumen/rast	**Da**	**Ne**
Podstiče biosintezu insulina	**Da**	**Ne**
Knockout mice (result in IGT)	**Da**	**Ne**

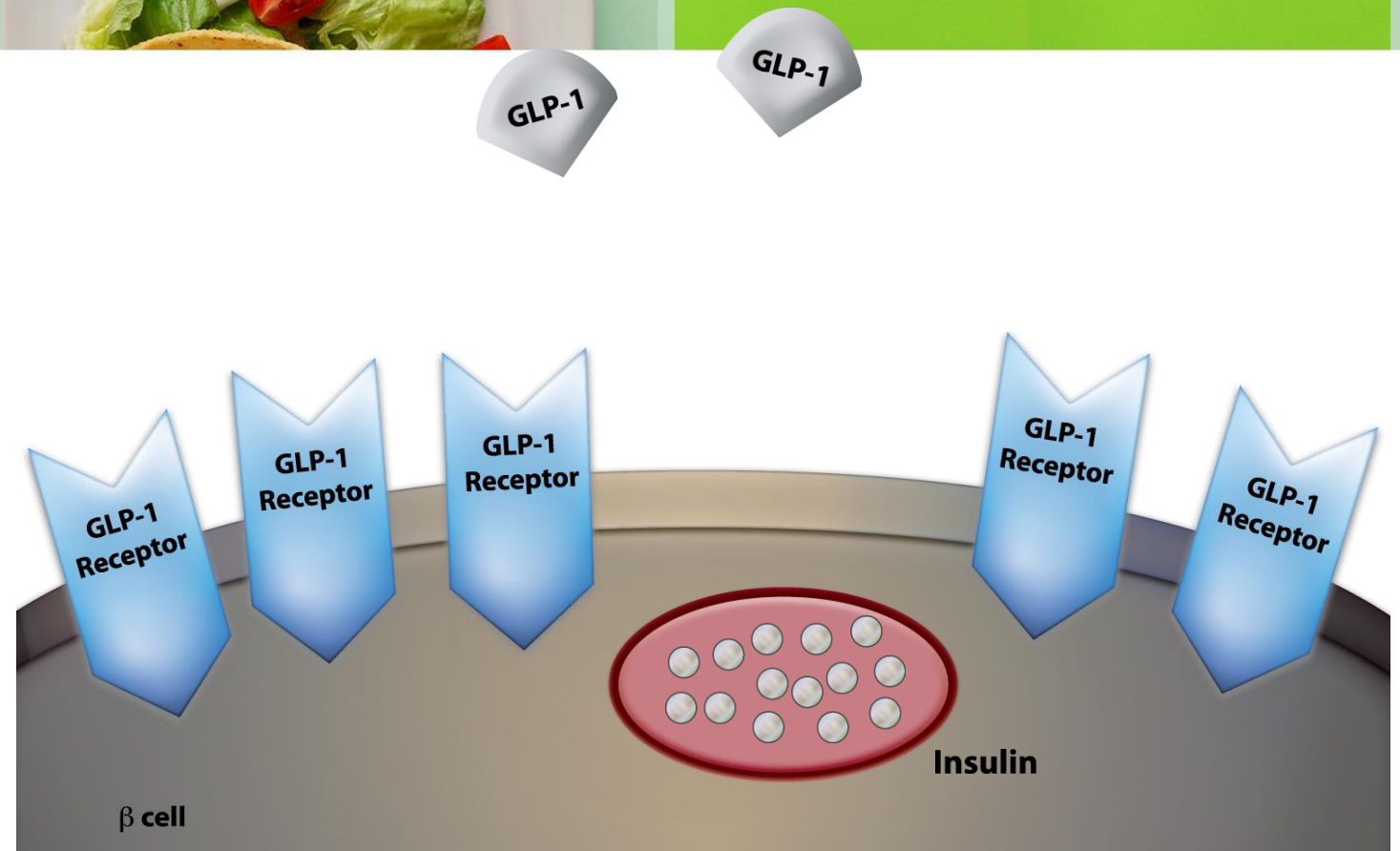
Adapted from Mayo KE, et al. Pharmacol Rev 2003;55:167-194.
Adapted from Drucker DJ. Diabetes Care 2003;26:2929-2940.
Adapted from Nauck M, et al. Diabetologia 1986;29:46-52.

GLP-1 Modulates Numerous Functions in Humans

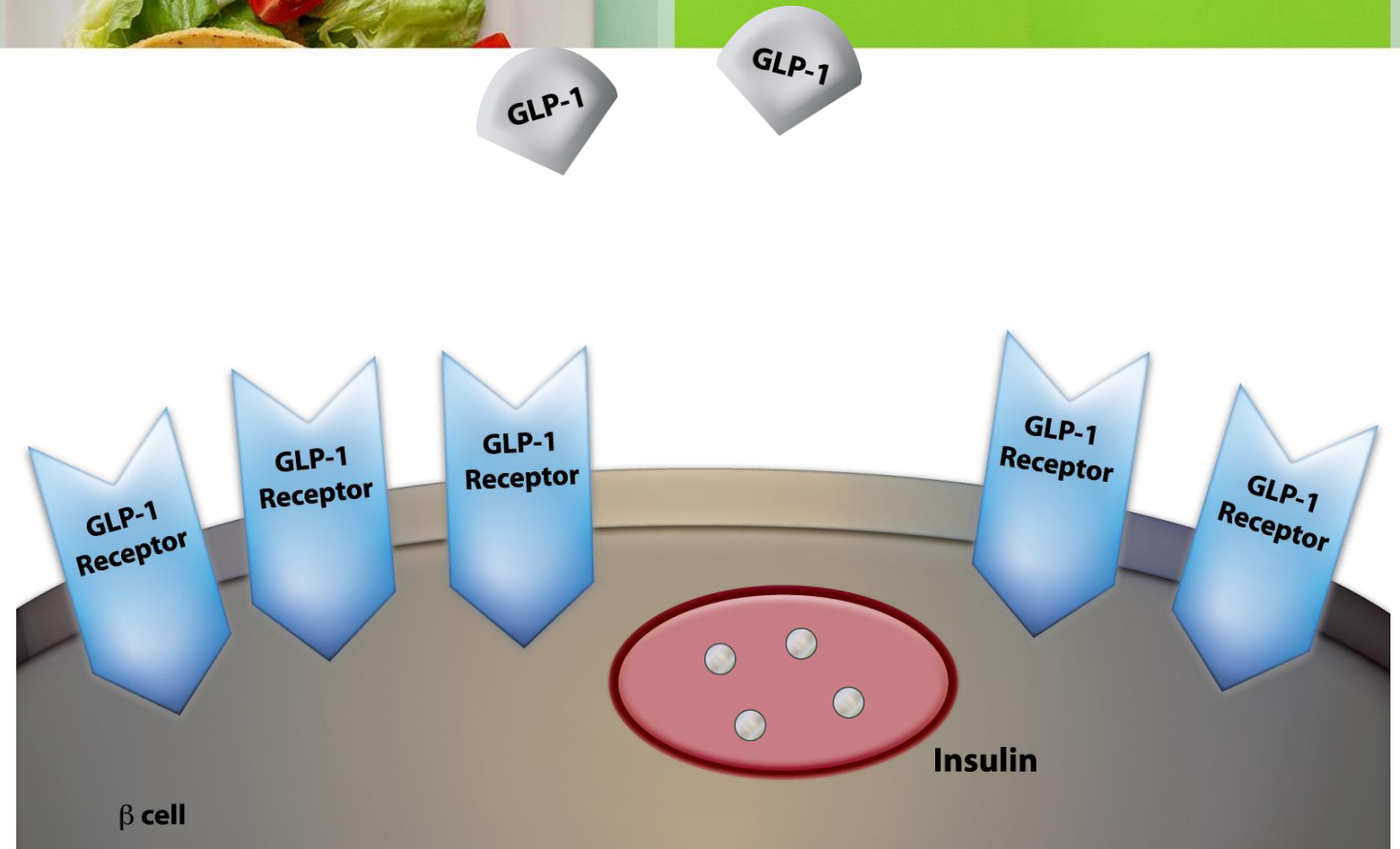


Data from Flint A, et al. J Clin Invest 1998;101:515-520. Data from Larsson H, et al. Acta Physiol Scand 1997;160:413-422. Data from Nauck MA, et al. Diabetologia 1996;39:1546-1553. Data from Drucker DJ. Diabetes 1998;47:159-169.

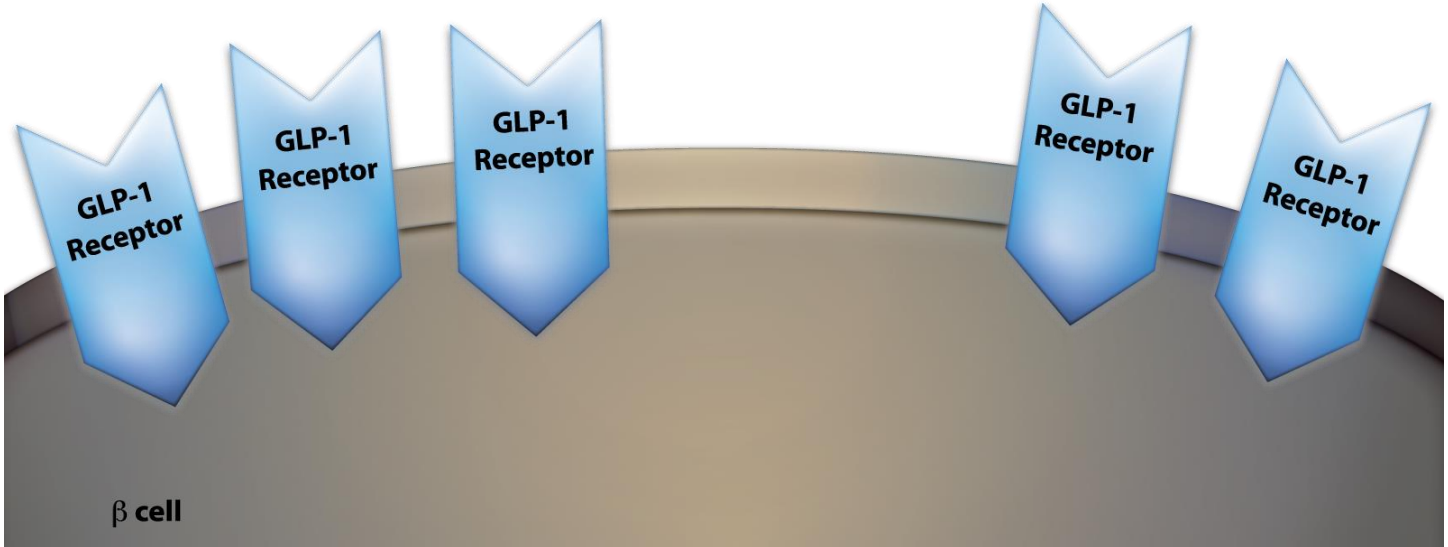
Delovanje GLP-1 na β ćelije zdravih osoba



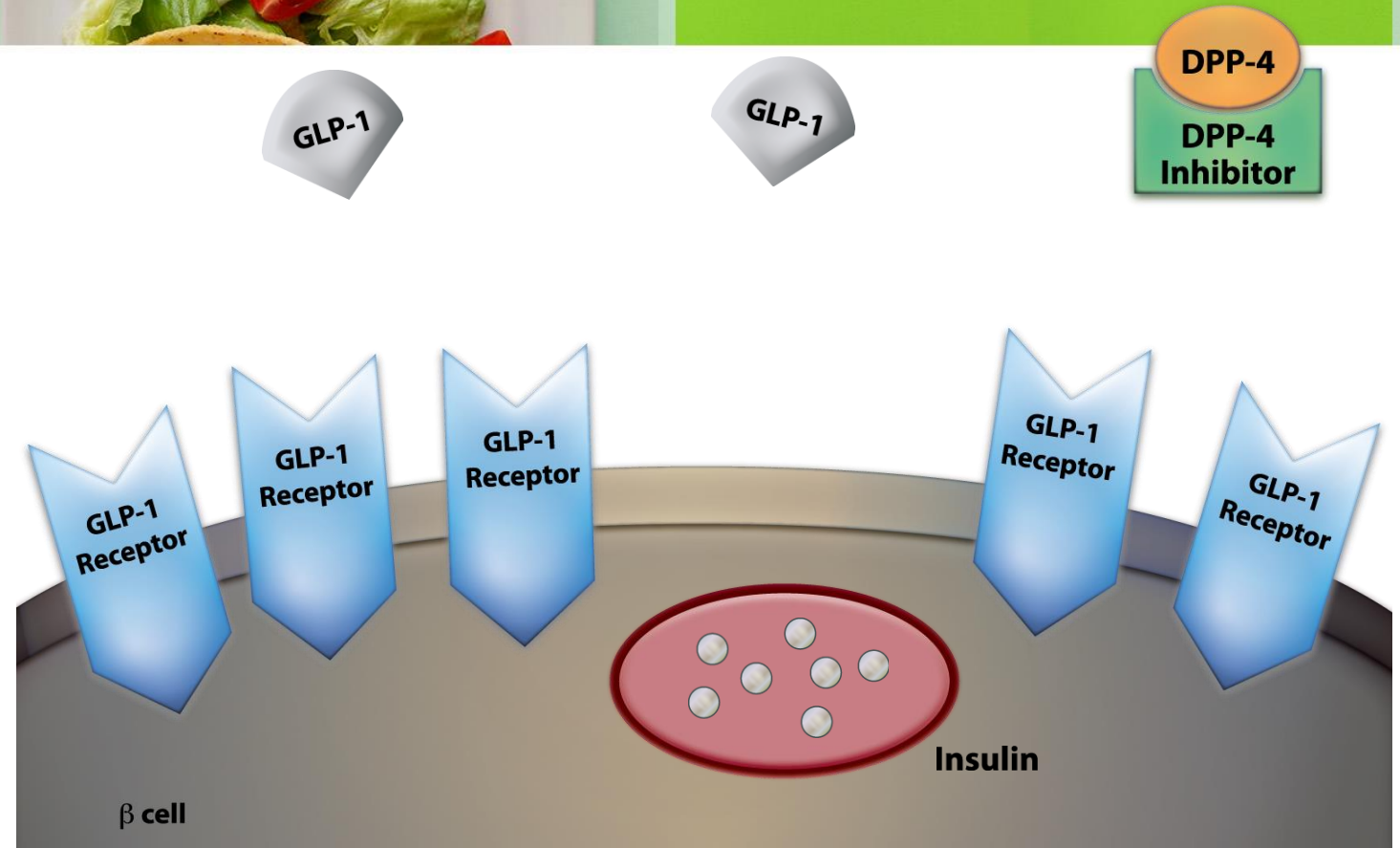
GLP-1 kod T2D


GLP-1
GLP-1
GLP-1 Receptor
GLP-1 Receptor
GLP-1 Receptor
GLP-1 Receptor
GLP-1 Receptor
Insulin
β cell

GLP-1 cepanje i inaktivacija sa DPP-4



DPP-4 Inhibitors Prevent the Inactivation of GLP-1

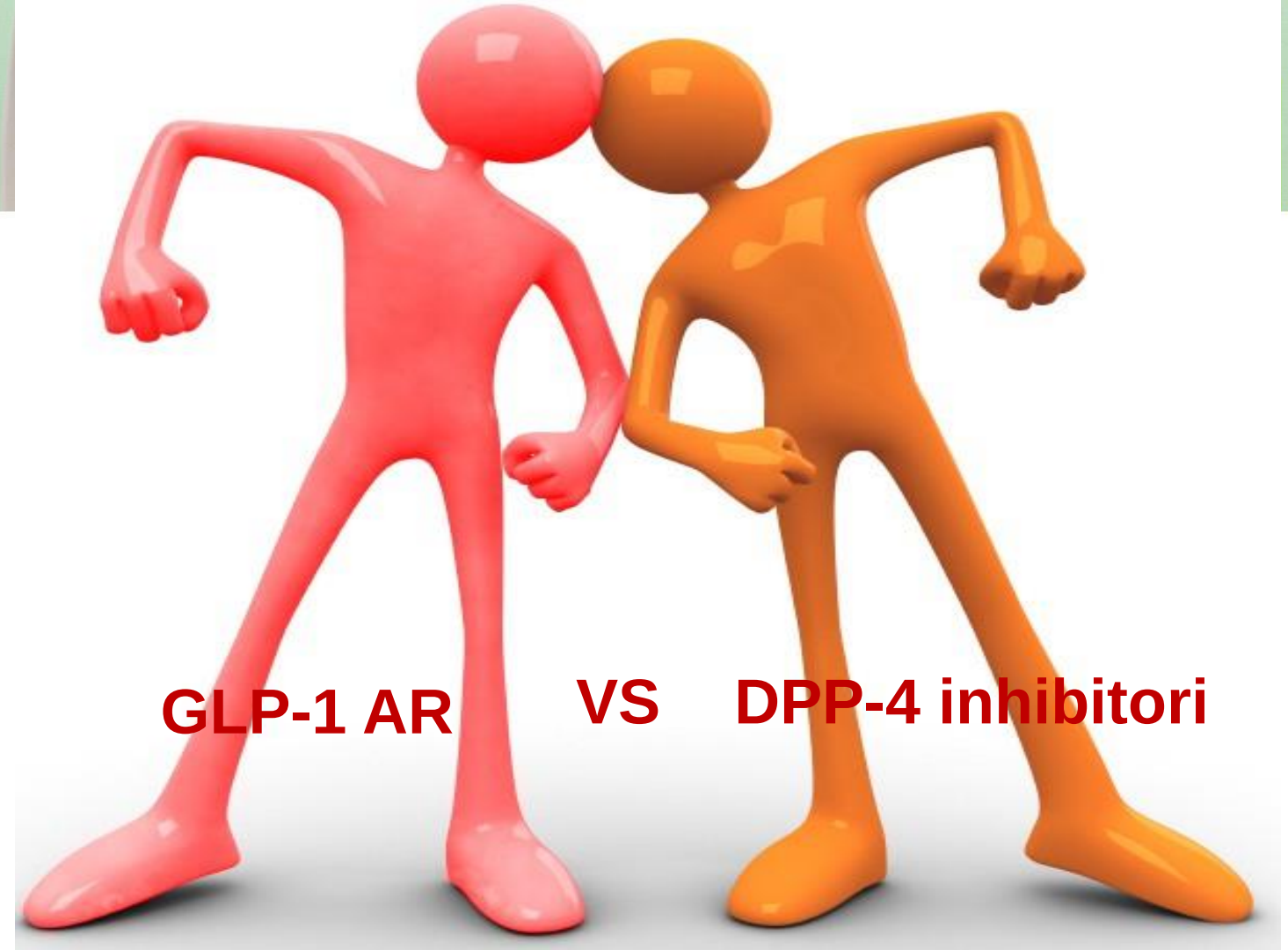


Uzroci smanjenog lučenja GLP-1 u T2DM

- Visok BMI;
- Insulinska rezistencija;
- Hiperglikemija;
- Usporeno gastrično pražnjenje;
- Dugo trajanje i loša kontrola (DM);
- *Washout* vs kontinuirana terapija (naročito za metformin, povećava GLP-1 sekrecija);

Farmakološki agensi bazirani na inkretinskom konceptu

- DPP-4 inhibitori;
  - "Gliptini"
    - **Sitagliptin**
    - **Vilagliptin**
    - **Saxagliptin**
    - **Linagliptin**
    - **Alogliptin**
    - Duotogliptin
    - Gemigliptin
- GLP-1 agonisti (Mimetici inkretina);
  - Agonist GLP-1 receptora
    - Egzenatid
  - Analog GLP-1
    - Liraglutid
  - Analozi sa produženom apsorpcijom


GLP-1 AR
VS
DPP-4 inhibitori

Razlike izmedju GLP-1 RA i DPP-4 inhibitora

Osobine/delovanje	**GLP-1 RA**	**DPP-4 Inhibitori**
Delovanje na GLP-1 receptor	Direktno	Indirektno
Aktivni GLP-1 koncetracije	~ 60 pmol//L farmakološke	~ 10 pmol//L fiziološke
HbA1c sniženje	0,5% - 2,0%	0,5% - 0,9%
Usporavanje gastričnog pražnjenja	Da	Ne
Pospešuju sitost	Da	Ne

Razlike izmedju GLP-1 RA i DPP-4 inhibitora

Osobine/delovanje	**GLP-1 RA**	**DPP-4 Inhibitori**
Telesna masa	Snižena	Neutralno
Hipoglikemija - učestalost	Niska	Niska
Neželjeni efekti	Mučnina, povraćanje	Dobro se podnose
Način primene	Sc	Oralno
Doziranje	Eksenatid BID Eksenatid QW Liraglutid QD	QD

Why not initiate incretin-based therapy early in the management of patients with T2DM?

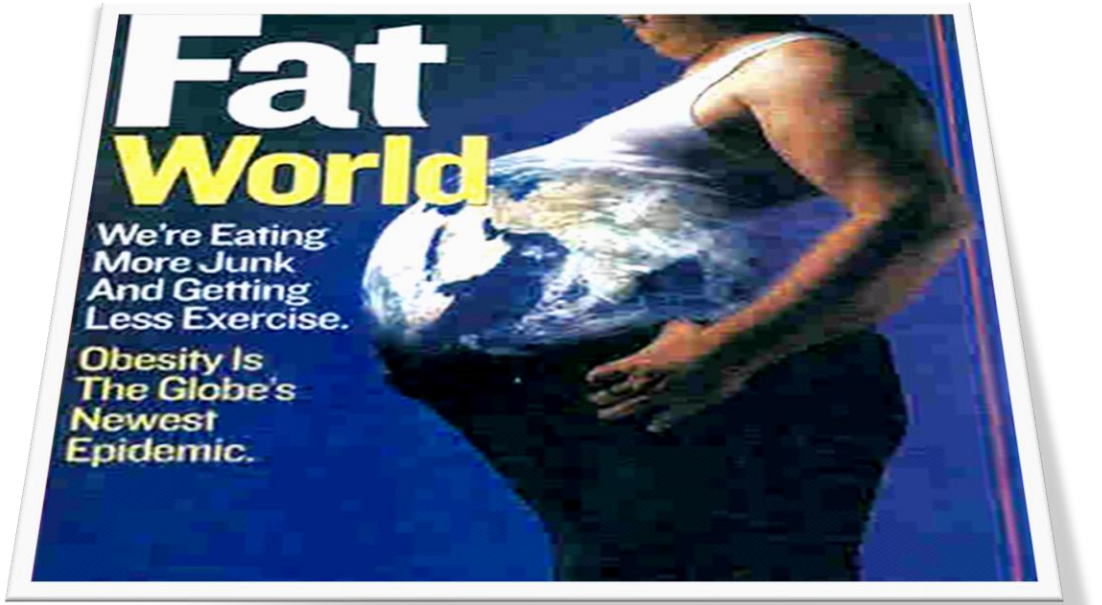
Old Antidiabetes drugs

Incretin

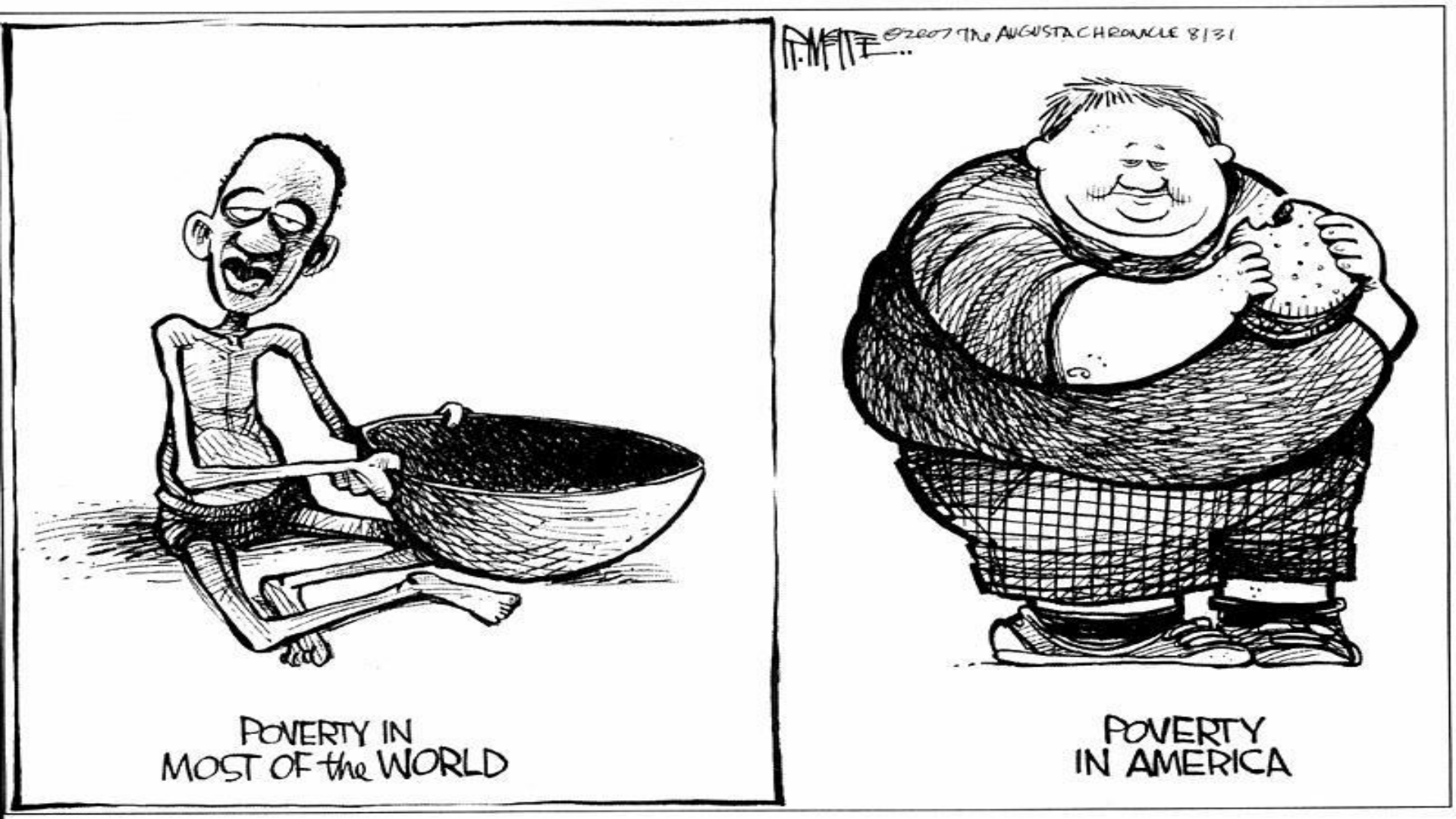
Epidemija?

Pandemija?

Estetski doživljaj?




The Economist
Gore anoints Dean
PAGES 12 AND 33
America's Taiwan test
PAGES 12 AND 29
The future of flight
PAGES 79–81
A SURVEY OF FOOD
AFTER PAGE 52
DECEMBER 13TH–19TH 2003
www.economist.com
The shape of things to come
US$4.95 • C$6.95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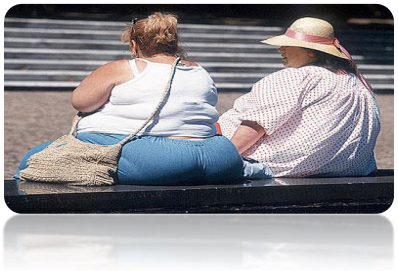
POVERTY IN MOST OF the WORLD
POVERTY IN AMERICA

Prekomerna telesna masa i gojaznost

Prekomerna telesna masa i gojaznost –

„problem epidemijskih razmera“[1]

- **Definicija SZO**
  - Gojaznost je hronična bolest koju karakteriše povećanje masnih depoa.
  - U svakodnevnoj kliničkoj praksi definiše se pomoću indeksa telesne mase (BMI)



BMI 25-29,9 kg/m^2 – PREKOMERNA TELESNA MASA

BMI > 30 kg/m^2 – GOJAZNOST

References. 1. World Health Organisation European Charter on Counteracting Obesity. Istanbul, Turkey: 16 November, 2006. 2. The challenge of obesity in the WHO European Region. Factsheet EURO/13/05. Bucharest: 12 September 2005. 3. ABC of Obesity. Eds. Sattar N and Lean M. 2007, Blackwell Publishing, Massachusetts, USA. 4. World Health Organisation European Conference on Counteracting Obesity: 10 things you need to know about obesity. Istanbul, Turkey: 15-17 November, 2006.

Prekomerna telesna masa i gojaznost

Prekomerna telesna masa i gojaznost – „problem epidemijskih razmera“[1]

- Preko 50 % odraslih u EU je gojazno ili pati od prekomerne telesne mase[1]
  - Gojaznost sa mogućim značajnim kliničkim komplikacijama je povećana za skoro 300% od osamdesetih godina prošlog veka[1]
- Prosečni indeks telesne mase (BMI) danas iznosi 26,5 kg/m^2
  - kategorija prekomerne telesne mase je 25 – 29,9 kg/m^2
- Oko polovine ljudi sa prekomernom telesnom masom će postati gojazno[3]
- Predviđa se da će 20% odraslih u EU postati gojazno do 2010. godine[4]

References. 1. World Health Organisation European Charter on Counteracting Obesity. Istanbul, Turkey: 16 November, 2006. 2. The challenge of obesity in the WHO European Region. Factsheet EURO/13/05. Bucharest: 12 September 2005. 3. ABC of Obesity. Eds. Sattar N and Lean M. 2007, Blackwell Publishing, Massachusetts, USA. 4. World Health Organisation European Conference on Counteracting Obesity: 10 things you need to know about obesity. Istanbul, Turkey: 15-17 November, 2006.

Global Prevalence of Obesity

- Globally, proportions of adults with a BMI of ≥ 25 increased from 28.8% in 1980 to 36.9% in 2013 for men and from 29.8% to 38.0% for women
- Prevalence of obesity has increased substantially among children and adolescents in both the developed world (23.8% of boys; 22.6% of girls; overweight/obese in 2013) and the developing world (12.9% of boys; 13.4% of girls; overweight/obese in 2013)

Ng M, et al. *Lancet*. 2014;384:766-781.

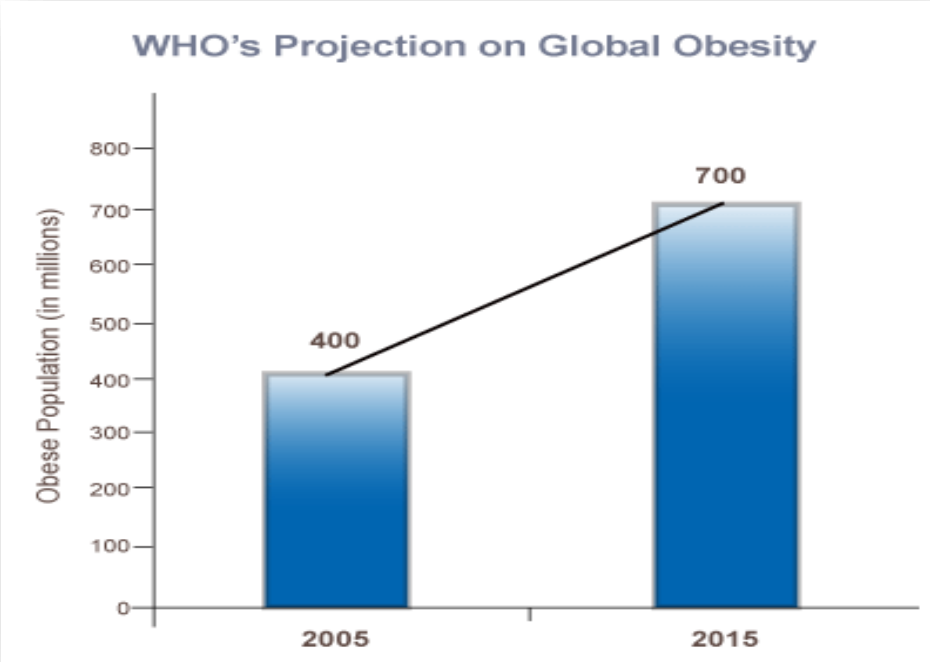
Tracking the Global Obesity Epidemic

- Worldwide, the rate of obesity has nearly doubled since 1980: Just over 200 million adult men and just under 300 million adult women have obesity[a]
  - 39% of adults aged 18 years and over had overweight in 2014, and 13% had obesity[a]
- Obesity rates have been steadily rising in children, too: in 2010, 43 million preschool children had overweight or obesity, a 60 percent increase since 1990[b]
- A 2014 study of overweight and obesity in children and adults from 1980-2013 found that worldwide, the proportion of adults with overweight or obesity increased, and prevalence also increased substantially in children and adolescents in both developed and developing countries[c]

a. Finucane MM, et al. Lancet. 2011;337:557-567.
b. de Onis M, et al. *Am J Clin Nutr*. 2010;92:1257-64.
c. Ng M, et al. *Lancet*. 2014; 384:766-781.

Gojaznost kao globalni problem

Gojaznost nije samo zdravstveni problem razvijenih zemalja!

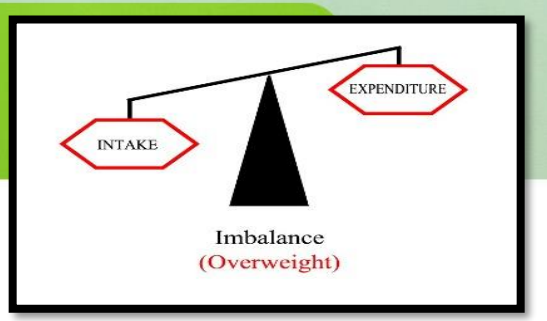


- Gojaznost dovodi do značajnog povećanja morbiditeta i mortaliteta uz smanjenje kvaliteta života
- Direktni troškovi gojaznosti procenjuju se u Evropi na 2-8% ukupnih troškova zdravstvenih fondova.

http://www.euro.who.int/obesity

Uzroci gojaznosti

Različiti su uzroci gojaznosti i prekomerne telesne mase



- **Životni stil**
  - Navike u ishrani
  - Nedostatak fizičke aktivnosti
  - Poslovi sa malo kretanja
- **Genetika**
- **Oboljenja**
  - Hipotiroidizam
  - *Cushing's syndrome*
  - Policistični ovarijalni sindrom
  - Nedostatak hormona rasta
  - Povrede hipotalamusa usled: traume, tumora, operativno

- **Lekovi**
  - Antidijabetici – sulphonilurea, glitazoni
  - Antidepresivi
  - Antikonvulzivi
  - Kortikosteroidi
  - Hormonska supstituciona terapija
  - Beta blokatori
  - Pizotifen
  - Litijum
  - Antihistaminici
  - Melatonin

Rizici prekomerne telesne mase/gojaznosti

Brojni su zdravstveni rizici kod pacijanta sa gojaznošću

Katarakta

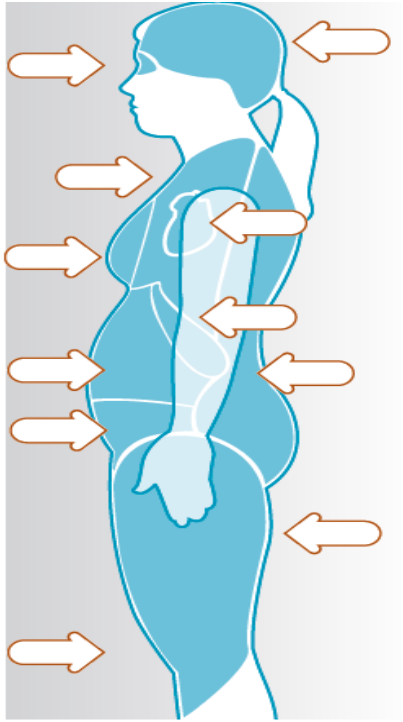
Hipoventilacioni sindrom

Karcinom dojke

Karcinom kolona

Poremećaji reprodukcije

Osteoartritis



Depresija
Sleep apnea sindrom

Arterijska hipertenzija,
Ishemijska bolest srca

Dijabetes Tip 2

Lumbalni sindrom

Kožna oboljenja

Izvor: Clinical Knowledge Summaries. Obesity 2008.

Prekomerna masa i gojaznost – veliki teret

Čak i malo povećanje BMI može uticati na zdravlje[1]

Povećan rizik od:[1]

- Dijabetesa tipa dva
- Hipertenzije
- Koronarnog oboljenja srca (CHD)
- Kamena u žuči

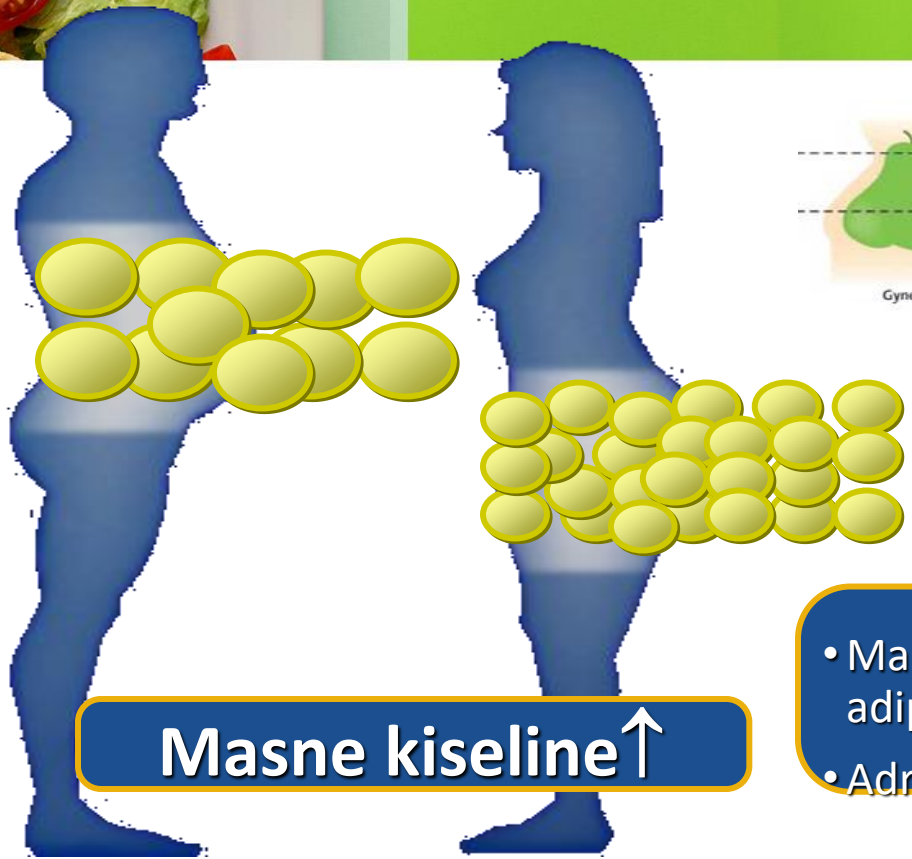
Takođe i:

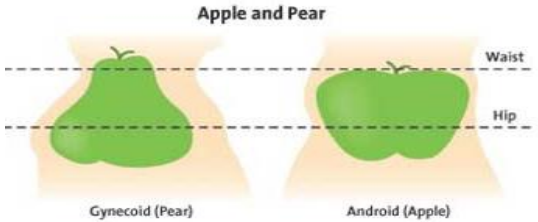
- Određenih vrsta karcinoma, osteoartritisa, smanjene plodnosti, apnee u snu, depresije, problema sa kičmom...[2]
- **Visceralne masti (masti koje obavijaju unutrašnje organe) su opasnije od potkožnih masti i nose veći rizik od nastanka oboljenja kao što su dijabetes i bolesti srca[3,4]**

References. 1. Willett WC *et al. N Engl J Med* 1999; **341**: 427– 434. 2. Clinical Knowledge Summary: Obesity. 3. Van Gaal L *et al. Int J Obesity* 1997; **21**(Suppl 1): S5-S9. 4. Haslam D. *Practice Nurse* 2008; **35**(6): 26-29.

Nisu sve naslage masti iste

- Veliki insulin rezistentni adipociti
- Adrenergički receptori↑
- Insulin – kontrolisana antilipoliza
- Kateholaminima kontrolisana lipoliza↑



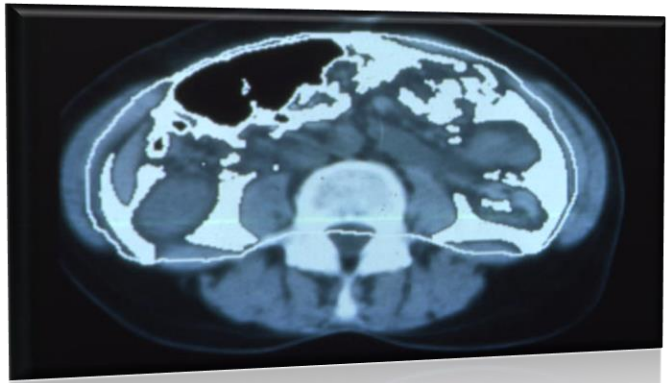


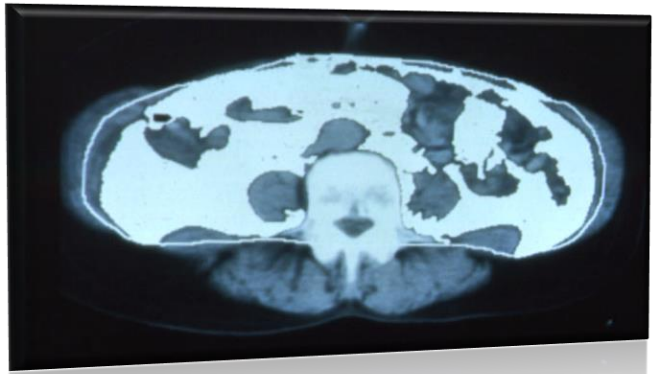
Masne kiseline↑

- Mali insulin senzitivni adipociti
- Adrenergički receptori↓

Visceralna distribucija masti

Ne-gojazni Vs gojazni

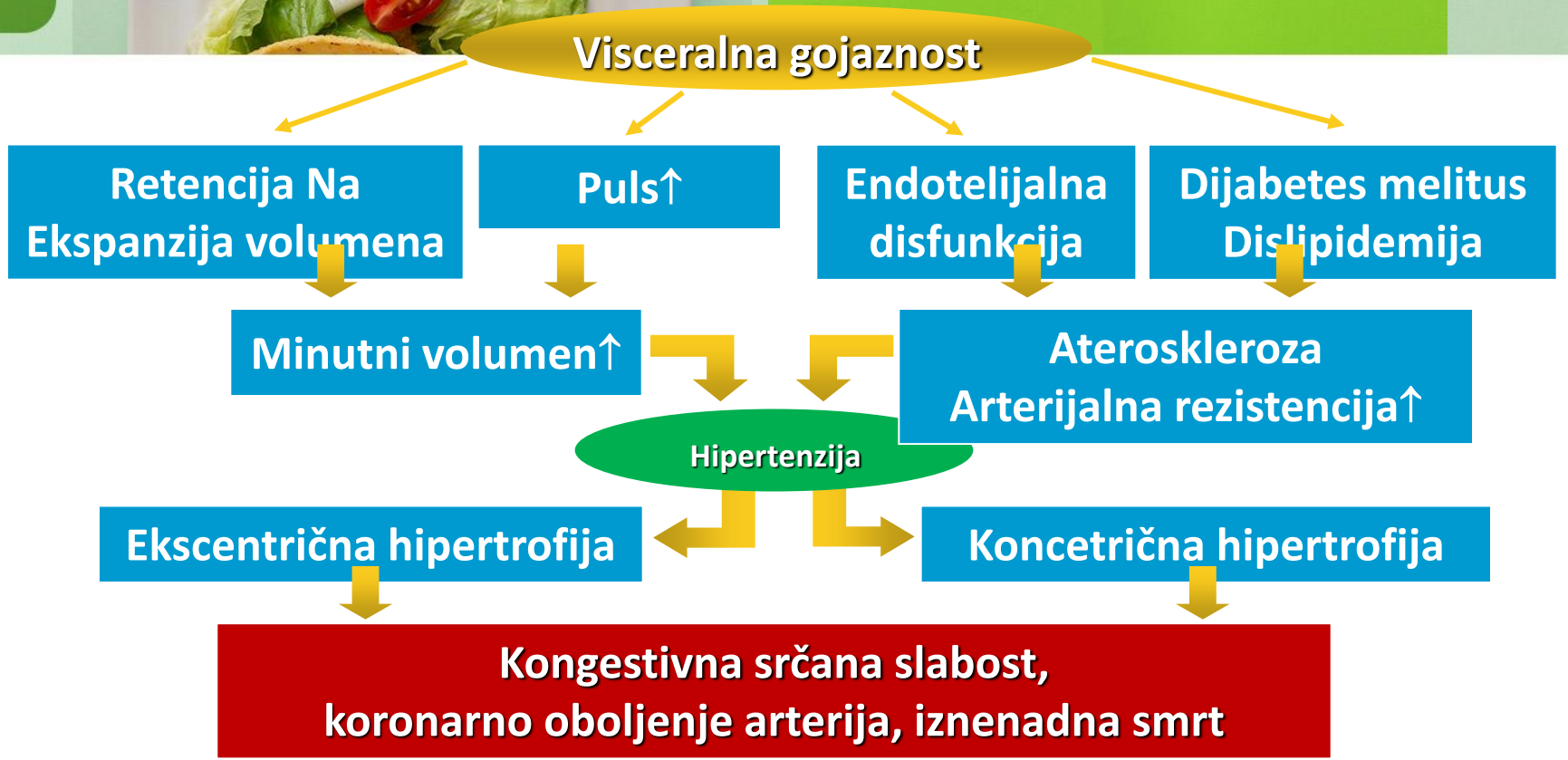




Visceralna gojaznost

Courtesy of Wilfred Y. Fujimoto, MD.

Gojaznost – kardiovaskularni rizik



Gojaznost i insulinska rezistencija

Hiperinsulinemija
+
Hiperglikemija

Aktiviranje simpatičkog nervnog sistema

Povišen tonus arterija

Na+ reapsorpcija

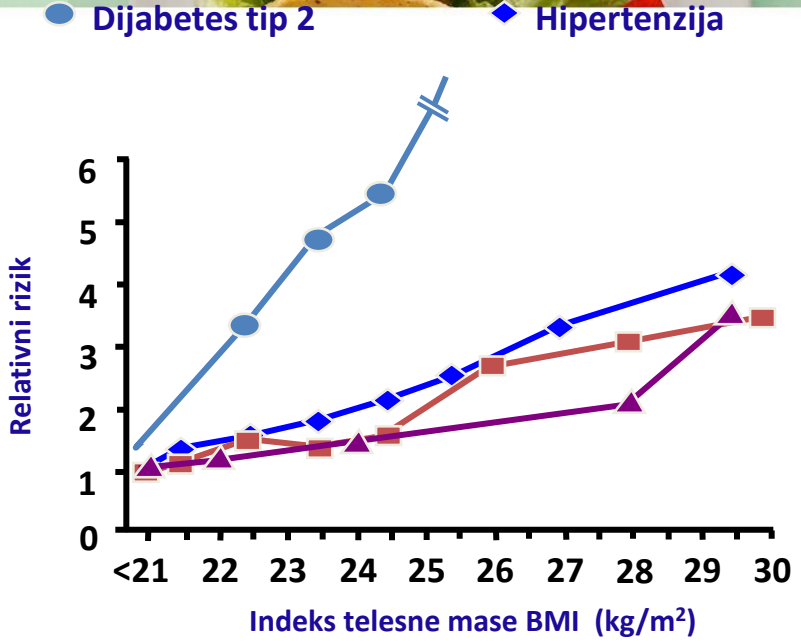
Prekomerna stimulacija β-ćelija pankreasa

Redukcija sekrecije insulina

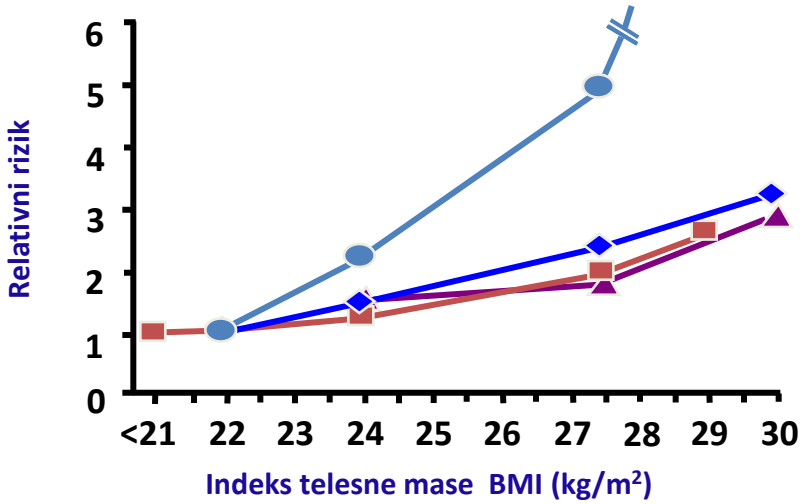
Hipertenzija

Tip 2 Dijabetes

Rizici od oboljenja



Žene



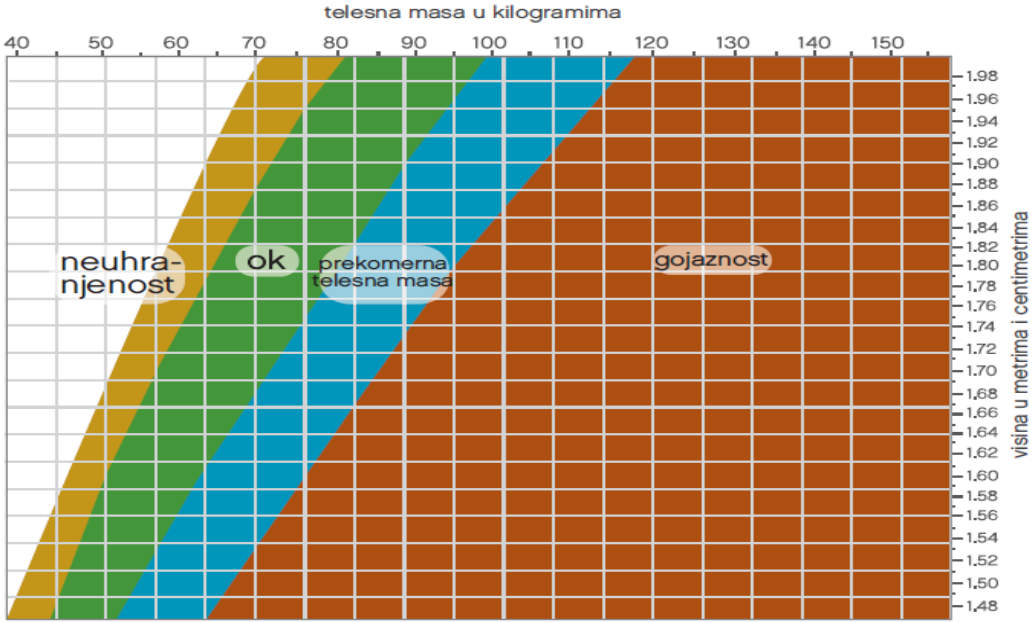
Muškarci

Indeks telesne mase (BMI)

Klasifikacija

$$BMI = \frac{\text{telesna masa (kg)}}{\text{visina}^2\ (\text{m}^2)}$$

Kategorija uhranjenosti	BMI (kg/m²)
Mršavost	< 18,5
Normalna uhranjenost	18.5-24.9
Prekomerna masa	25
Predgojaznost	25-29.9
Gojaznost • Gojaznost I stepena • Gojaznost II stepena • Gojaznost III stepena	 30-34.9 35-39.9 40

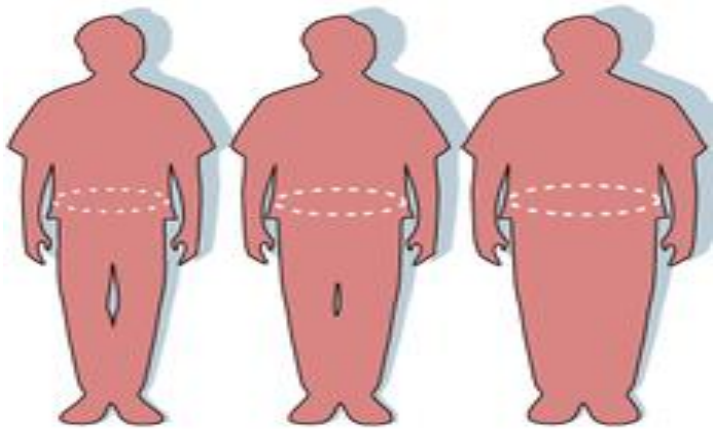


Indeks telesne mase (BMI) i obim struka

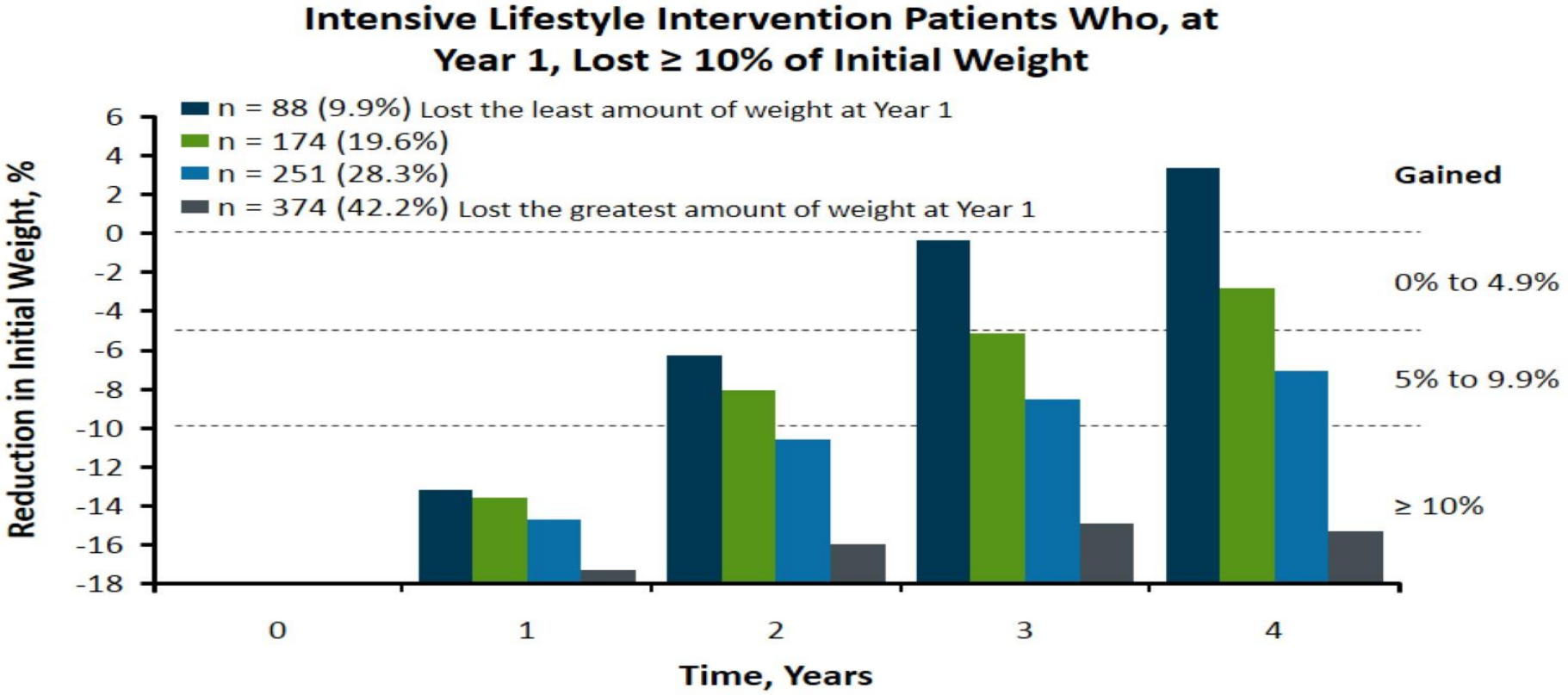
Obim struka kao još jedan pokazatelj

Ketegorija uhranjenosti	BMI (kg/m^2)	Obim struka
Mršavost	< 18,5	
Normalna uhranjenost	18.5-24.9	< 80 ž < 94 m
Prekomerna	25	80 ž 94 m
Predgojaznost	25-29.9	80 – 88 ž 94 – 102 m
Gojaznost •Gojaznost I stepena •Gojaznost II stepena •Gojaznost III stepena	30 30-34.9 35-39.9 40	 88 ž 102 m

$$\text{BMI} = \frac{\text{telesna masa (kg)}}{\text{visina (m}^2\text{)}}$$



Look AHEAD Weight-Loss Maintenance



Wadden TA, et al. *Obesity (Silver Spring).* 2011;19:1987-1998.

Rates of Comorbidity Reduction After Bariatric Surgery

Disease or Symptom	Improvement or Remission at ≤ 2 Y	Improvement or Remission at 5 to 7 Y	Improvement or Remission at 10 Y
Diabetes mellitus	72%	54%	30%
Hypertension	24%	66%	41%
Hypertriglyceridemia	62%	82%	40%
Hypercholesterolemia	22%	53%	21%
Sleep apnea	94%	66%	-
Fatty liver disease	84%	-	-
Stress urinary incontinence	64% resolved, 92% improved	-	-
Depression	50%	-	-

Table incorporates results from multiple trials.

Vest AR, et al. *Circulation*. 2013;127:945-959.

Uticaj smanjenja telesne mase na kardiovaskularne rizike

	~5% Sniženje TM	5%-10% Sniženje TM
HbA1c	↓ 1	↓ 1
Arterijska tenzija	↓ 2	↓ 2
Ukupni holesterol	↓ 3	↓ 3
HDL Holesterol	↑ 3	↑ 3
Triglyceridi		↓ 4

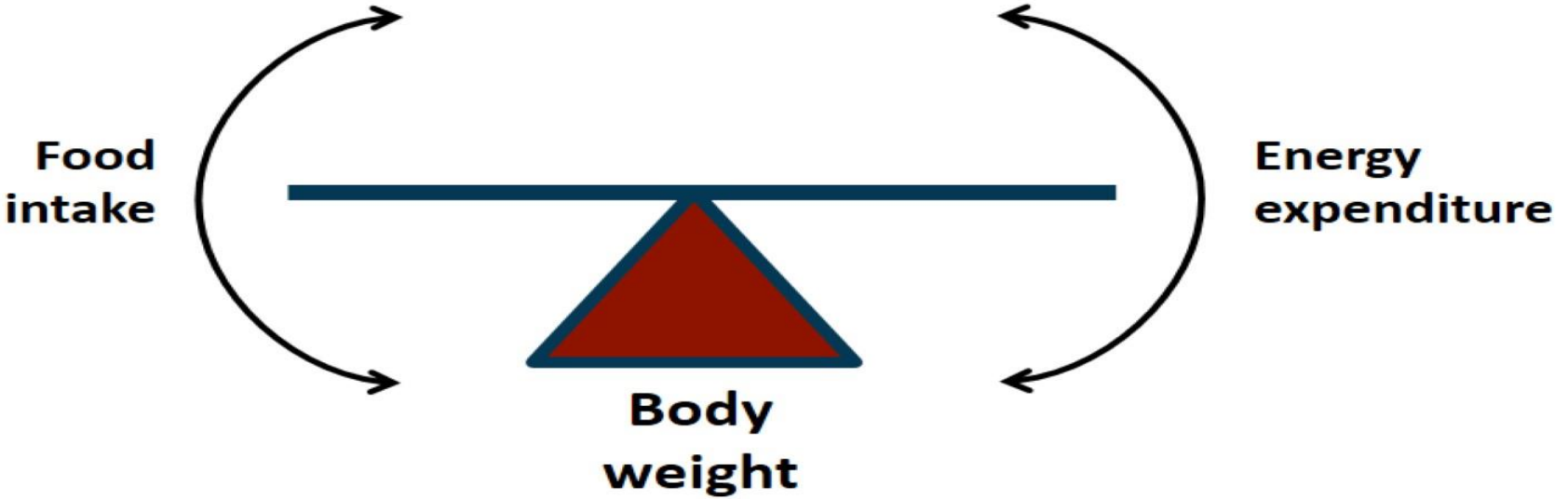
1. Wing RR et al. Arch Intern Med. 1987;147:1749-1753.
2. Mertens IL, Van Gaal LF. Obes Res. 2000;8:270-278.
3. Blackburn G. Obes Res. 1995;3 (Suppl 2):211S-216S.
4. Ditschuneit HH et al. Eur J Clin Nutr. 2003;56:264-270.

Zdravstvene koristi smanjenja 10kg telesne mase

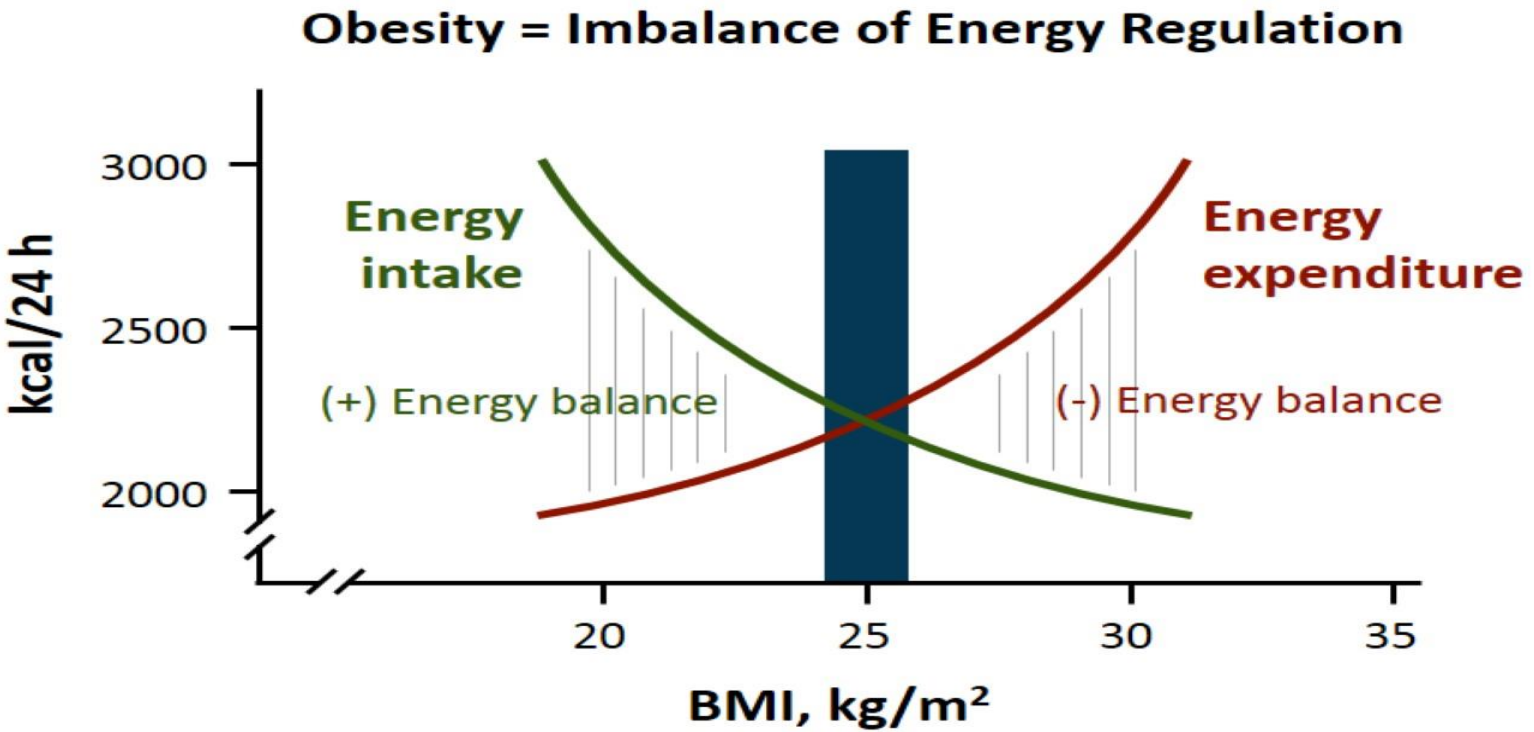
Stanje	Korist
Smrt	•20-25% sniženje ukupnih uzroka smrti
Karcinomi	•40-50% sniženje gojaznošću uslovljenih karcinoma, koji su doveli do smrti
Dijabetes	•30-40% sniženje dijabetesom uslovljenih komplikacija, koje su dovele do smrti •Sniženje za više od 50% za nastanak dijabetesa
Povišen arterijski pritisak	•Sniženje arterijskog krvnog pritiska
Angina	•Sniženje učestalosti simptoma za 90%
Holesterol	•Sniženje nivoa ukupnog holesterola za 10% •Povišenje nivoa HDL holesterola za 8%
Ostale koristi	•Poboljšana funkcija pluća •Smanjeni bolovi u leđima i zglobovima •Smanjena zadihanost •Sniženi poremećaji spavanja

Clinical Knowledge Summaries. Obesity 2008.
Jung RT. Obesity as a disease. Br Med Bull 1997; 53(2): 307-321.

Weight and Energy Balance: Historical Perspective

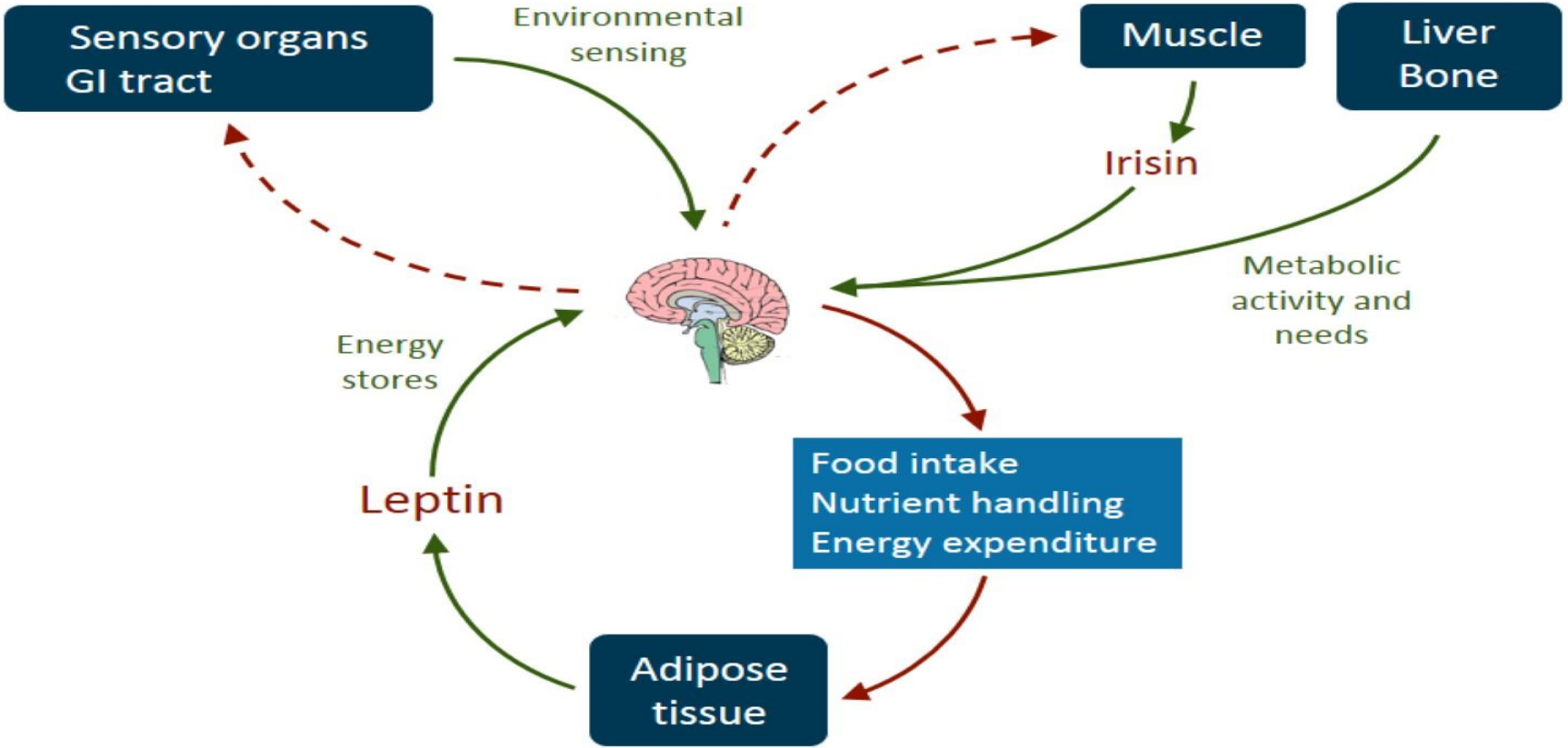


Weight and Energy Balance: Current Perspective



Weigle DS, et al. 1996;18:867-874.

Feedback Regulation of Energy Metabolism



Tchernof A, et al. *Physiol Rev*. 2013;93:359-404.

Weight Loss Improves Obesity-Related Comorbidities

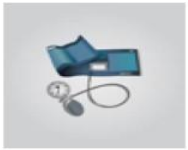
Benefits of 5%-10% weight loss

- Reduction in risk of T2DM[a]

- Reduction in CV mortality[b]

- Improvements in blood lipid profile[c]

- Improvements in blood pressure[d]



- Improvements in severity of obstructive sleep apnea[e,f]

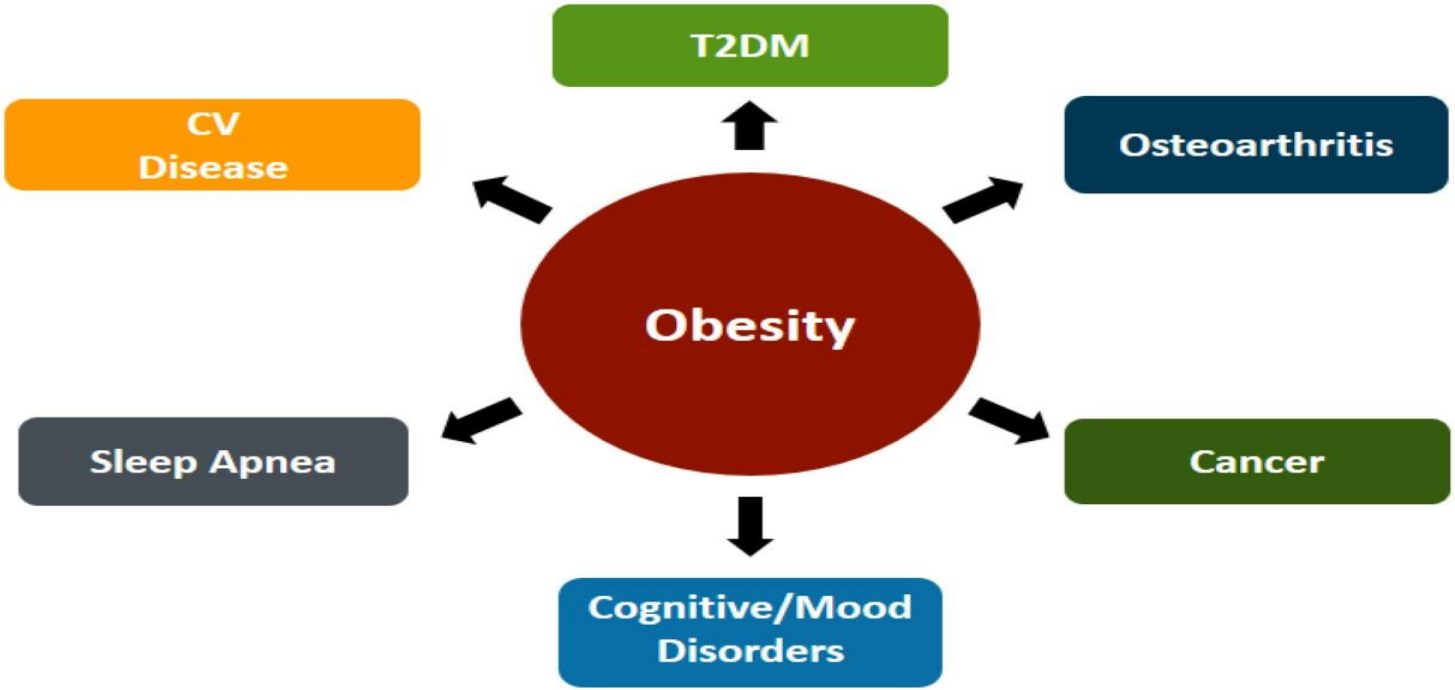
- Improvements in health-related QoL[g,h]

a. Knowler, et al. *N Engl J Med*. 2002;346:393-403.
b. Li, et al. *Lancet Diabetes Endocrinol*. 2014;2:474-480.
c. Datillo, et al. *Am J Clin Nutr*. 1992;56:320-328.
d. Wing, et al. *Diabetes Care*. 2011;34:1481-1486.
e. Foster, et al. *Arch Intern Med*. 2009;169:1619-1626.
f. Kuna, et al. *Sleep*. 2013;36:641-649.
g. Warkentin, et al. *Obes Rev*. 2014;15:169-182.
h. Wright, et al. *J Health Psychol*. 2013;18:574-586.

The Impact of Obesity Upon Individuals

Slide courtesy of Jason Halford, PhD, C. Psychol. (Health) AFBPsS.

Obesity as a Risk Factor for a Range of Comorbid Conditions[a,b]

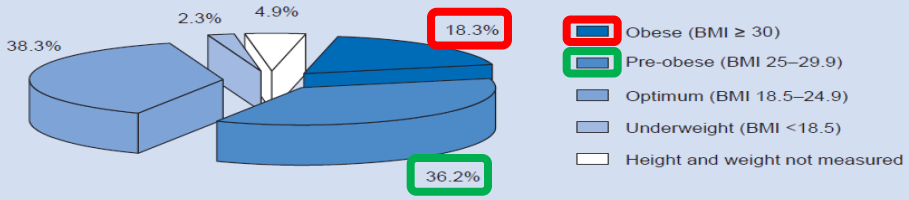


a. Pi-Sunyer X. *Postgrad Med*. 2009;121:21-33.
b. Calle EE, et al. *N Engl J Med*. 1999;341:1097-1105.

Problem gojaznosti u Srbiji

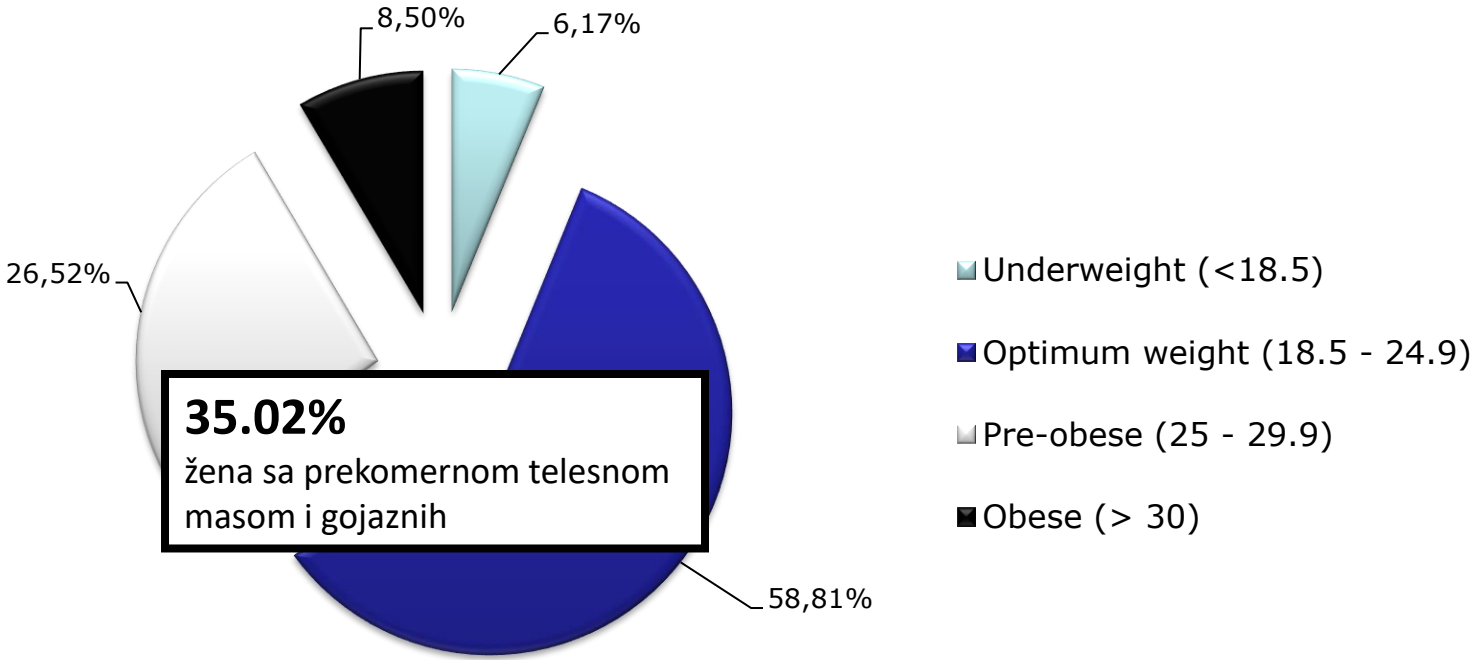
- **Totalna populacija u Srbiji: cca 7.400.000**
  - Muškarci: cca 3.600.000
  - Žene: cca 3.800.000
- **1 od 2 osobe ima prekomernu telesnu masu (54.5%) = 3,997,540 osoba**
  - Gojaznih 18.3% = 1,342,293
  - Sa prekomernom telesnom masom 36.2% = 2,655,246
- **Vojvodina – najviše osoba sa prekomernom telesnom masom**

Figure 10. *Adult population by body mass index categories, Serbia, 2006*



Sources:
National Health Survey. 2006,
www.statserb.rs.gov.yu
RTS, national TV network, January 2010

Koliko su žene gojazne u Srbiji?



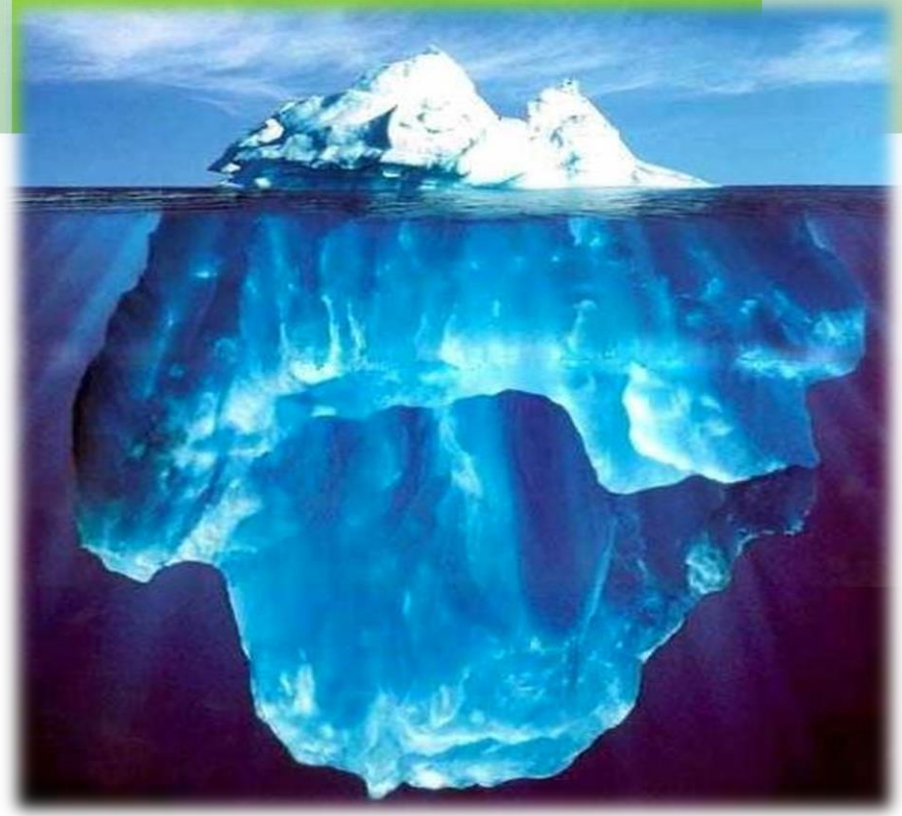
Ypsos: 2009

Podaci iz istraživanja u Srbiji

- Srčana oboljenja uzročnik su 57% smrtnih slučajeva
- Kardiovaskularna oboljenja u Srbiji su ujednačena među muškarcima i ženama
- U skladu sa nedavnim istraživanjem, 15% dece u osnovnim školama je gojazno, dok 10% imaju povišeni krvni pritisak

*Izvor: BMI, Serbia Pharmaceutical & Healthcare Report, Q1 2008

Koliko je takvih?



Gojaznost

- Metaboličko oboljenje;
- ICD – 10; E66
- Epidemijskih razmera
- Globalni hronični zdravstveni problem

Prekomerna telesna masa i gojaznost

Prekomerna telesna masa i gojaznost –

„problem epidemijskih razmera“[1]

- **Definicija SZO**
  - Gojaznost je hronična bolest koju karakteriše povećanje masnih depoa.
  - U svakodnevnoj kliničkoj praksi definiše se pomoću indeksa telesne mase (BMI)

BMI 25-29,9 kg/m^2 – PREKOMERNA TELESNA MASA

BMI > 30 kg/m^2 – GOJAZNOST

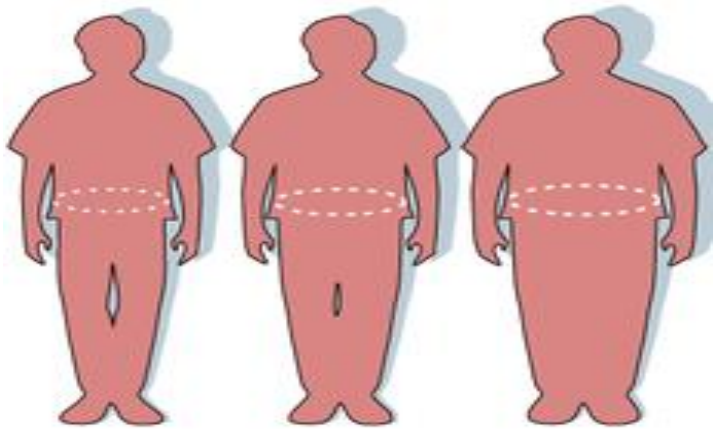
References. 1. World Health Organisation European Charter on Counteracting Obesity. Istanbul, Turkey: 16 November, 2006. 2. The challenge of obesity in the WHO European Region. Factsheet EURO/13/05. Bucharest: 12 September 2005. 3. ABC of Obesity. Eds. Sattar N and Lean M. 2007, Blackwell Publishing, Massachusetts, USA. 4. World Health Organisation European Conference on Counteracting Obesity: 10 things you need to know about obesity. Istanbul, Turkey: 15-17 November, 2006.

Indeks telesne mase (BMI) i obim struka

Obim struka kao još jedan pokazatelj

Ketegorija uhranjenosti	BMI (kg/m^2)	Obim struka
Mršavost	< 18,5	
Normalna uhranjenost	18.5-24.9	< 80 ž < 94 m
Prekomerna	25	80 ž 94 m
Predgojaznost	25-29.9	80 – 88 ž 94 – 102 m
Gojaznost •**Gojaznost I stepena** •**Gojaznost II stepena** •**Gojaznost III stepena**	30 30-34.9 35-39.9 40	88 ž 102 m

$$\text{BMI} = \frac{\text{telesna masa (kg)}}{\text{visina (m}^2\text{)}}$$



Centralna gojaznost (*central obesity*) najčešći sinonimi

- Visceralna (*visceral*)
- Androidna (*android*)
- Oblik jabuke (*apple-shaped*)
- “Gojaznost gornjeg dela tela” (*upper body obesity*)

Patogeneza gojaznosti - kompleksna interakcija brojnih faktora

- Biološki:
  - Genetski;
  - Epigenetski;
- Bihejvioralni;
- Socijalni;
- Enviromentalni (uključujuću hronični stres);

Gojaznost
izmena strukture masnog tkiva

- Hipertrofija
- Hiperplazija adipocita
- inflamacija

- Telesna masa regulisana je endokrinim i neuralnim putevima koji utiču na mehanizme koji odredjuju unos i potrošnju energije.

- Ovaj kompleksni regulatorni sistem je potreban, jer i mali poremećaj ravnoteže izmedju odnosa i potrošene energije imaće veliki efekat na masu.

- Promene u stabilnoj težini putem forsiranog uzimanja hrane, ili njenog neuzimanja, indukuju fiziološke promene koje pružaju otpor ovim pertubacijama:
  - **Sa gubitkom težine, apetit se pojačava a potrošnja energije smanjuje;**
  - **Sa prekomernim unosom hrane, apetit opada, a potrošnja energije raste;**
- Glavni regulator ovih adaptivnih odgovora organizma je hormon **leptin** iz adipocitnog tkiva, koji ima aktivnost u mozgu (predominantno u hipotalamusu) i utiče na:
  - **Apetit**
  - **Potrošnju energije**
  - **Neuroendokrinu funkciju**

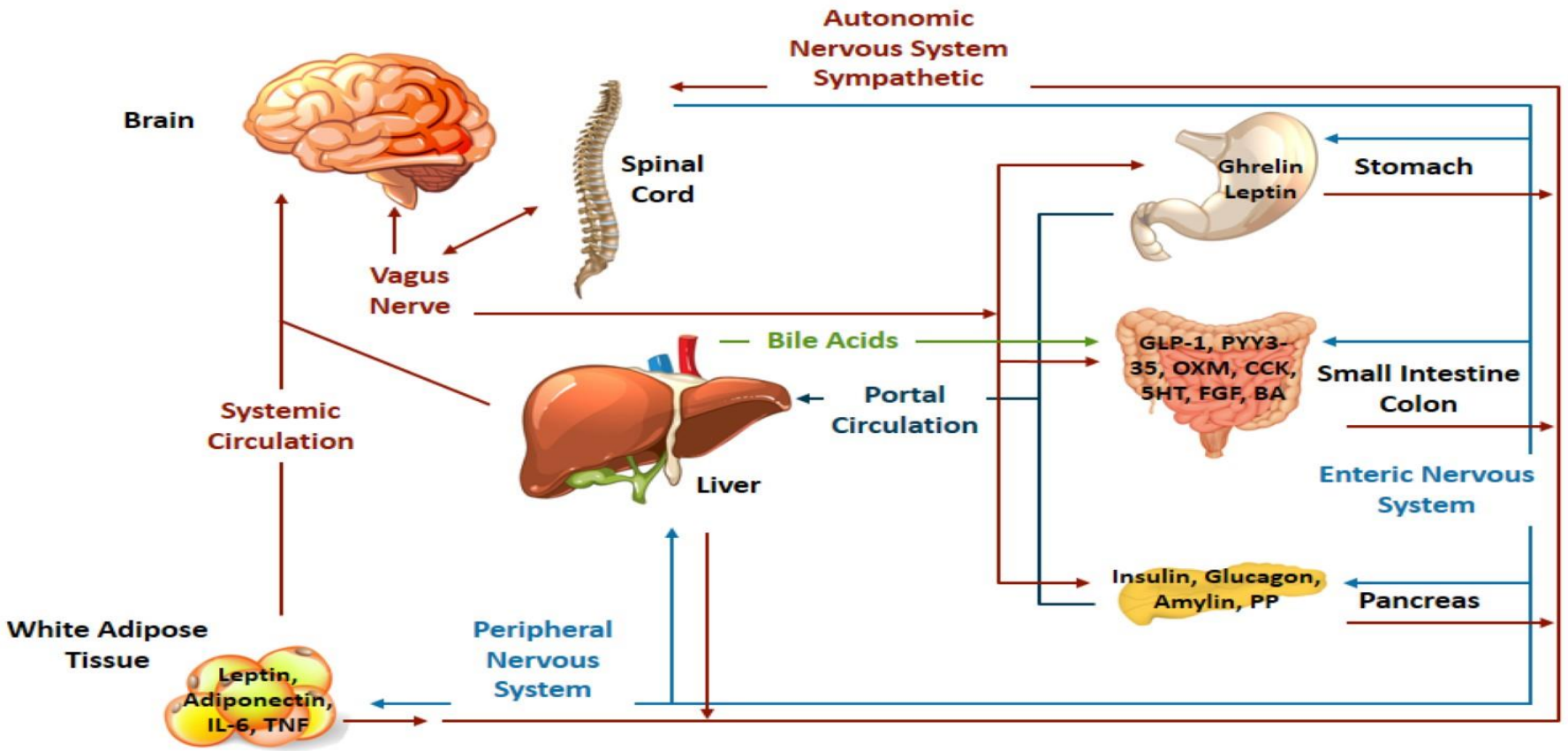
CNS strukture odgovorne za unos hrane

- Hipotalamus
- Moždano stablo
- Srednji mozak

Unos hrane definišu:

- Homeostazni sistem
  - Posle-konzumiranja
  - Posle apsorpcije
- Hedonizam/zadovoljstvo-nagrada sistem:
  - konzumiranje
- Interakcije homeostaznih i hedonističkih mehanizama

Mechanisms of Food Intake Regulation



Acosta A, et al. *Gut*. 2014;63:687-695.

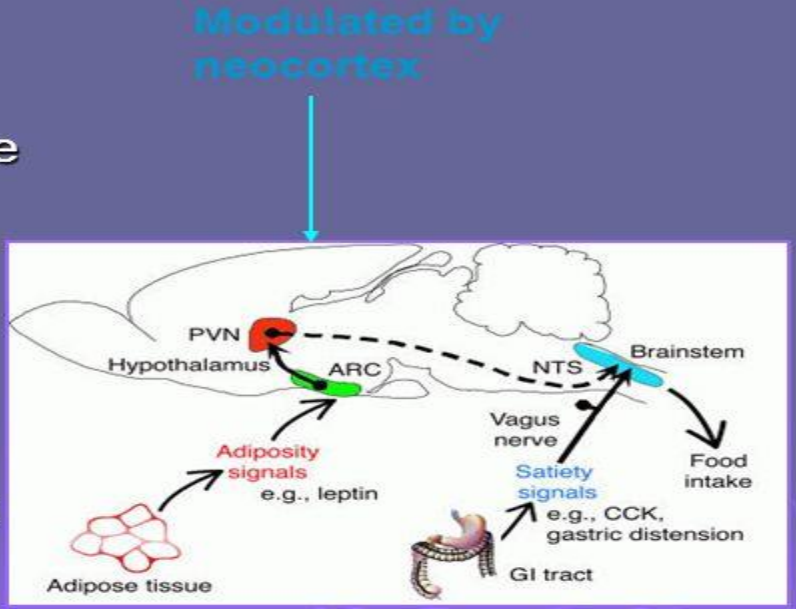
Homeostazni sistem – ključne komponente

- Hipotalamus
  - **Oreksogeni neuroni** (na njih deluju *neurpeptide Y* – NPY; *agouti-related peptide* – AgRP)
  - **Anoreksogeni neuroni** (na njih deluju *propiomelanocortin – POMC; cocaine and amphetamine regulated transcript – CART*)
- Signali adipoznosti
  - Leptin
  - Insulun
- Gastrointestinalni hormoni, regulatori apetita
  - **Oreksogeni** (apetit ↑)
  - **Anoreksogeni** (apetit ↓)
- Hranom uslovljeni signali
- *N. vagus*

Hypothalamus and brain stem are crucial in central regulation of feeding

Integration of brain neurotransmiters, peripheral neurohumoral afferents, adipocyte-derived signals, GIT peptides

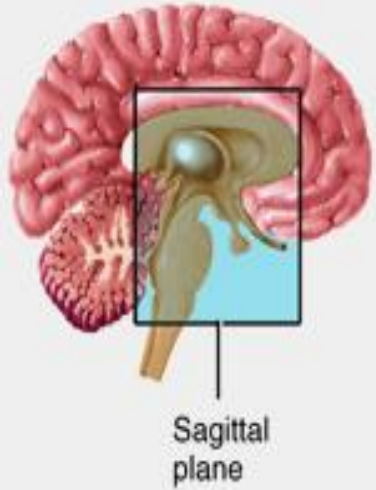
- **N. arcuatus (ARC)** — receptors for hormones and neuropetides that regulate feeding
- **N. paraventricularis (PVN)** — integration of signals from ARC with thyroid and HPA axes
- **N. vagus** — satiety signals to the brain stem after ingestion of a meal
- **N. tractus solitarius + PVN** — connection of brainstem with hypothalamus (serotoninergic neurons)

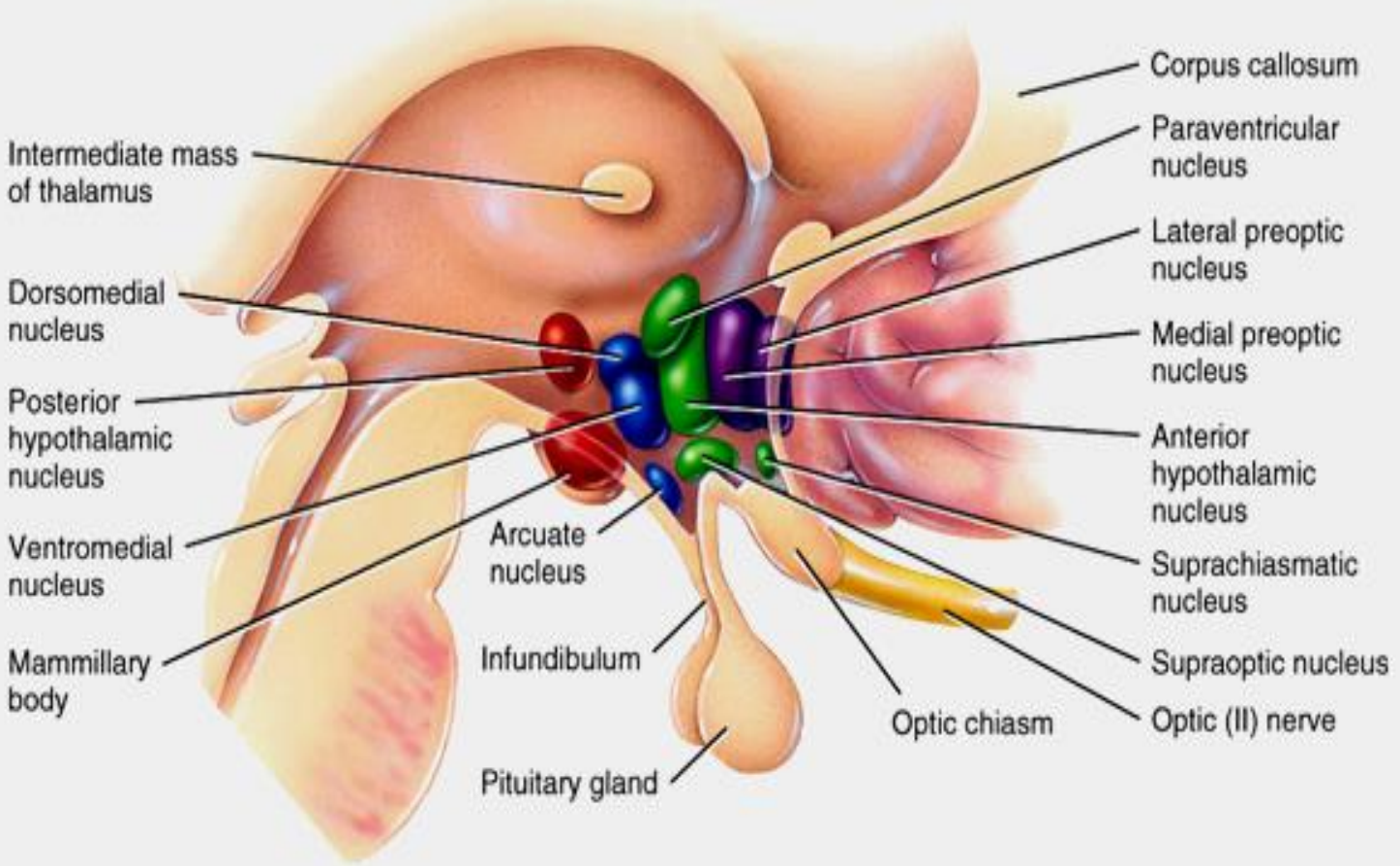


Source: Morton et al. 2005

Hipotalamus

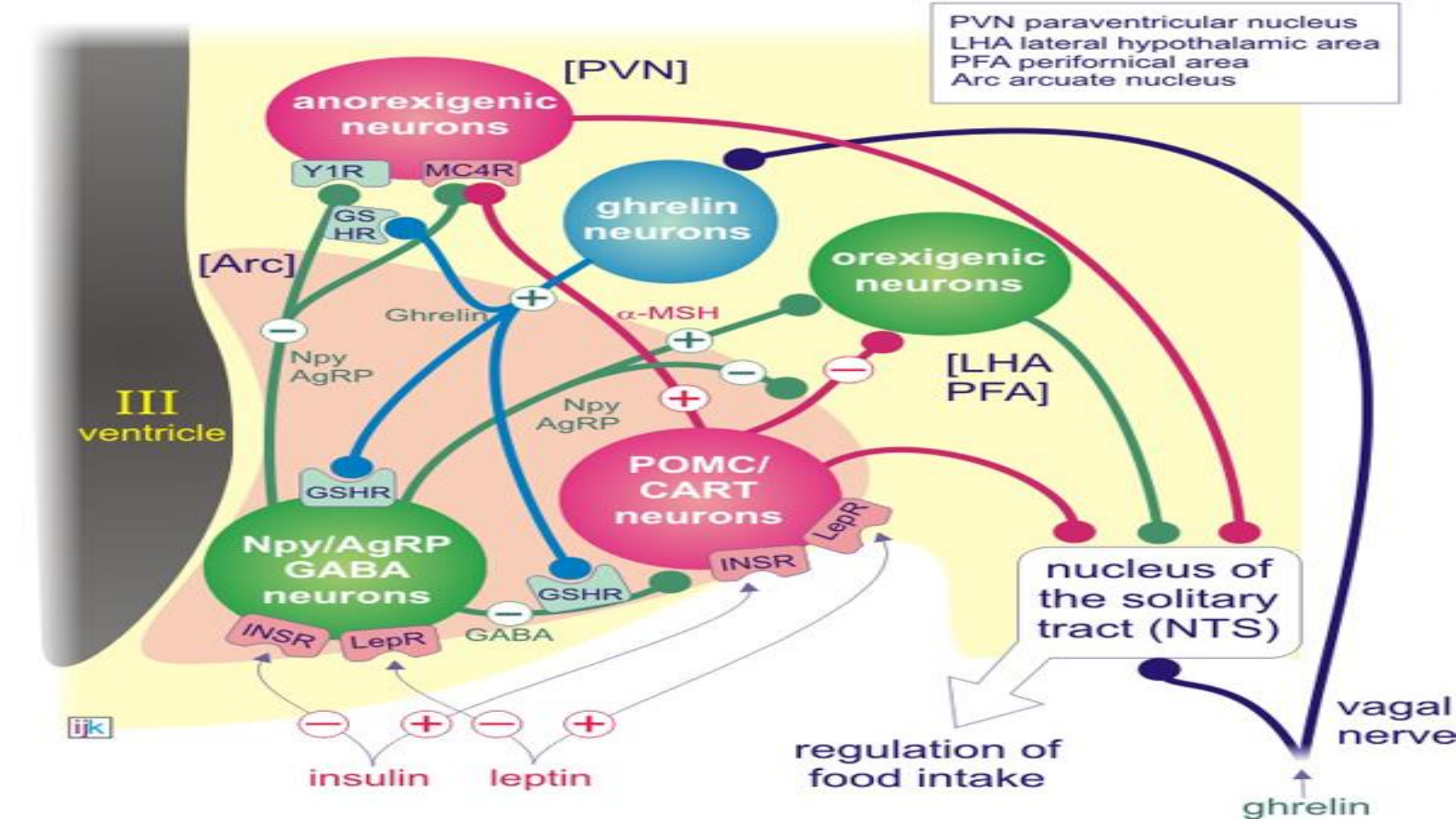
- Reguliše energetsku ravnotežu
  - Kontroliše unos i trošenje energije
  - Endogeni melanokortinski receptori
- *Nucleus arcuatus*
  - Integracija neuronskih i signala iz krvi
- Moždani sistem nagrade (*pons + medula oblongata*)
  - Hedonički unos hrane (dopamin)
  - Mezolimbički i mezokortikalni dopaminergički putevi





Key:

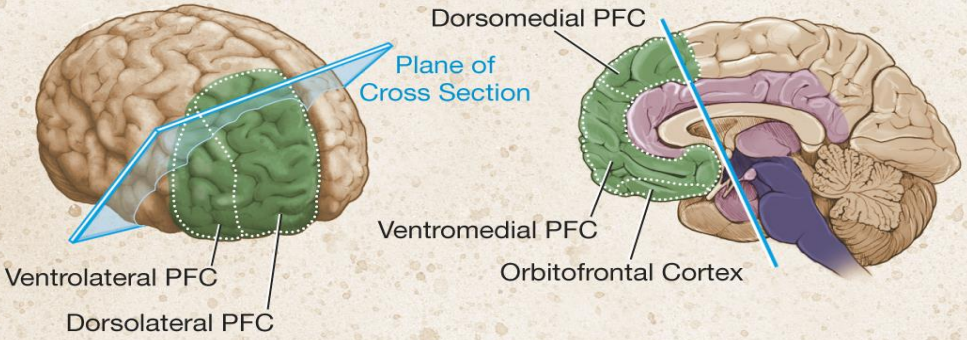
- Mammillary region
- Tuberal region
- Supraoptic region
- Preoptic region


PVN paraventricular nucleus
LHA lateral hypothalamic area
PFA perifornical area
Arc arcuate nucleus
[PVN]
anorexigenic neurons
Y1R
MC4R
GS HR
ghrelin neurons
orexigenic neurons
[Arc]
Ghrelin
α-MSH
Npy AgRP
[LHA PFA]
III ventricle
Npy AgRP
GSHR
POMC/ CART neurons
LepR
INSR
Npy/AgRP GABA neurons
GSHR
INSR
LepR
GABA
nucleus of the solitary tract (NTS)
vagal nerve
insulin
leptin
regulation of food intake
ghrelin

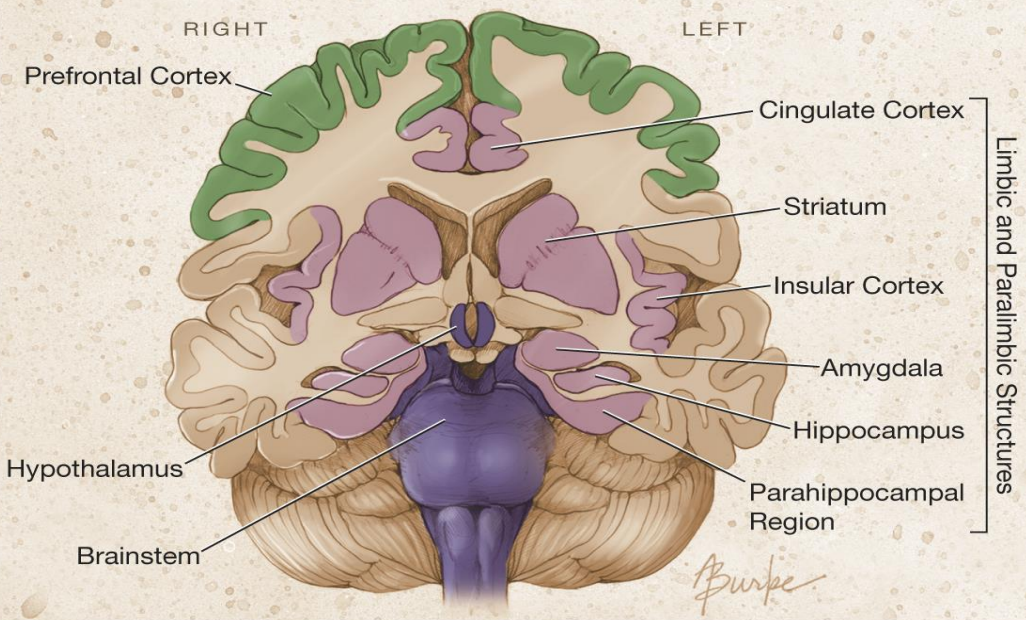
Tegmentum mesencephali

- Sadrži dopaminergičke neurone koji imaju prokekcije ka kortiko-limbičkim strukturama
  - *Nucleus accumbens* (zadovoljstvo)
  - Medijalni prefrontalni korteks (kognitivne funkcije)
  - *Hippocampus* (pamćenje)
  - *Nuclei amigdali* (emocionalna reakcija)
- Direktne uticaje od hipotalamusa
  upravlja sa nekoliko endokrinih procesa (leptin, grelin)

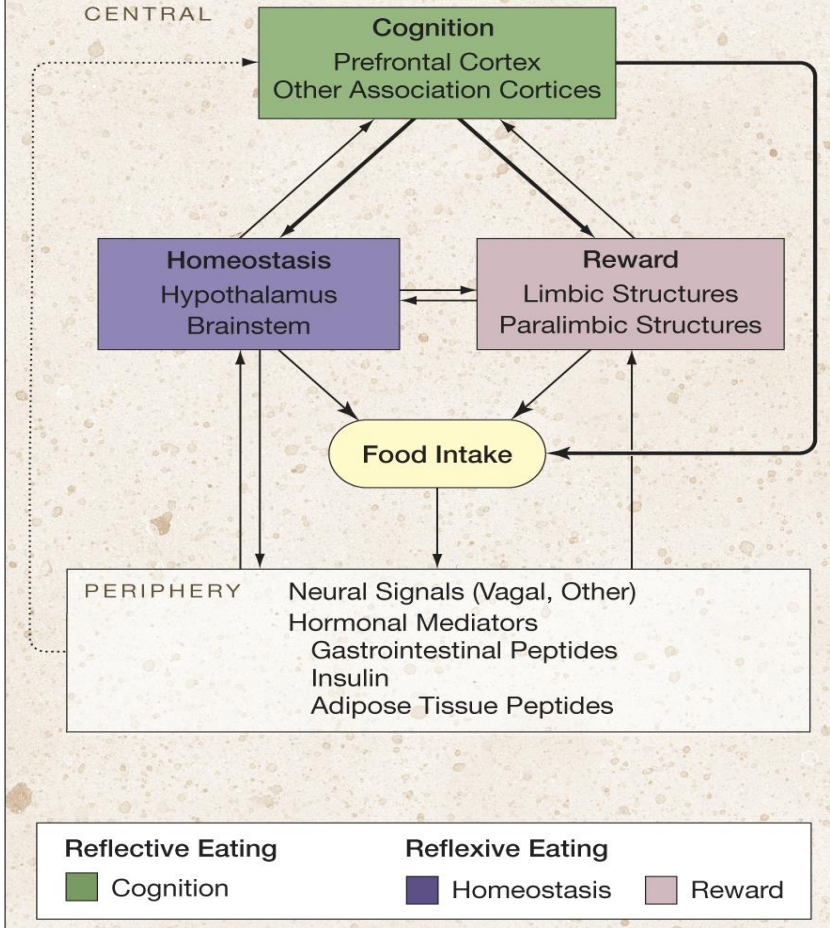
Anatomical Structures Involved in Regulation of Food Intake



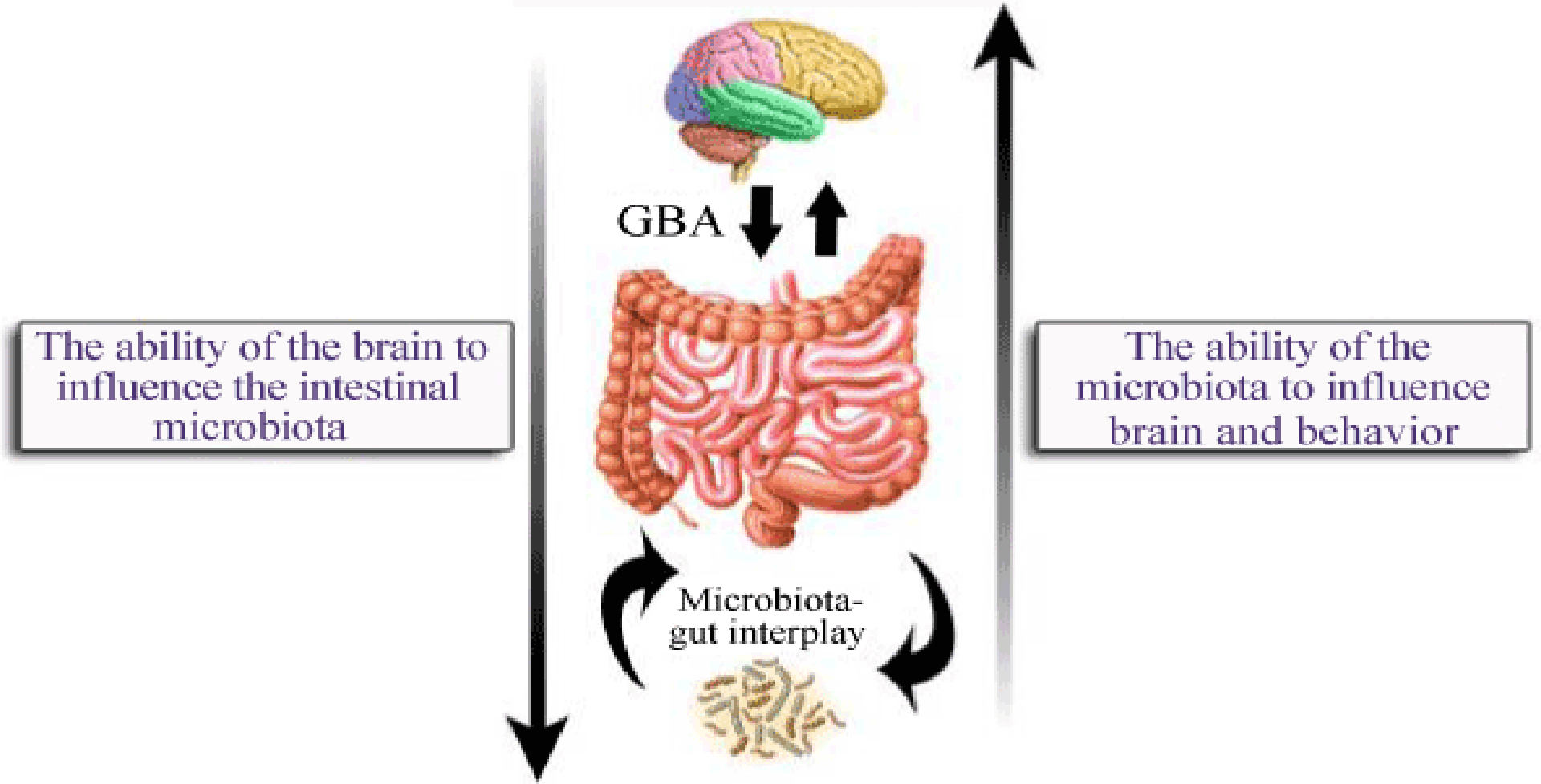
Cross Section of the Brain



Interactions of Reflective and Reflexive Eating Pathways



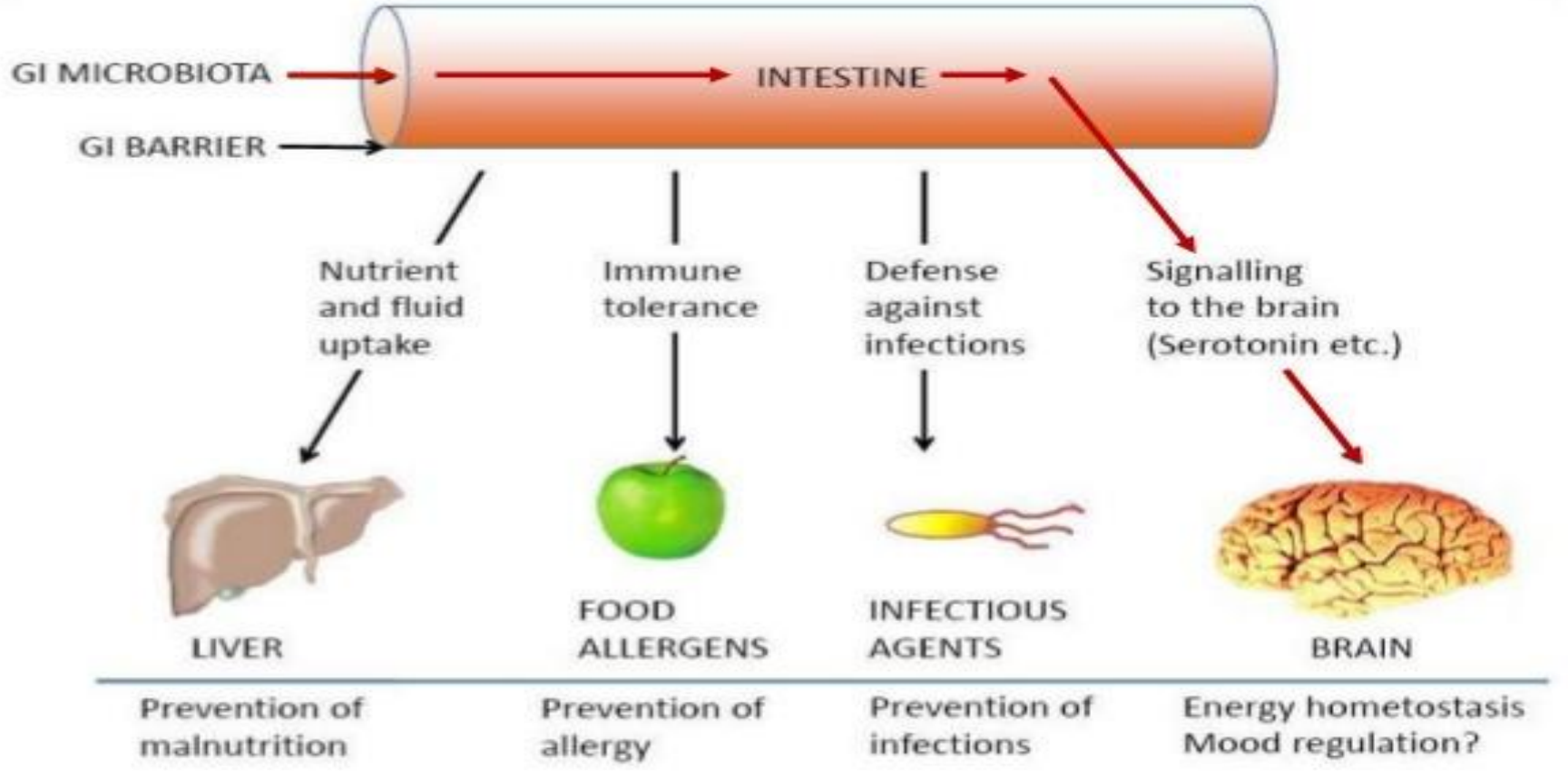
Gut-brain axis



The ability of the brain to influence the intestinal microbiota

The ability of the microbiota to influence brain and behavior

The microbiota-gut-brain axis



Healthy Gut Microbiota

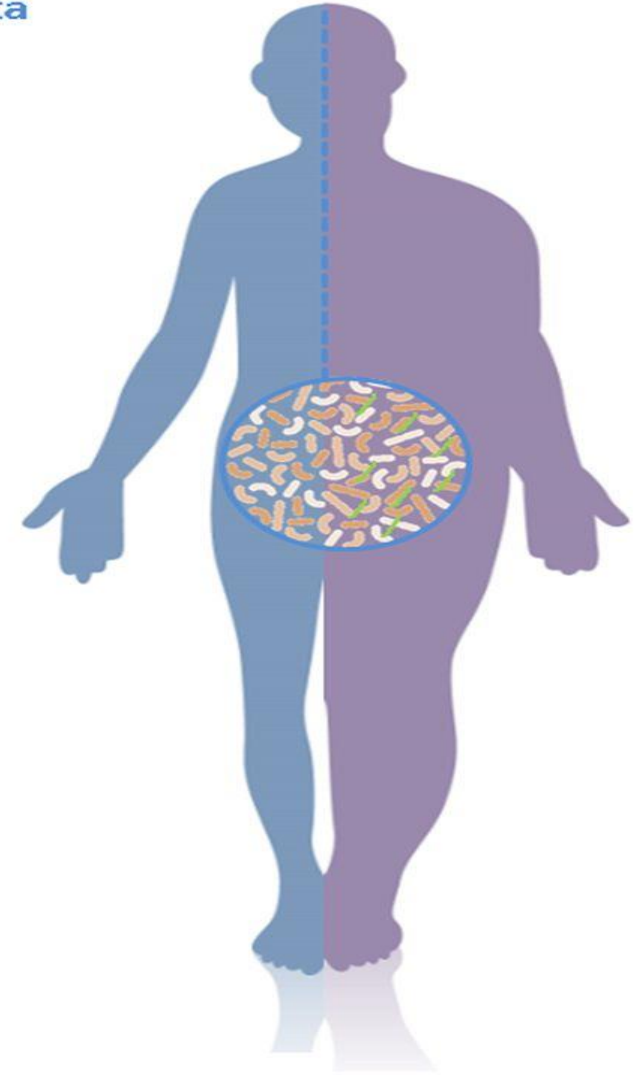
Composition
Bacteroidetes : Firmicutes

Epithelium

IEC differentiation
Tight junction function
Intestinal barrier integrity
Energy harvest
Vitamin K synthesis
SCFA production

Immune System
Innate and adaptive immune response stimulation

Liver
Acetate and propionate
(Gluconeogenesis / lipogenesis)



Obese-Diabetic Microbiota

Composition
Bacteroidetes : Firmicutes

Epithelium

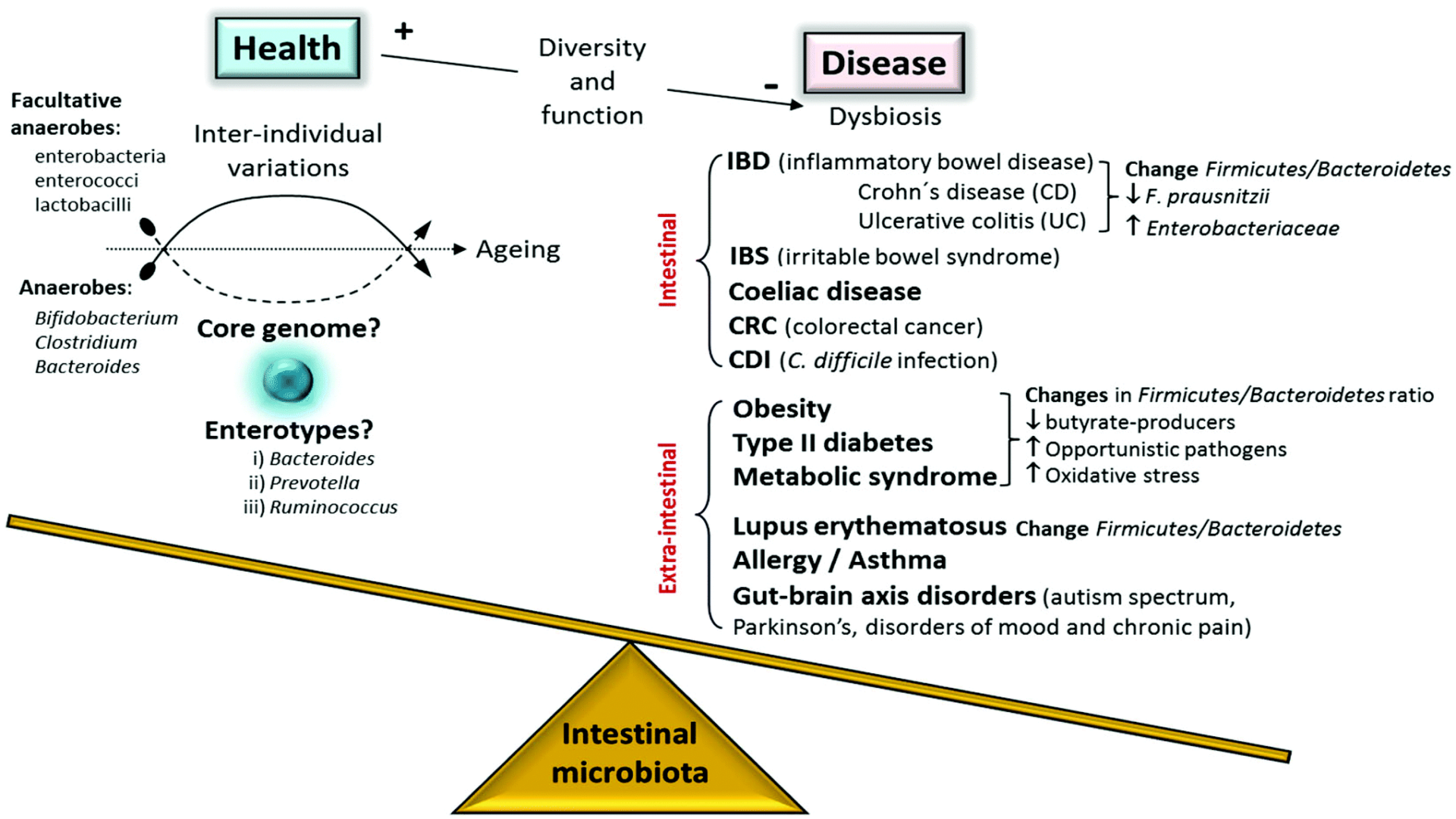
IEC differentiation
Tight junction function
Intestinal barrier integrity
Leaky gut
Pathogen colonisation
Energy harvest
SCFA production

Circulatory System
Metabolic endotoxemia (LPS)

Liver

Lipogenesis
Inflammation
Oxidative stress
Insulin resistance

Adipose Tissue
Inflammation
Oxidative stress
Macrophage infiltration
Insulin resistance


Health
+
Diversity and function
-
Disease
Dysbiosis
Facultative anaerobes:
enterobacteria
enterococci
lactobacilli
Inter-individual variations
Ageing
Anaerobes:
Bifidobacterium
Clostridium
Bacteroides
Core genome?
Enterotypes?
i) Bacteroides
ii) Prevotella
iii) Ruminococcus
Intestinal
IBD (inflammatory bowel disease)
Crohn´s disease (CD)
Ulcerative colitis (UC)
Change Firmicutes/Bacteroidetes
↓ F. prausnitzii
↑ Enterobacteriaceae
IBS (irritable bowel syndrome)
Coeliac disease
CRC (colorectal cancer)
CDI (C. difficile infection)
Extra-intestinal
Obesity
Type II diabetes
Metabolic syndrome
Changes in Firmicutes/Bacteroidetes ratio
↓ butyrate-producers
↑ Opportunistic pathogens
↑ Oxidative stress
Lupus erythematosus Change Firmicutes/Bacteroidetes
Allergy / Asthma
Gut-brain axis disorders (autism spectrum, Parkinson's, disorders of mood and chronic pain)
Intestinal microbiota

DavidAWiss@NutritionInRecovery.com

"ADDICTION" – DSM-5???

- Non-Substance-Related
  - Gambling
- Behavioral Addictions?
  - Sex Addiction
  - Exercise Addiction
  - Shopping Addiction
  - Gaming

➡ **Currently insufficient evidence for diagnostic criteria**

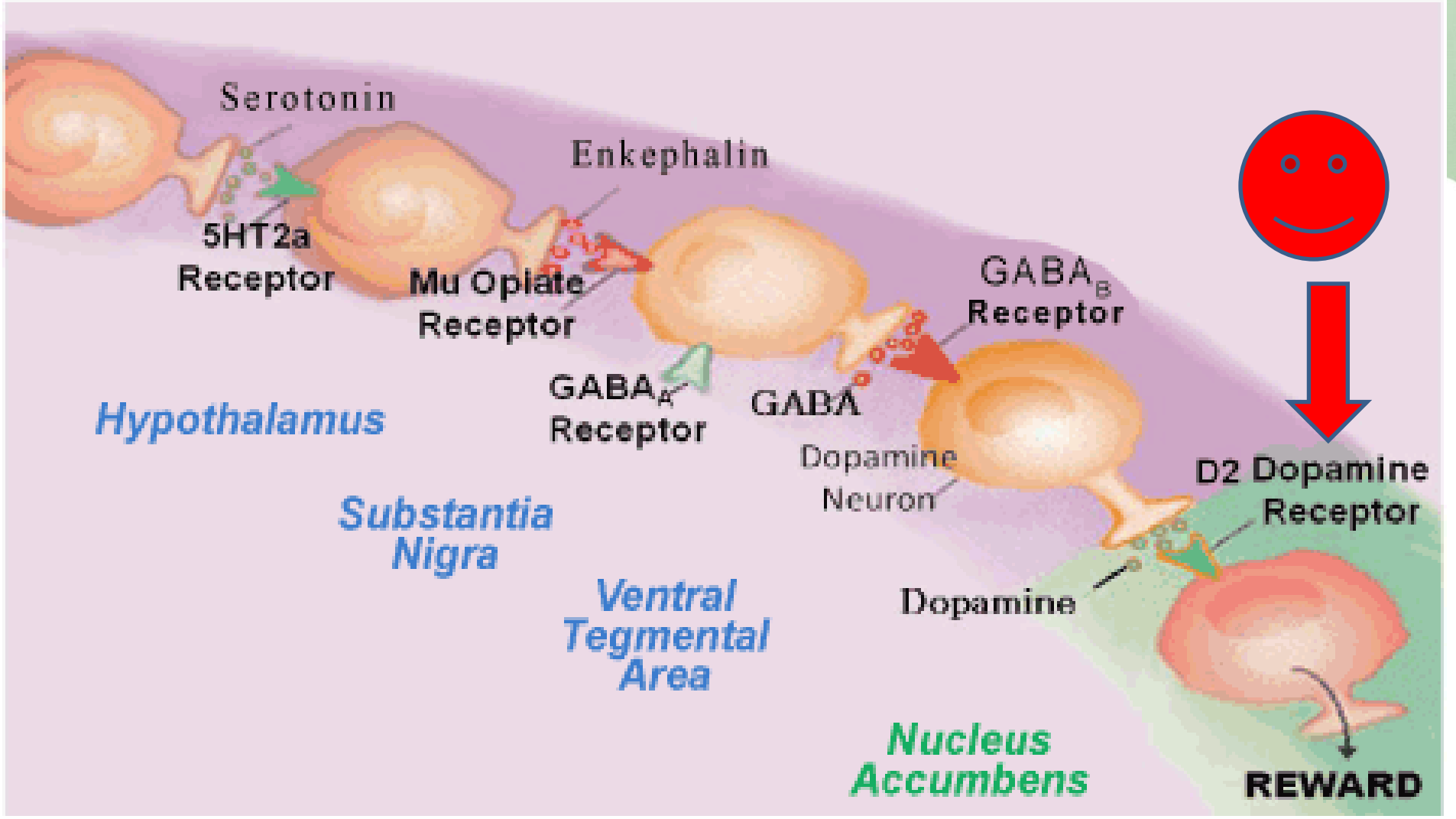
What about food???

Is it substance-related?

Behavioral?

Both?

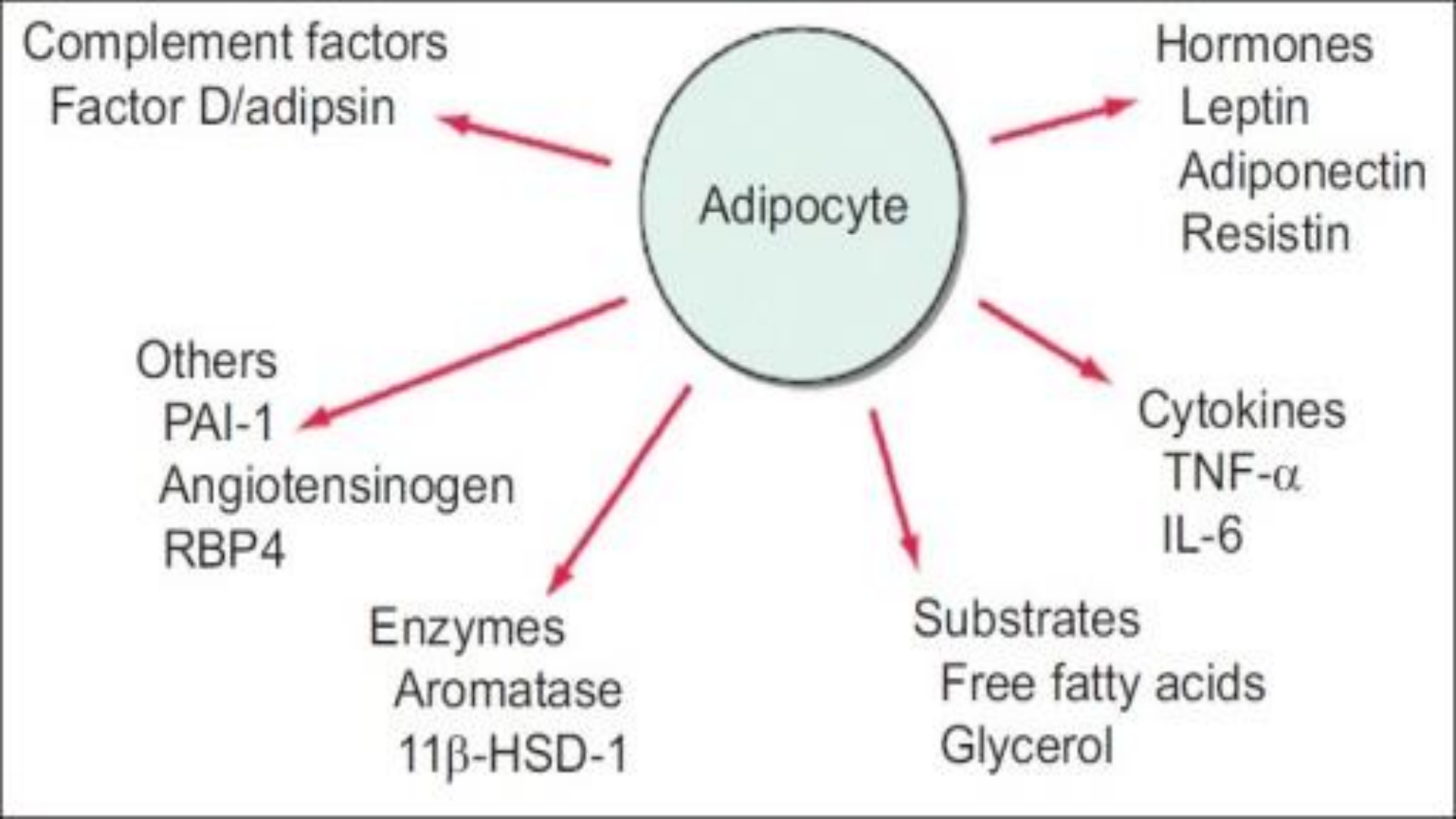
I CAN DO ANYTHING IN ORDER TO LOSE WEIGHT - EXCEPT CHANGING MY EATING HABITS.

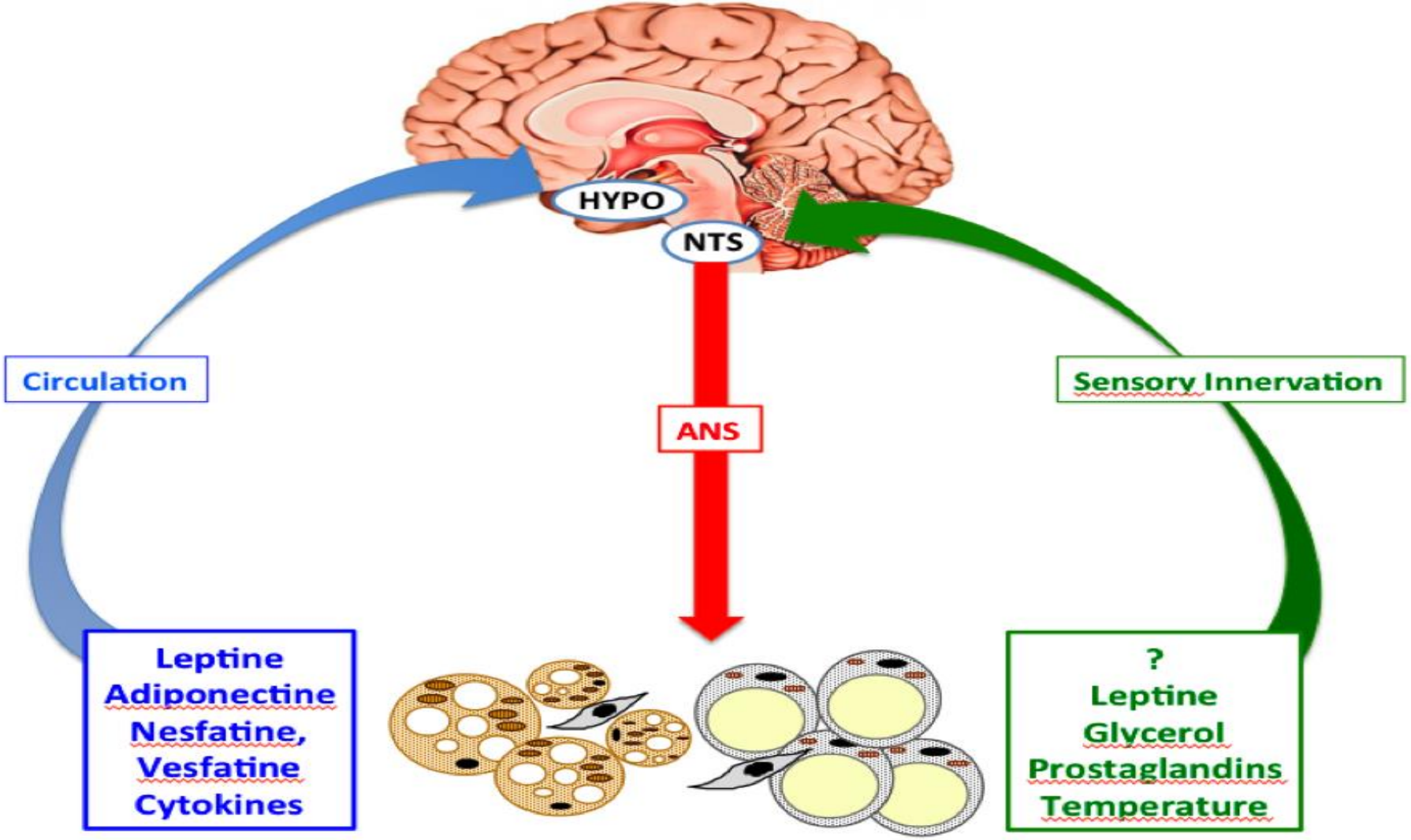

Serotonin
5HT2a
Receptor
Enkephalin
Mu Opiate
Receptor
GABA$_A$
Receptor
GABA$_B$
Receptor
GABA
Hypothalamus
Substantia
Nigra
Dopamine
Neuron
Ventral
Tegmental
Area
Dopamine
D2 Dopamine
Receptor
Nucleus
Accumbens
REWARD

Potrošnja energije obuhvata sledeće komponente

- Bazalna metabolička potrošnja u mirovanju;
- Energetska potrošnja za metabolisanje i skladištenje hrane;
- Termički efekat fizičke aktivnosti;
- Adaptivna termogeneza koja varira zavisno od hroničnog kalorijskog unosa (raste kada je unos veći)

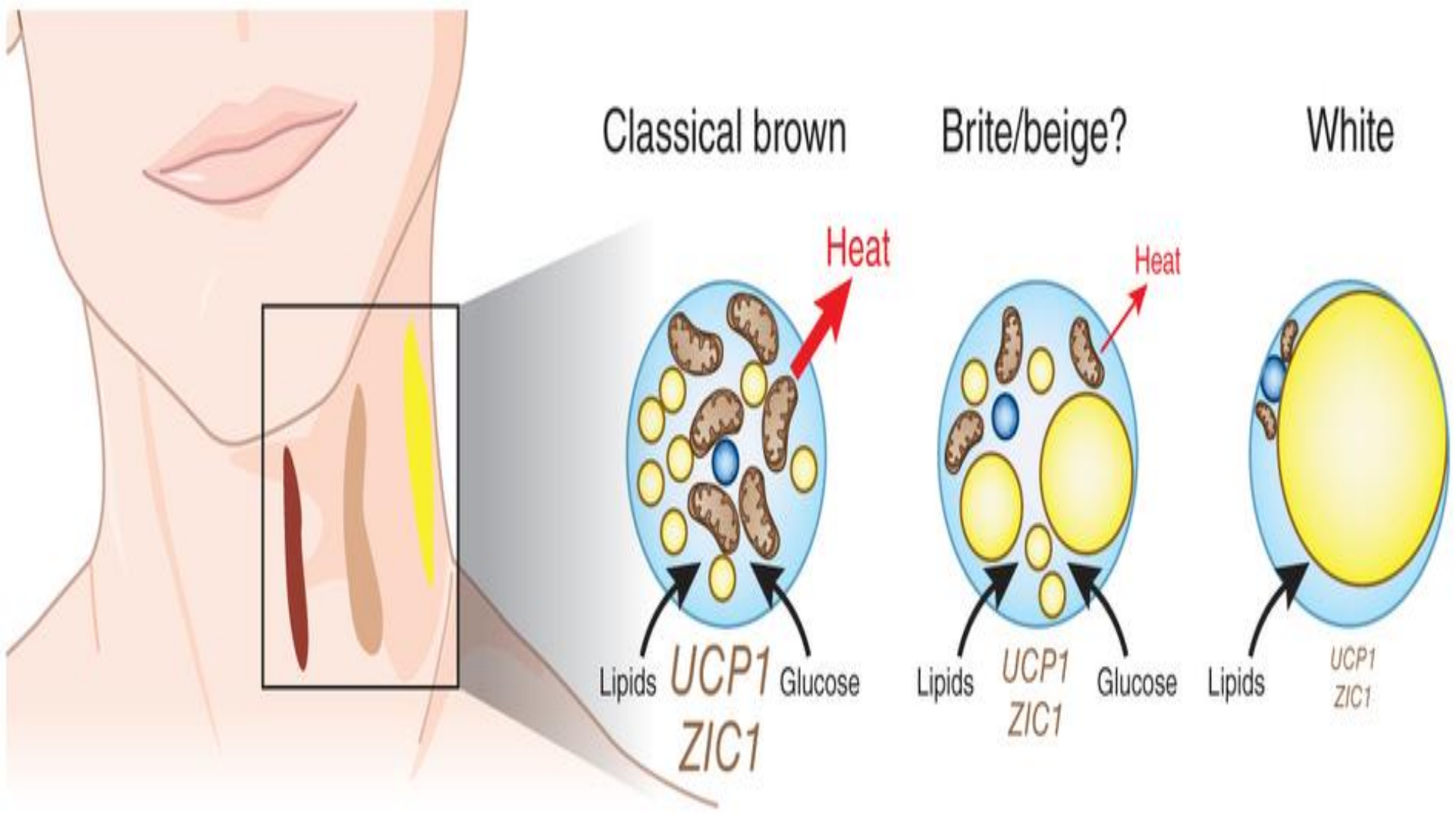
Bazalna metabolička stopa je odgovorna za oko 70% dnevne potrošnje energije, kojoj fizička aktivnost doprinosi sa 5-10%.


Complement factors
Factor D/adipsin
Adipocyte
Hormones
Leptin
Adiponectin
Resistin
Others
PAI-1
Angiotensinogen
RBP4
Cytokines
TNF-α
IL-6
Enzymes
Aromatase
11β-HSD-1
Substrates
Free fatty acids
Glycerol


HYPO
NTS
Circulation
ANS
Sensory Innervation
Leptine
Adiponectine
Nesfatine,
Vesfatine
Cytokines
?
Leptine
Glycerol
Prostaglandins
Temperature

- Adaptivna termogeneza se dešava u smedjem masnom tkivu-SMT, koje ima značajnu ulogu u metabolizmu mnogih sisara.

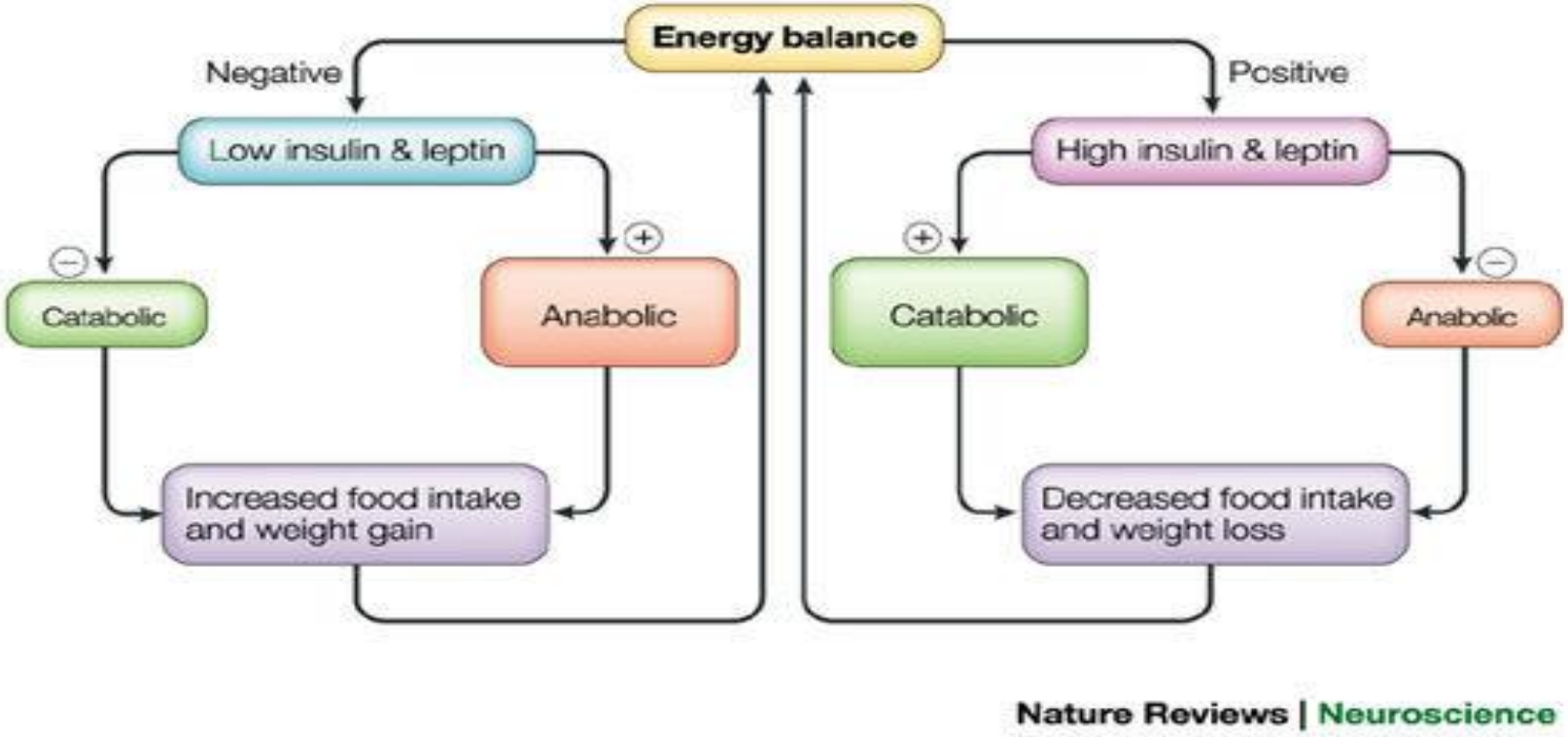
- Za razliku od belog masnog tkiva, koje koristi za skladištenje energije u formi lipida, SMS troši uskladištenu energiju kao toplotu.

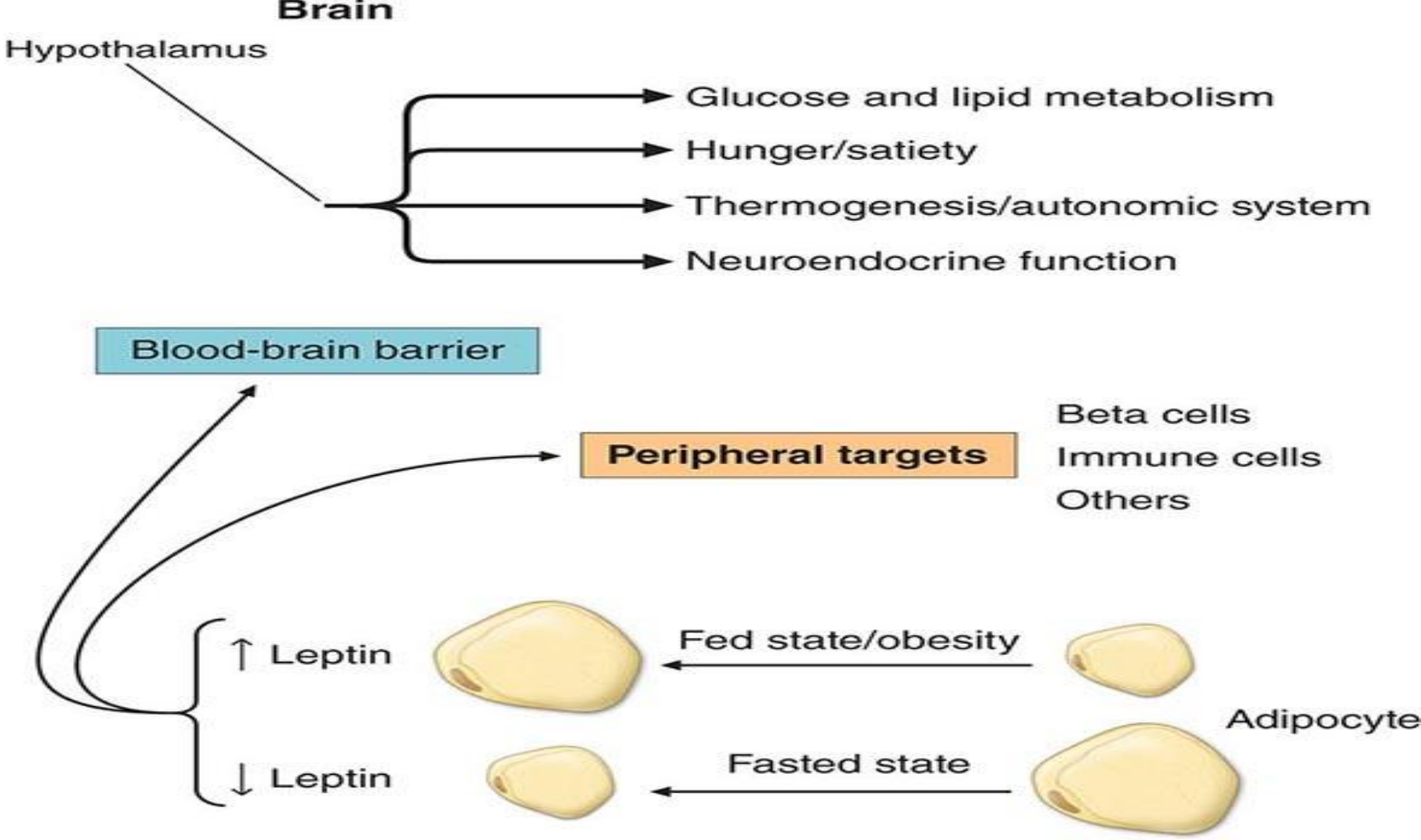

Classical brown
Brite/beige?
White
Heat
Heat
Lipids
UCP1
ZIC1
Glucose
Lipids
UCP1
ZIC1
Glucose
Lipids
UCP1
ZIC1

- Mitohondrijalni nespareni (*uncoupling*) protein – UCP-1 u smedjem masnom tkivu (SMT) “rasipa” gradijent vodonikovih jona u lancu oksidativne respiracije i oslobadja energiju u obliku toplote.

- Metabolička aktivnost SMT povećava se centralnom aktivnošću leptina, putem simpatičkog nervnog sistema, koji masivno inerviše ovo tkivo.

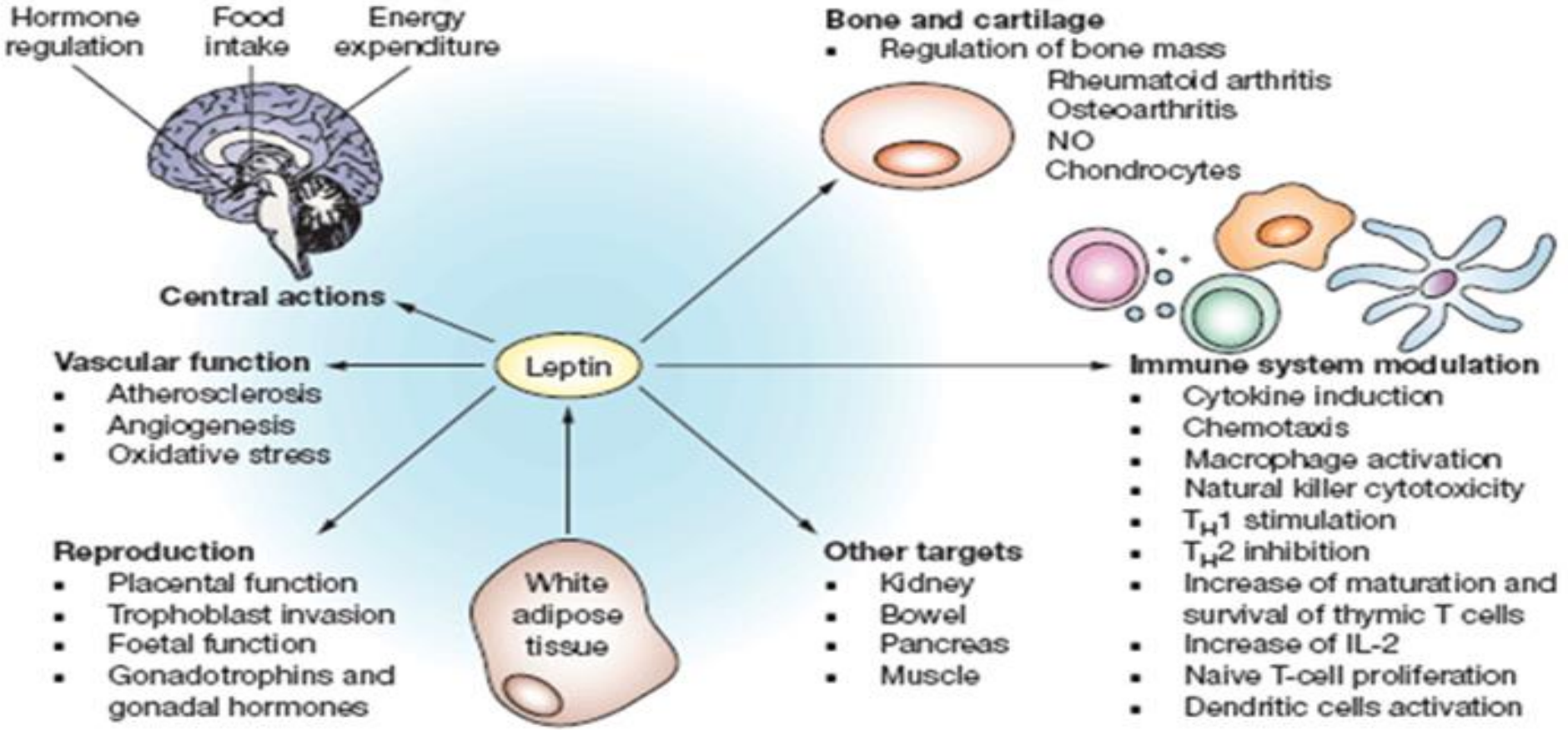
Leptin & Insulin = Anoreksogeni signali




Brain
Hypothalamus
Glucose and lipid metabolism
Hunger/satiety
Thermogenesis/autonomic system
Neuroendocrine function
Blood-brain barrier
Peripheral targets
Beta cells
Immune cells
Others
↑ Leptin
↓ Leptin
Fed state/obesity
Fasted state
Adipocyte

- Adipozno tkivo se sastoji od adipoznih ćelija u kojima se skladište lipidi i stromalnog/vaskularnog dela, u kojem se nalaze preadipociti.
- Masa adipocita se povećava uvećanjem adipoznih ćelija skladištenjem količine lipida, kao i umnožavanjem broja adipocita.
- Proces kojim nastaju adipociti od preadipocitnih mezenhimalnih ćelija je kontrolisan serijom koraka diferencijacije, koja je opet regulisana kaskadom specifičnih transkripcionih faktora.
- Jedan od ključnih transkripcionih faktora je peroksizom-proliferator-aktivirajući receptora ϒ (PPAR ϒ), jedarni receptor koji vezuje tiazolidinedionsku klasu insulin-senzitivnih lekova koji se koriste u tretmanu dijabetesa tip 2.

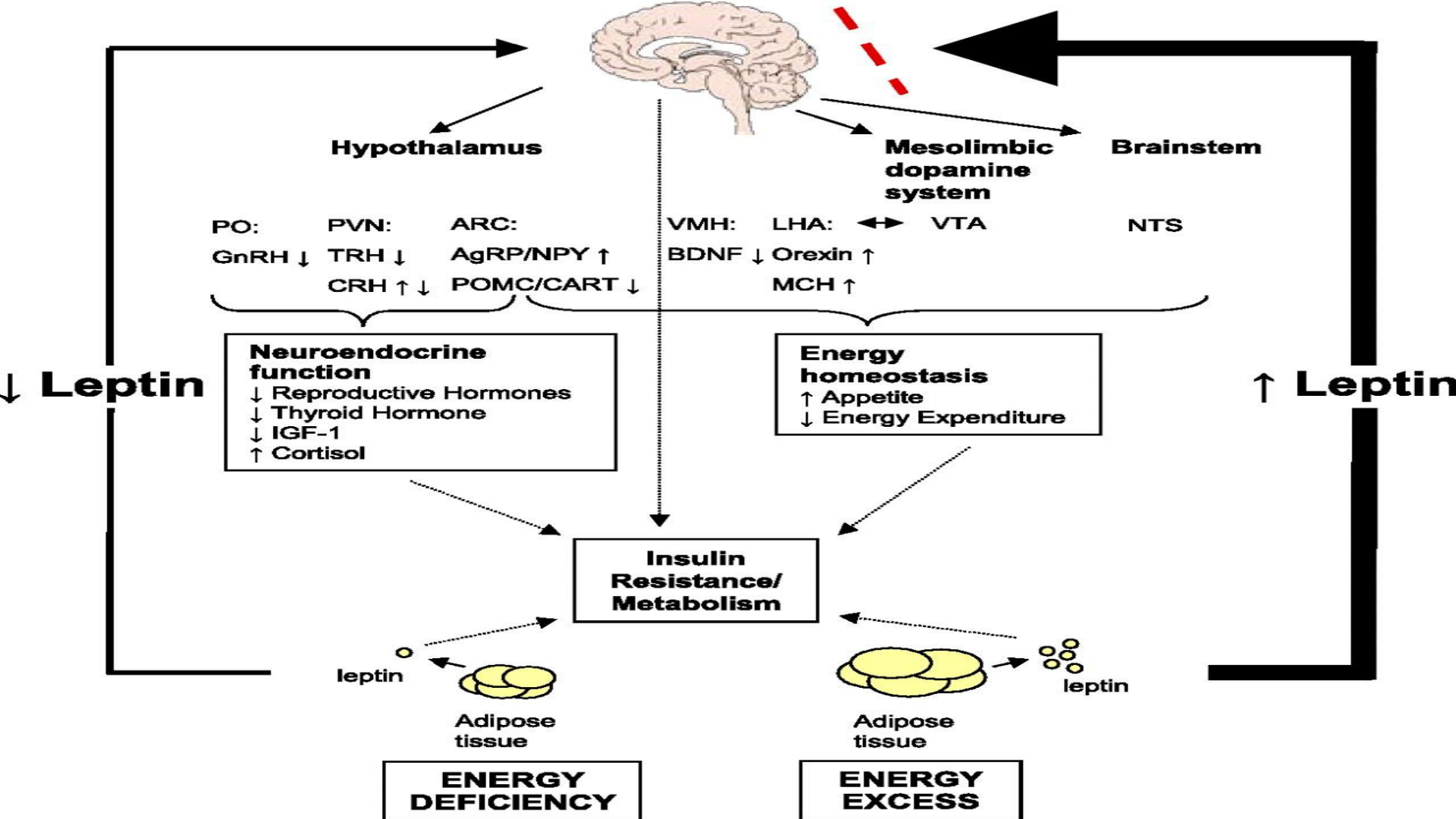
Importance Of Leptin



Source: Nat Clin Pract Rheumatol ©2007 Nature Publishing Group

Leptin I/II

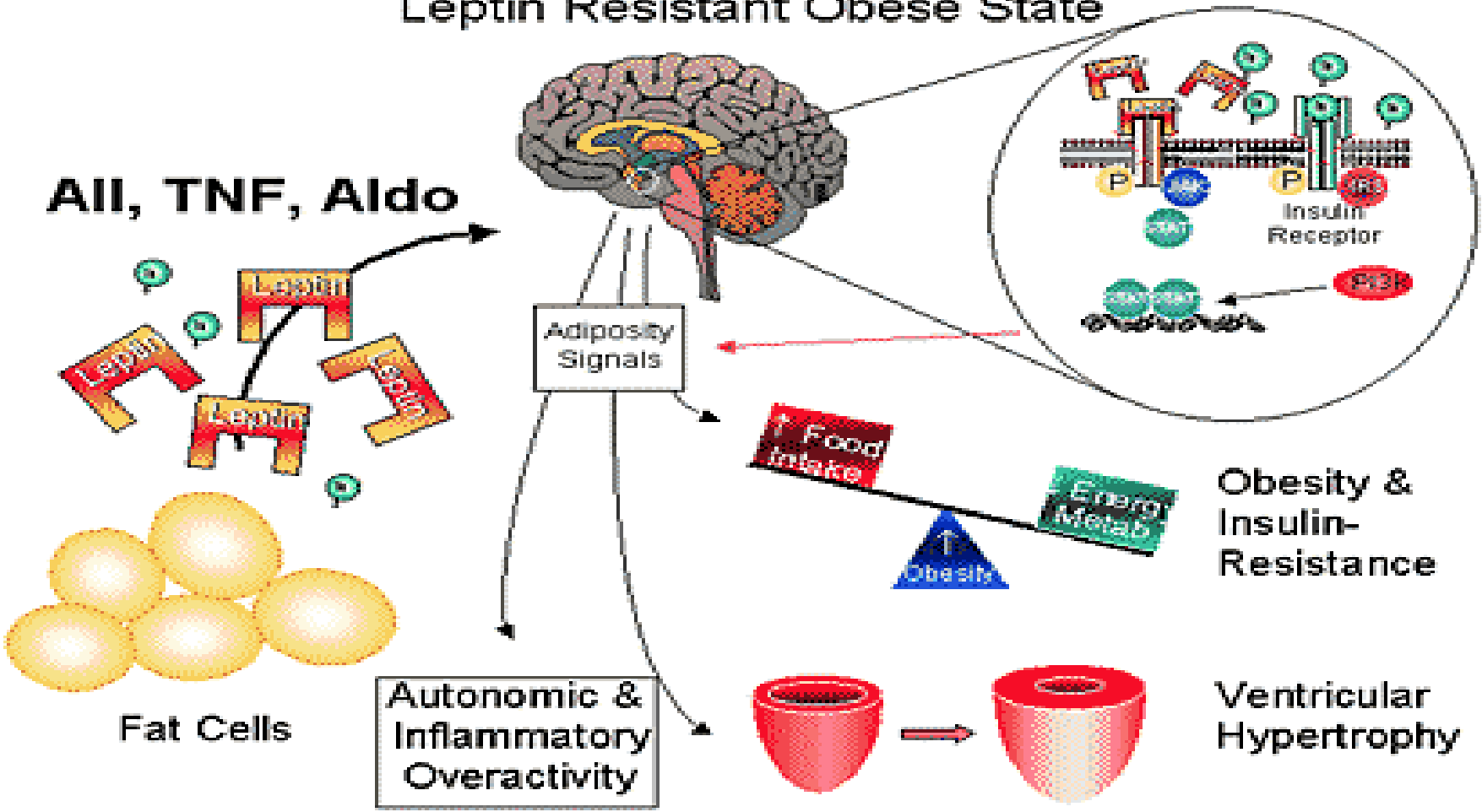
- Luče beli adipociti i oslobadja se u cirkulaciju;
- Koncetracije u krvi srazmerne količini masnog tkiva (biomarker masnog tkiva);
- Vezuje za receptore u ARC (*arcuate nucleus)*
  - Redukuje unos hrane
  - Povećava potrošnju energije.
  - Snižava prag za osećaj slatkog na receptorima jezika
- Oslobadja se i u gastričnom epitelu
  - Lokalno pojačava crevne signale sitosti - holesistokinin


Hypothalamus
Mesolimbic dopamine system
Brainstem
PO:
GnRH ↓
PVN:
TRH ↓
CRH ↑ ↓
ARC:
AgRP/NPY ↑
POMC/CART ↓
VMH:
BDNF ↓
LHA:
Orexin ↑
MCH ↑
VTA
NTS
↓ Leptin
Neuroendocrine function
↓ Reproductive Hormones
↓ Thyroid Hormone
↓ IGF-1
↑ Cortisol
Energy homeostasis
↑ Appetite
↓ Energy Expenditure
↑ Leptin
Insulin Resistance/ Metabolism
leptin
Adipose tissue
leptin
Adipose tissue
ENERGY DEFICIENCY
ENERGY EXCESS

Leptin II/II

- Primena leptina u gojaznih sa endogenim nedostatkom leptina uspešna za tretman hiperfagije;
- Gojazni pacijenti često imaju povišen nivo leptina (dodatna primena leptina nedelotvorna), što ukazuje na **rezistenciju na leptin**:
  - Saturacija leptinskih transportera (hematoencefalna barijera);
  - Povišen nivo proinflamatornih citokina i slobodnih masnih kiselina blokira transport;
  - Redukovan leptin sistem signala u neuronima hipotalamusa;

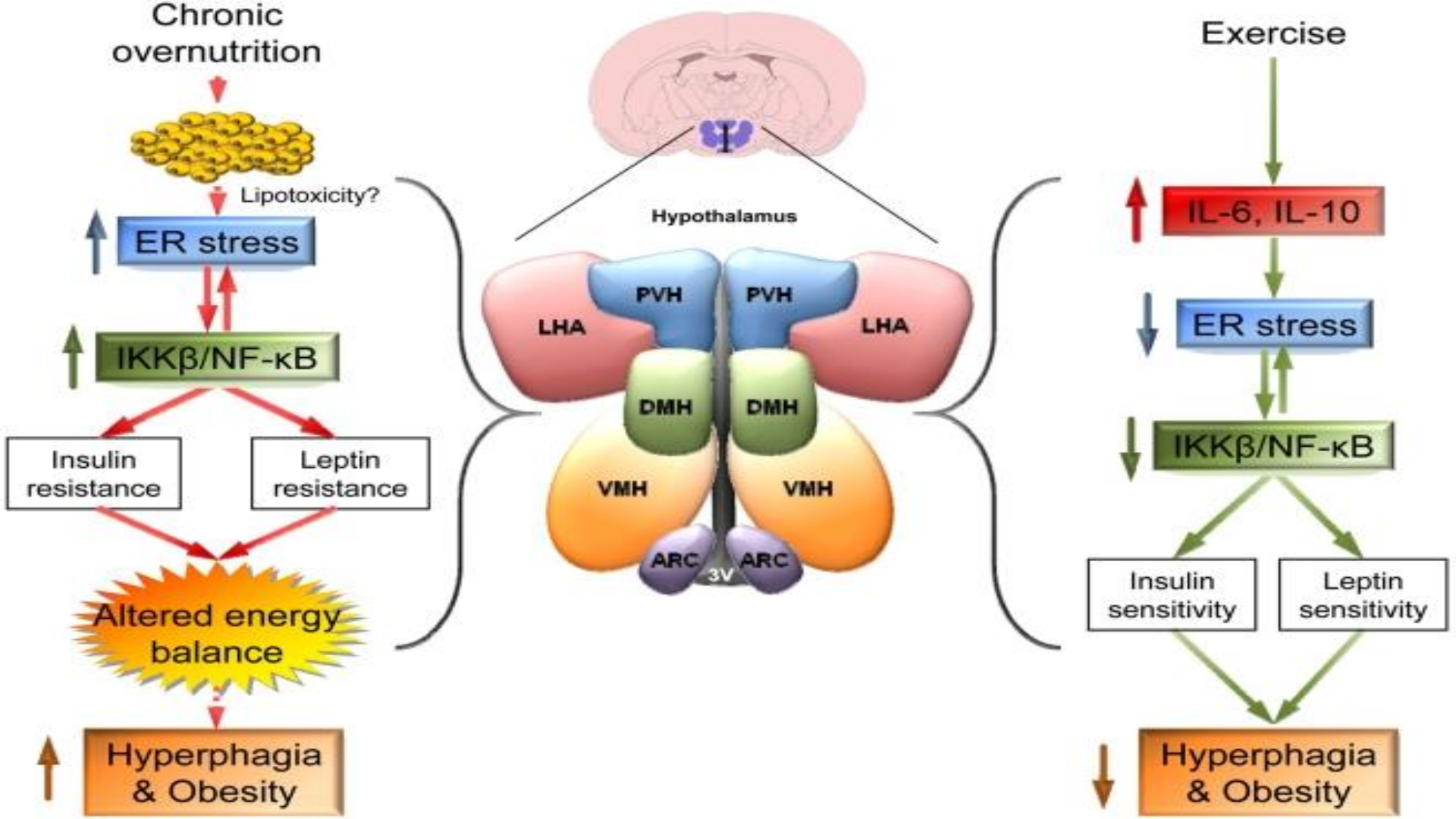
Leptin Resistant Obese State



Seder S, Liu P. Circulation 2003; 108:644-6

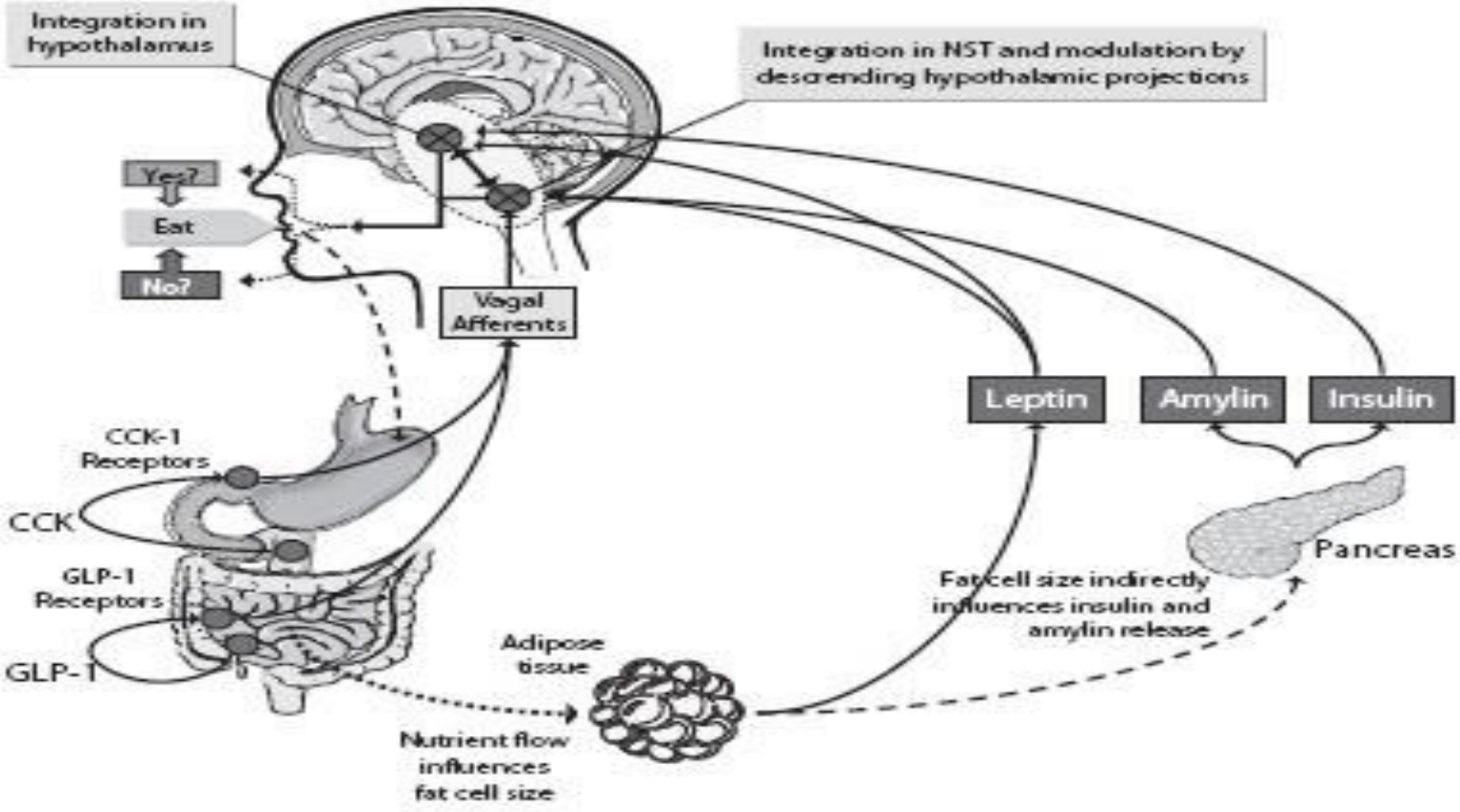
Dejstva insulina

Dejstvo	Tkivo/organ
Efekti na metabolizam ugljenih hidrata	
Popravlja preuzimanje glukoze u ć.	Adipozno i mišićno
Povećava glikolizu	Adipozno i mišićno
Povećava sintezu glikogena	Mišići i jetra
Smanjuje razgradnju glikogena	Mišići i jetra
Smanjuje glikoneogenezu	jetra
Efekti na metabolizam masti	
Smanjuje razgradnju (lipolizu) masti	Adipozno
Povećava sintezu masnih kiselina	Adipozno
Povećava sintezu LDL lipoproteina niske gustine	Jetra
Povećava sintezu holesterola	Jetra
Efekti na metabolizam proteina	
Povećava transport aminokiselina	Razna tkiva
Povećava sintezu proteina	Mišići i druga tkiva
Smanjuje razlaganje proteina	Mišići i druga tkiva

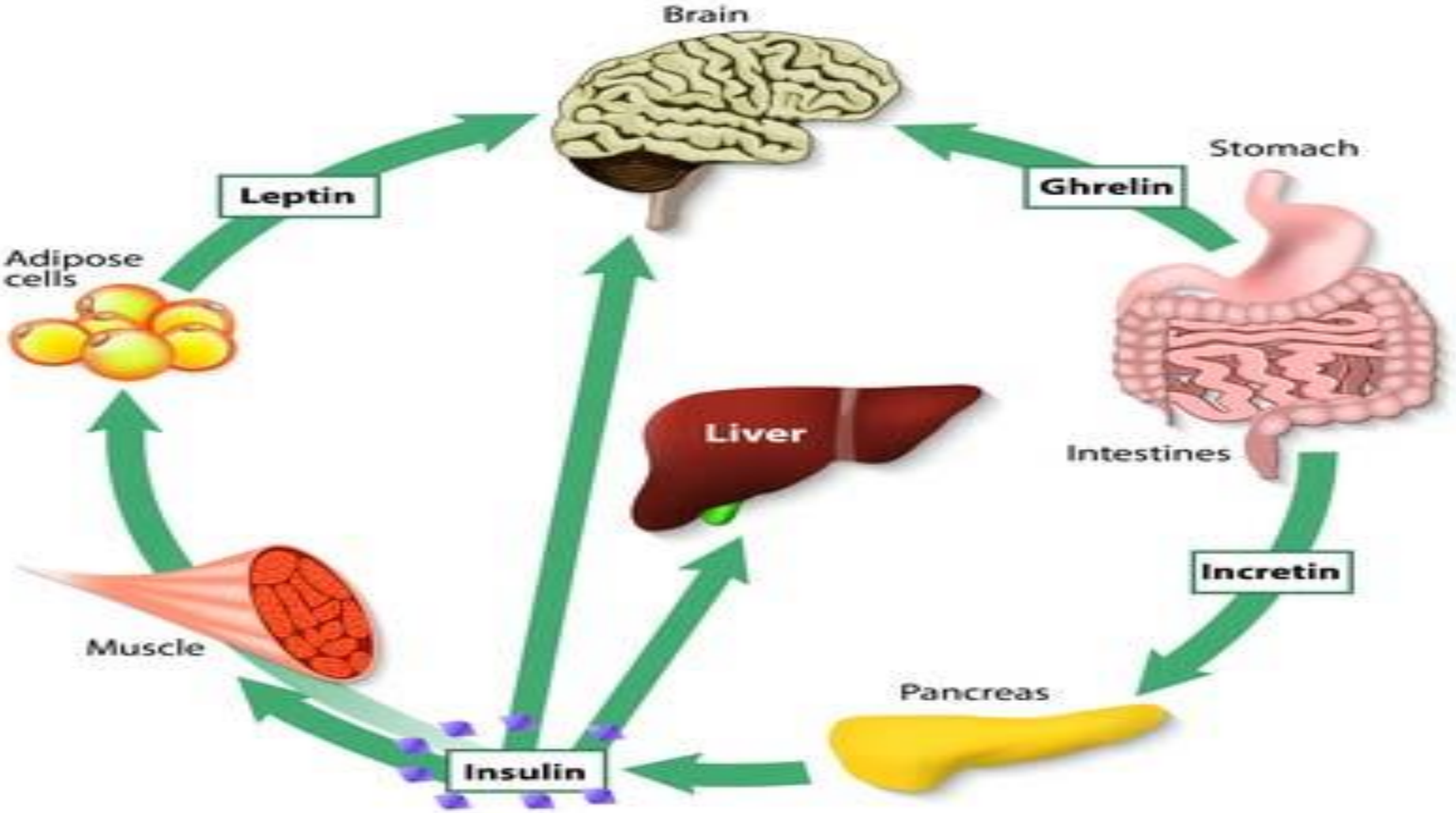

Chronic overnutrition
Lipotoxicity?
ER stress
IKKβ/NF-κB
Insulin resistance
Leptin resistance
Altered energy balance
Hyperphagia & Obesity
Hypothalamus
PVH
PVH
LHA
LHA
DMH
DMH
VMH
VMH
ARC
ARC
3V
Exercise
IL-6, IL-10
ER stress
IKKβ/NF-κB
Insulin sensitivity
Leptin sensitivity
Hyperphagia & Obesity

Insulin

- Brza sekrecija iz pankreasnih beta-ćelija posle obroka i transport do CNS;
- Našte nivo insulina u plazmi u dobroj pozitivnoj korelaciji sa masom masnog tkiva u telu – “surogatni marker za adipoznost”;
- U hipotalamusnim jedrima ekspresija insulinskih receptora u: *arcuate nucleus* (ARC), *dorsomedial nucleus* (DMN), *paraventricular nucleus* (PVN);
- Poput leptina vezuje se za insulinske receptore, što rezultira u aktiviranju POMC neurona i inhibiciji NPY/AgRP neurona preko insulin receptor substrate (IRS)-2;

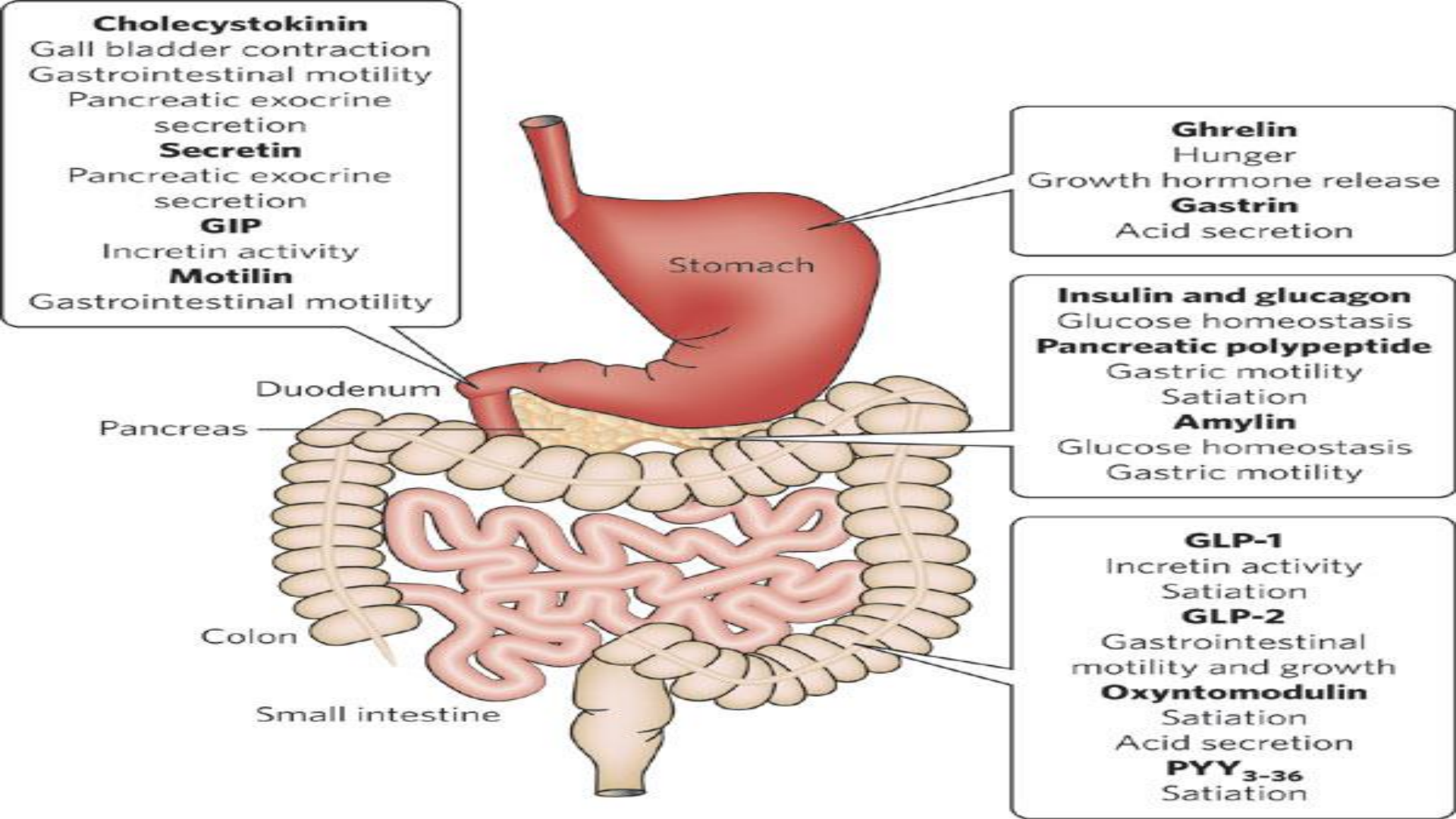

Integration in hypothalamus
Integration in NST and modulation by descending hypothalamic projections
Yes?
Eat
No?
Vagal Afferents
Leptin
Amylin
Insulin
CCK-1 Receptors
CCK
GLP-1 Receptors
GLP-1
Pancreas
Fat cell size indirectly influences insulin and amylin release
Adipose tissue
Nutrient flow influences fat cell size

APPETITE & HUNGER
(hormones)



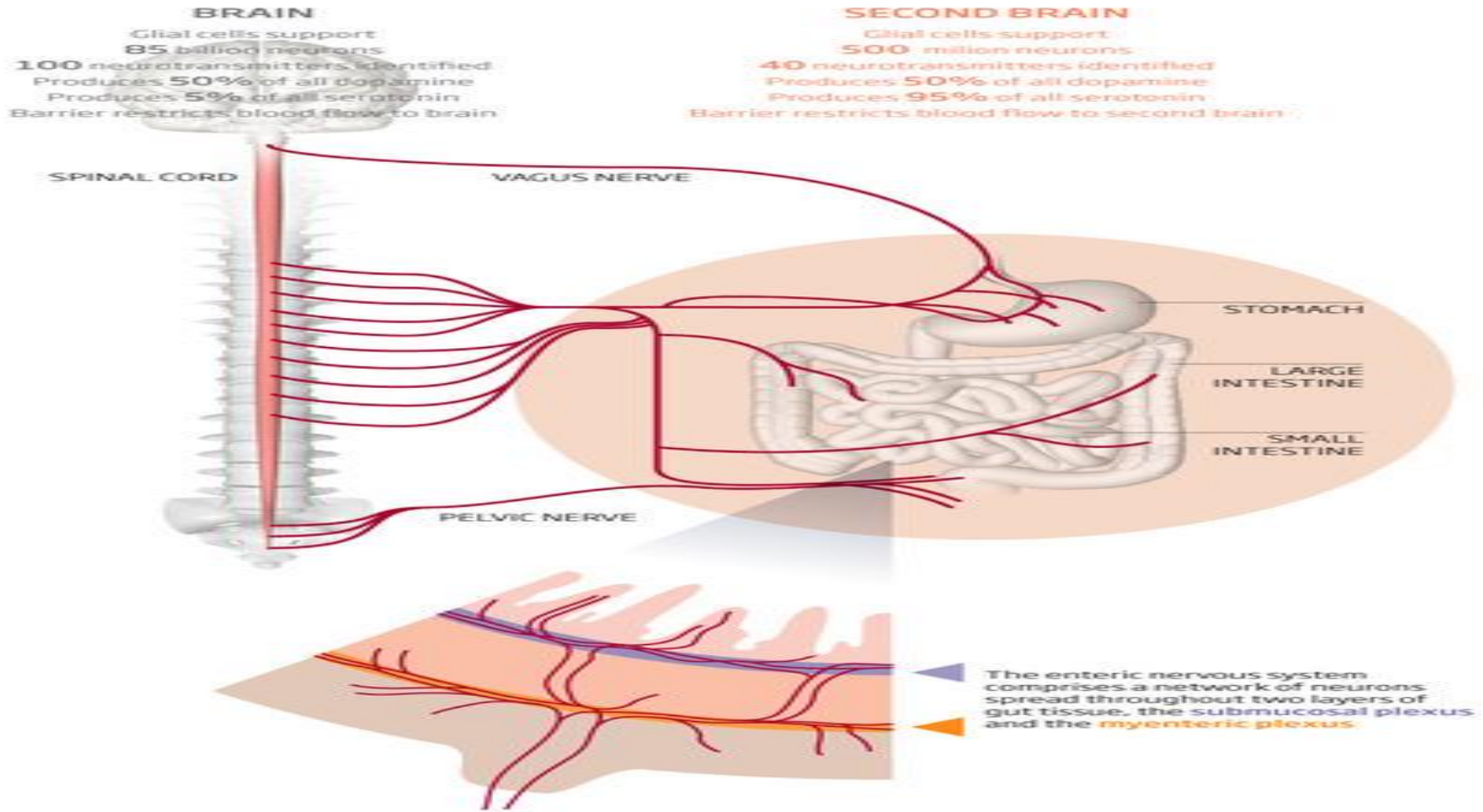
S obzirom da je više od **40 peptida indentifikovano u gastrointestinalnom traktu**, on predstavlja najveci endokrini organ našeg organizma. Veliki napedak u upoznavanju njihove uloge nacinjen je u poslednjoj deceniji.

- Prema slicnosti u hemijskoj grai peptidni hormoni su podeljeni u više grupa (familija):
  - gastrinska familija: gastrin, holecistokinin(CCK)
  - sekretinska familija: sekretin, vazoaktivni intestinalni peptid (VIP), glukagon, gastricni inhibitorni peptid (GIP), peptid histidil izoleucin (PHI)
  - familija pankreasnih polipeptida: PP, PYY, NPY
  - bombesinska familija: bombesin, GRP, neuromedin B
  - ostali individualni peptidi


Cholecystokinin
Gall bladder contraction
Gastrointestinal motility
Pancreatic exocrine secretion
Secretin
Pancreatic exocrine secretion
GIP
Incretin activity
Motilin
Gastrointestinal motility
Ghrelin
Hunger
Growth hormone release
Gastrin
Acid secretion
Stomach
Insulin and glucagon
Glucose homeostasis
Pancreatic polypeptide
Gastric motility
Satiation
Amylin
Glucose homeostasis
Gastric motility
Duodenum
Pancreas
Colon
Small intestine
GLP-1
Incretin activity
Satiation
GLP-2
Gastrointestinal motility and growth
Oxyntomodulin
Satiation
Acid secretion
PYY$_{3-36}$
Satiation

Two brains in one body

The enteric nervous system in the gut, or "second brain", shares many features with the brain in your head. It can act autonomously and even influences behaviour by sending messages up the vagus nerve to the brain



Holecistokinin (CCK)

- Luče ga tip-I enterociti u duodenumu i tankom crevu, deluje preko:
  - CCK-A receptora u GIT traktu
  - CCK-B receptora u CNS
- Deluje na pankreasne acinusne celije i izaziva sekreciju neutralnog soka bogatog pankreasnim enzimima.
- Deluje na celije pankreasnih kanalica, potencira dejstvo sekretina i dovodi do sekrecije alkalnog, bikarbonatima bogatog pankreasnog soka.
- Deluje na žucnu kesu, snažno je kontrahuje, relaksira Odijev sfinkter pa tako žuc dospeva u duodenum.
- Posreduje u osecaju sitosti preko CCK-B receptora koji su široko rasprostranjeni u centralnom nervnom sistemu. U suprimiranju osecaja gladi igra ulogu i usporeno pražnjenje želuca koje CCK izaziva. CCK stimuliše vagusne nervne završetke, prenosi signale sitosti u moždano stablo i parabrahijalna jedra.

Pankreasni polipeptid (PP)

- Obrok uzrokuje lučenje sekreciju PP iz PP ćelija ostrvaca vagalno regulisanim mehanizmima;
- Porast cirkulišućeg PP u srazmeri je kalorijskim unosom obroka i traje do 6 sati;
- Anoreksogeni efekti PP traju do 24 časa (uloga u dugotrajnoj kontroli apetita?);
- Bazalni i postprandijalni nivo PP snižen kod gojaznih osoba (hiperfagija).

Peptid tirozin-tirozin (PYY)

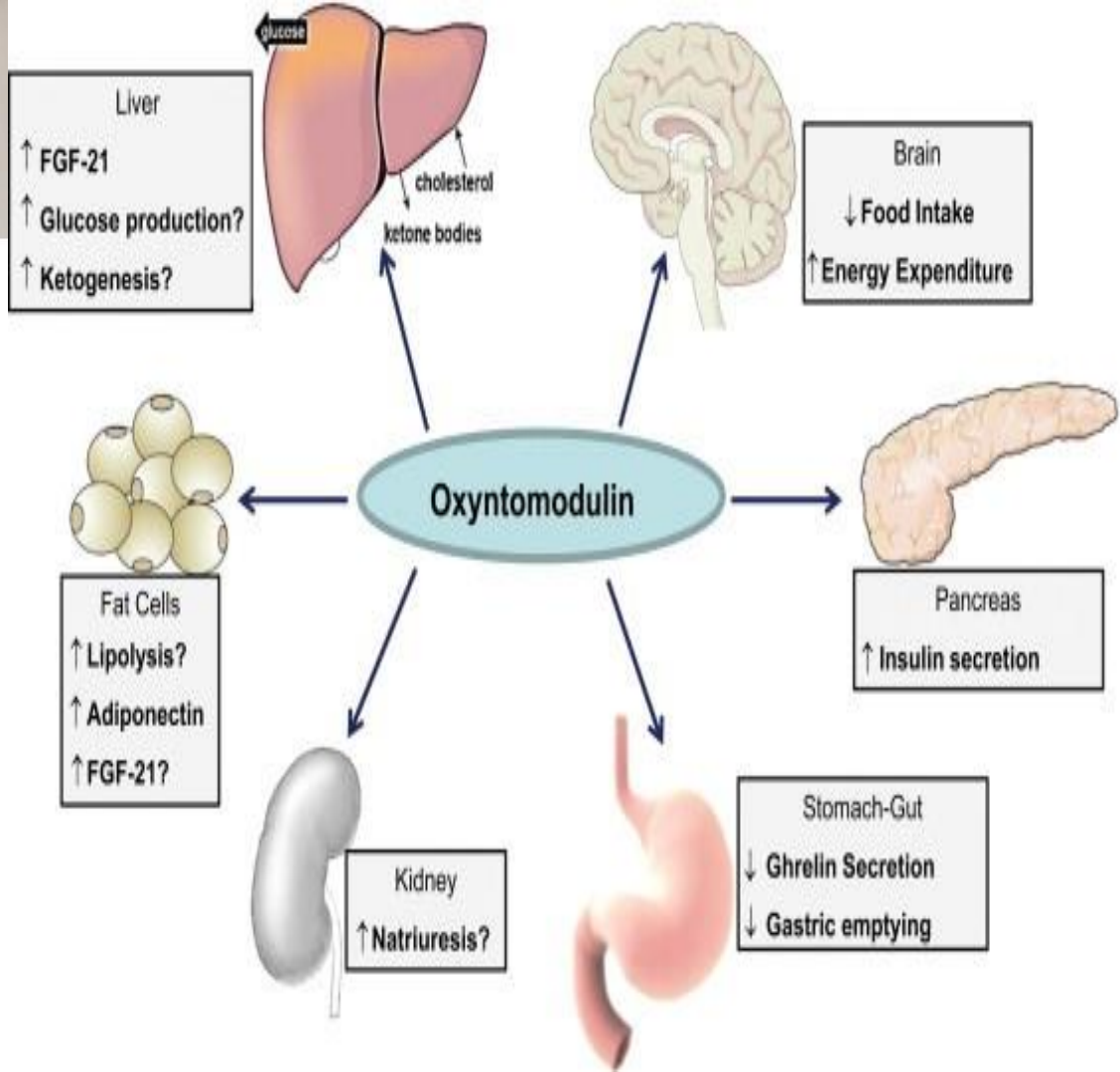
- Luči se postprandijalno iz L ćelija ileuma, kolona i rektuma u formi PYY_{1-36}, brzo metaboliše u PYY_{3-36} pomoću dipeptidil peptidaze (DPP)-4 u cirkulaciji;
- Cirkulišući PYY_{3-36} vezuje se za Y2 receptor na presinaptičkim završecima hipotalamusnih NPY/AgRP neurona, inaktiviše ih uzrokujući anoreksiju;
- Povećanje telesne mase može biti uzrokovano:
  - Redukovanom sekrecijom PYY u postprandijalnom periodu
  - Oštećenim vezivanjem PYY za Y2 receptor

Glukagon-like peptide 1 (GLP-1)

- GLP-1 se luči kao preproglukagon u L ćelijama ileuma i kolona i sekretuje u sistemsku cirkulaciju gde se brzo inaktivira preko DPP-4;
- Poluvreme eliminacije za GLP-1 je 1-2 minuta;
- GLP-1 vrši anoreksigene efekte preko GLP-1 receptora (GLP-1R), široko rasprostranjenih u CNS, GIT, i pankreasu kako kod gojaznih tako i kod mršavih pacijenata;
- Anoreksigeno delovanje GLP-1 stimuliše glukoza-zavisnu sekreciju insulina delovanjem na beta ćelije pankreasa;
- DPP-4 inhibitori i GLP-1 analozi se koriste u terapiji gojaznih DM2 pacijenata;

Oksintomodulin (OXM)

- OXM nastaje od preproglukagona zajedno sa GLP-1 u intestinalnim L ćelijama i ima umerena anoreksigena delovanja.

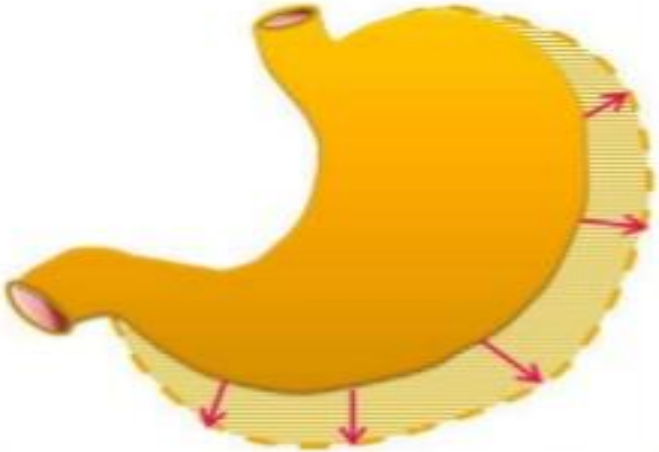


Ghrelin Regulation (short & long term)

CCK – Cholecystokinin
GLP1 – Glucagon-like peptide 1
PYY – Peptide YY

Primarily regulated by feeding

(Crespo *et al.*, 2014)

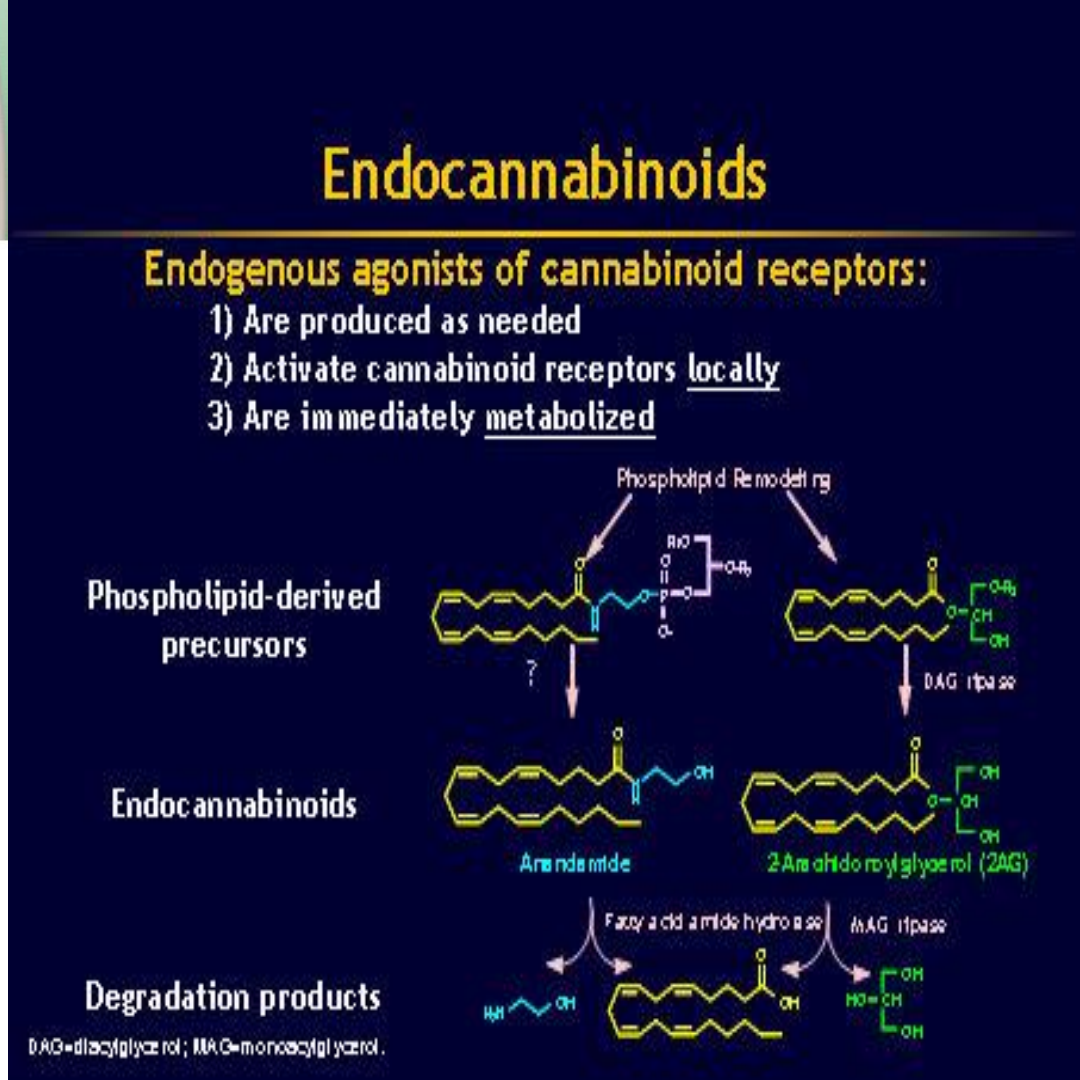
Stomach Empty	Stomach Full
	
↑ Ghrelin = ↑ Appetite	↓ Ghrelin = ↓ Appetite
CCK, GLP-1, PYY – all ↓	CCK, GLP-1, PYY – all ↑

http://www.nutridesk.com.au/stomach-intestine-ghrelin-cck-glp-1-gut-hormones.phtml

Grelin

- Sekretuju ga P/D1 endokrine celije fundusa želuca kada je osoba gladna i elipsoidne celije pankreasa.
- Nivo grelina raste pre uzimanja hrane, a smanjuje se nakon uzetog obroka(cikardijalni ritam).
- Deluje na hipotalamus i stimuliše unos hrane.
- Njegovo dejstvo se suprotstavlja inhibitornom uticaju leptina i PYY na centar za glad. (hormon gladi)
- Grelin se takodje stvara u hipotalamusu (*nukleus arkuatus*) i stimuliše sekreciju hormona rasta iz adenohipofize.
- Klinicke studije su pokazale da je nivo grelina u plazmi kod gojaznih osoba snižen, a povišen kod osoba koje pate od anoreksije nervoze.

- Primena CB1 agonista povećava uzimanje hrane i redukuje gastrični motilitet;
- Primena selektivnih CB1 antagonista smanjuje uzimanje hrane i porast telesne mase;
- Endogeni endokanabinoidi imaju oreksigeni efekat;

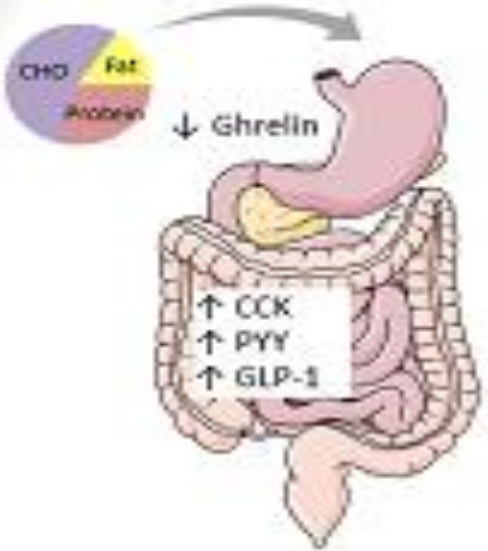


Consumer understanding / individual differences / health implications

SATIETY

Sensory factors

Nutrients and satiety



SPECTRUM OF HUNGER

When you're hungry because you haven't eaten in 12+ hours

When you just had a full meal but you still want dessert

HOMEOSTATIC HUNGER

Eating for calories and pleasure

HEDONIC HUNGER

Eating just for pleasure

livescience

SOURCE: LOWE ET AL., PHYSIOLOGY AND BEHAVIOR, 2007

Recent Guidelines for Obesity Management

Source	Release Date	Emphases
AHA/ACC/TOS[a]	November 2013	• Health risks of obesity • Benefits of weight loss • Diet and lifestyle changes • Selection of patients for bariatric surgery
AACE/ACE[b]	September 2014	• Staged approach to diagnosis, evaluation, and intervention • Weight loss as key to reversing or ameliorating weight-associated comorbidities
TES[c]	February 2015	• Causes of obesity • Weight-centric approach to obesity management • Medications that can promote weight loss • Medications that may contribute to weight gain

AHA = American Heart Association; ACC = American College of Cardiology; TOS = The Obesity Society; AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; TES = The Endocrine Society

a. Jensen MD, et al. *Circulation*. 2014;129:S102-S138[5]; b Garvey WT, et al. *Endocrine Practice*. 2014;20:977-989[4]; c. Apovian CM, et al. *J Clin Endocrinol Metabolism*. 2015;100:342-362.[6]


Obesity Facts

Clinical Endocrinology

European Guidelines for Obesity Management in Adults

Key Words

Abstract

KARGER

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

AACE

The Voice of Clinical Endocrinology

Founded 1991

AMERICAN COLLEGE OF ENDOCRINOLOGY

1993

ACE

AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY

Patient Presentation	Screen positive for overweight or obesity BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)	Presence of weight-related disease or complication that could be improved by weight loss therapy

Diagnosis

Evaluation

- Medical history • Physical examination • Clinical laboratory
- Review of systems, emphasizing weight related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions

Anthropometric Diagnosis

- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

BMI kg/m²

<25 NORMAL WEIGHT <23 in certain ethnicities	25–29.9 OVERWEIGHT | ≥30 OBESITY		
Clinical Diagnosis	**Checklist of Obesity-Related Complications** (staging and risk stratification based on complication-specific criteria)		
Waist circumference below regional/ethnic cutoffs	**None**	**Mild to Moderate**	**Severe**
	STAGE 0	**STAGE 1**	**STAGE 2**

Anamneza

- Etnička pripadnost
- Porodična anmneza
- Navike u ishrani
- Fizička aktivnost (učestalost i struktura)
- Obrasci ishrane i mogući poremećaji *(binge eating disorder, night eating syndrome, bulimia)*
- Prisustvo depresije i drugih poremećaja raspoloženja
- Ostale determinante (genetika, lekovi, endokrini poremećaji, psihosocijalni faktori, hronični stres, prestanak pušenja)
- Zdravstvene konsekvence gojaznosti (promena životnog stila, medikamentno lečenje, hirurške intervencije)
- Pacijentova očekivanja i motivacija za promene
- Prethodni tretman gojaznosti

Fizikalni pregled

- Merenje visine i težine (ITM – izračunati), obim struka, arterijska tenzija (adekvatna manžetna);
- Procena prisustva i značaj gojaznošću-uslovljenih oboljenja (dijabetes, hipertenzija, dislipidemija, kardiovaskularna, respiratorna i oboljenja zglobova, nealkoholna masna jetra, poremećaji spavanja)
- Prisustvo *acanthosis nigricans* kao znak insulinske rezistencije
  - Dermatoza koja se javlja na pregibnim površinama
  - U vidu hiperkeratoze i hiperpigmentacije
  - Neravne, nabrane površine somotastog izgleda
  - Može se javiti kao paraneoplastična dermatoza ili bez postojanja maligniteta

Laboratorijske analize “**minimum**”

- Glikemija našte
- Profil serumskih lipida (ukupni , HDL i LDL holesterol, trigliceridi)
- Mokraćna kiselina
- Funkcije tireodeje (*thyroid-stimulating hormone (TSH) level*)
- Funkcije jetre
- Kardiovaskularna procena, ukoliko je indikovano
- Endokrina ispitivanja ako se sumnja na: *Cushing’s syndrome* i oboljenja hipotalamusa
- Dodatni pregledi jetre ukoliko su nalazi enzima jetre patološki (ultrazvuk, biopsija)
- Somnološka ispitivanja

Body Composition Analysis Form

Name: _____ Telephone: _____

Email: _____ Height _____ Inches Age _____

Weight	
Body Fat %	
Total Body Water %	
Muscle Mass	
Physique Rating	
BMR	
Metabolic Age	
Bone Mass	
Visceral Fat	
Daily Protein Need	
Recommended Ideal Weight	
Daily Caloric Intake for Wt Loss or Gain	

Healthy Body Water % Range

45 - 60 %	50 - 65 %

Visceral Fat Rating

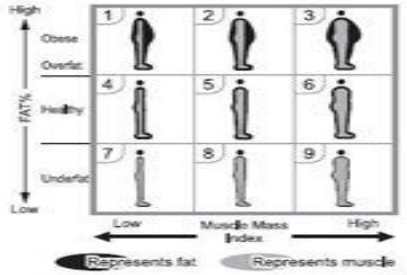
Healthy level	0	: 1 - 12
Excess level	+	: 13 - 59

Bone Mass Ranges

Average of estimated bone mass (lb)

	Weight		
	Less than 110 lb	110 lb - 165 lb	165 lb and up
	4.3 lb	5.3 lb	6.5 lb
	Less than 143 lb	143 lb - 209 lb	209 lb and up
	5.9 lb	7.3 lb	8.1 lb

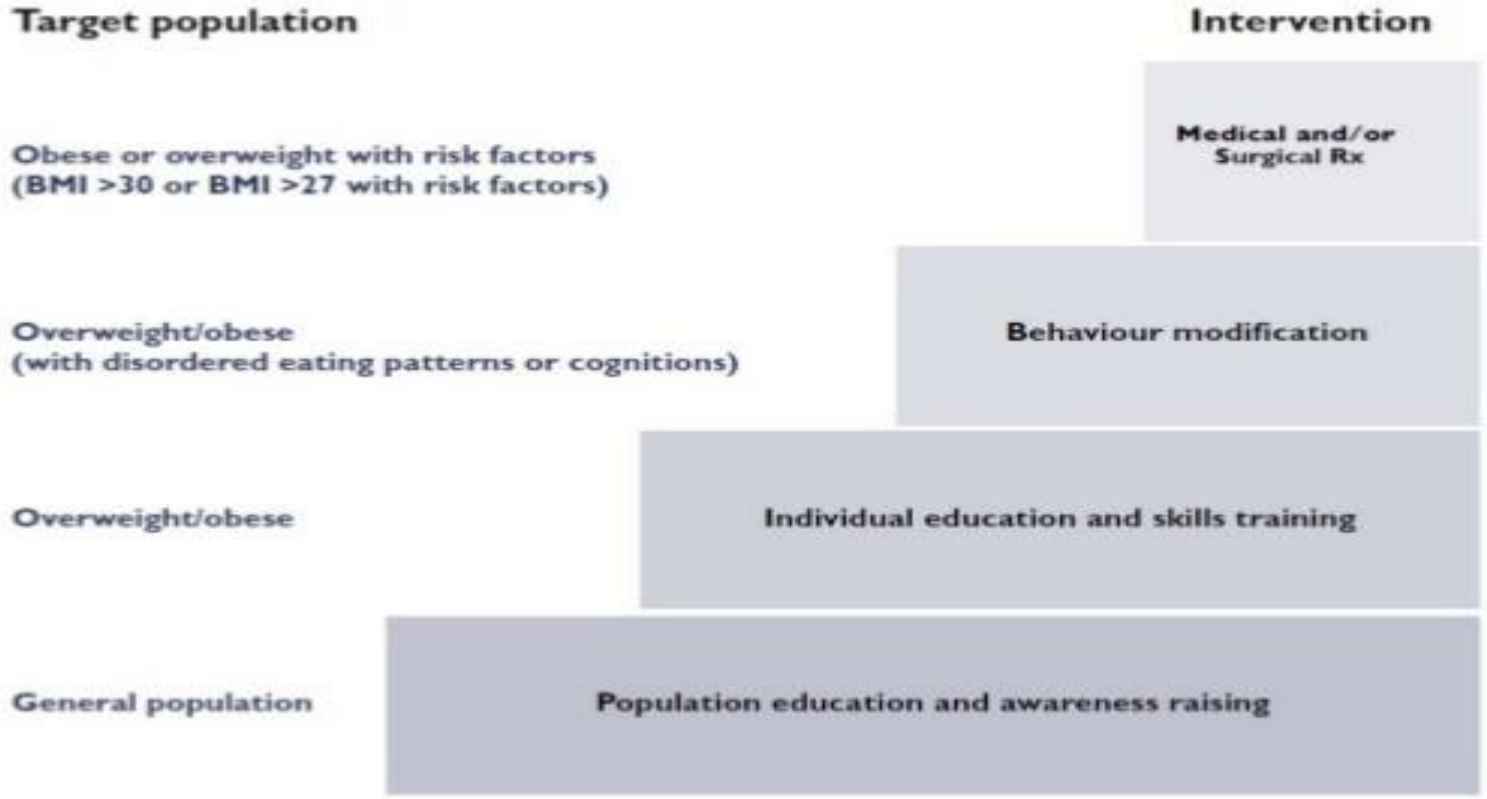
Physique Ratings



Body Fat % Classification	Female	Male
At risk/Obese	*Over 35%*	*Over 25%*
Too Much/Over Fat	29.1 – 34.9%	20.1 – 24.9%
A Bit Much	25.1 – 29%	18.1 - 20%
Normal – with some visible tummy fat	22.1 – 25%	15.1 - 18%
Lean	17.1 – 22%	10-15%
Very Lean/Athletic	*Under 17%*	*Under 10%*

BCOxxxxxx

Stepwise Model for Clinical Management



Clinical care pathway for overweight and obese adults

Determine degree of overweight and obesity
- Measure height (cm) and weight (kg) and calculate BMI (kg/m^2)
- Measure waist circumference (WC) cm

If BMI ≥ 25 kg/m^2*
or WC ≥ 94 cm for men*
or WC ≥ 80 cm for women*

Assess
Presenting symptoms and underlying causes
Co-morbidities and health risks
Weight loss history
Lifestyle (nutrition and physical activity)
Eating behaviour
Depression and mood disorders
Chronic psychological stress
Potential of weight loss to improve health
Motivation to change
Barriers to weight loss

Set goals and propose realistic, individualised and sustainable lifestyle changes at the long term
Weight loss goal
5–15% of body weight or 0.5–1.0 kg/week

Management
Nutrition
Reduce energy intake by 500–1,000 kcal/day
Physical activity
Initially at least 150 min/week moderate aerobic exercise combined with 1–3 sessions/week resistance exercise
Cognitive behaviour therapy
Pharmacotherapy
BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with co-morbidities
Adjunct to lifestyle modification
Bariatric/metabolic surgery
BMI≥40 kg/m^2 or BMI between 35.0–39.9 kg/m^2 + co-morbidities or BMI between 30.0-34.9 kg/m^2 with type 2 diabetes on individual basis. Consider if other weight loss attempts fail; requires lifelong medical monitoring
Prevention and treatment of co-morbidities

Considering referring to obesity specialist services or Collaborating Centres for Obesity Management (COMs)
- If the person has complex disease states or needs that can not be managed in primary or secondary care
- If the underlying causes of obesity need to be assessed
- If conventional treatment has failed
- If specialist interventions such as VLCD is needed
- If bariatric/metabolic surgery is needed

Weight loss goal is achieved

Assess effect on co-morbidities, weight maintenance and weight regain
- Regular monitorng of weight, BMI and WC
- Reinforce lifestyle modification
- Address other risk factors

Tretmani o kojima treba razgovarati sa pacijentom

BMI, Kg/m²	Obim struka, cm		Komorbiditet
	M < 94	M ≥ 94	
	Ž < 80	Ž ≥ 80	
25,5 – 29,9	IŽS	IŽS	IŽS ± L
30,0 – 34,9	IŽS	IŽS ± L	IŽS ± L ± H
35,0 – 39,9	IŽS ± L	IŽS ± L	IŽS ± L ± H
≥ 40,0	IŽS ± L ± H	IŽS ± L ± H	IŽS ± L ± H
IŽS – izmena životnog		L - lekovi	H - hirurgija

Lečenje

- Promene ponašanja i životnih navika
  - Dijeta
  - Fizičko vežbanje
- Lekovi
- Hirurgija

Farmakološki tretman

- Razumna strategija upravljanja bolešću;
- Da pacijent održi komplijansu, smanji rizike uslovljene gojaznošću i poboljša kvalitet života;
- Prevencija razvoja komorbiditeta (DM2);
- Preporučuje se pacijentima sa BMI ≥ 30 kg/m2 ili BMI ≥ 27 kg/m2 gojaznošću uslovljenim oboljenjima (hipertenzija, DM2, sleep apnoea);
- Lekove koristiti prema registrovanim indikacijama uz poštovanje kontraindikacija;
- Delotvornost farmakoterapije procenjivati posle prva 3 meseca;
- Ako je gubitak težine zadovoljavajući (< 5% za nedijabetične pacijente i > 3% za dijabetične) tretman nastaviti;
- Tretman obustaviti u slučaju da pacijenti ne reaguju na terapiju;

Lekovi koji se koriste

- Orlistat
- Lorkaserin
- Fentermin/topiramat
- Bupropion/naltrekson
- Liraglutid

Orlistat

- Potentan i selektivan inhibitor pankreasne lipaze;
- Redukuje intestinalnu digestiju masti;
- Na proskripciju od 120 mg, OTC od 60 mg;
- Oba dozna oblika primenjena pre jela uz poštovanje nutritivnih preporuka uzrokuju gubitak telesne mase;
- Delotvornost i bezbednost leka procenjivani u randominizovanim kliničkim istraživanjima: XENDOS i X-PERT;
- Fekalni gubitak masti i gastrointestinalni simptomi su česti;
- Može uzrokovati manji gubitak liposolubilnih vitamina, pa je poželjna dodatna multivitaminska proskripcija;

Liraglutid

- Dugodelujući *glukagon-like peptide 1* (GLP-1) agonist za parenteralnu upotrebu, koji sporo metabolišu dipeptidyl peptidase-IV;
- Glukozom indukovano oslobađanje insulina je stimulisano; glukagonski odgovor je redukovan; uticaji na želudačno pražnjenje;
- U upotrebi je terapiju DM T2 (1,2-1,8 mg), jednom dnevno;
- Lek je odobren za ovu indikaciju *FDA – 2014, European Medicinal Agency –EMA – 2015;*
- Primenjuje se parenteralno u dozi od 3 mg, jednom dnevno;
- U okviru registracionih indikacija neophodno je da primenom leka pacijent izgubi 5% težine posle 12 nedelja terapije. Ukoliko pacijent ne ostvari predviđene ciljeve lek se ukida;
- Delotvornost i bezbednost leka procenjivani u randominizovanim kliničkim istraživanjima *SCALE-Maintenance, SCALE-Obesity i LEADER;*
- Pacijenti liraglutid dobro podnese;
- Muka i povraćanje su prolazna neženjena delovanja koja daju doprinos gubitku telesne mase.

Medications Approved by the FDA for Obesity Tx

Table 8.2—Medications approved by the FDA for the treatment of obesity

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (108)	National Average Drug Acquisition Cost (30-day supply) (109)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (110–115)	Possible safety concerns/considerations (110–115)
				Treatment arm	Weight loss (% loss from baseline)		
Short-term treatment (≤12 weeks)							
Phentermine (116)	8–37.5 mg q.d.*	$5–$56 (37.5 mg dose)	$3 (37.5 mg dose)	15 mg q.d.† 7.5 mg q.d.† PBO	6.1 5.5 1.2	Dry mouth, insomnia, dizziness, irritability, increased BP	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (3)	60 mg t.i.d. (OTC)	$41–$82	$43	120 mg t.i.d.‡	9.6	Abdominal pain, flatulence, fecal urgency, back pain, headache	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
	120 mg t.i.d. (Rx)	$823	$556	PBO	5.6		
Selective serotonin (5-HT) 5-HT_2C receptor agonist							
Lorcaserin (14)**	10 mg b.i.d.	$360	$288	10 mg b.i.d.	4.5	Headache, nausea, dizziness, fatigue, nasopharyngitis, increased BP	• Serotonin syndrome–like and neuroleptic malignant syndrome–like reactions theoretically possible when coadministered with other serotonergic or antidopaminergic agents • Monitor for depression or suicidal thoughts • Avoid in liver and renal failure
Lorcaserin XR	20 mg q.d.	$360	$287	PBO	1.5		

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Medications Approved by the FDA for Obesity Tx (continued)

Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/topiramate ER (117)	7.5 mg/46 mg q.d.§	$223 (7.5 mg/46 mg dose)	$178 (7.5 mg/46 mg dose)	15 mg/92 mg q.d.‖ 7.5 mg/46 mg q.d.‖ PBO	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased BP	• Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/bupropion ER (15)	8 mg/90 mg, 2 tablets b.i.d.	$334	$268	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia	• Contraindicated in patients with uncontrolled hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation
Glucagon-like peptide 1 receptor agonist							
Liraglutide (16)**	3 mg q.d.	$1,497	$1,199	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects common (nausea, vomiting, diarrhea), injection site reactions	• ?Acute pancreatitis • Caution when initiating or increasing dose due to potential risk of acute kidney injury **Black box warning:** • Risk of thyroid C-cell tumors

All medications are contraindicated in women who are or may become pregnant. Women of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; BP, blood pressure; ER, extended release; MEN 2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; OTC, over the counter; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily; XR, extended release. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general obese adult population. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (118,119). ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ‖Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance.

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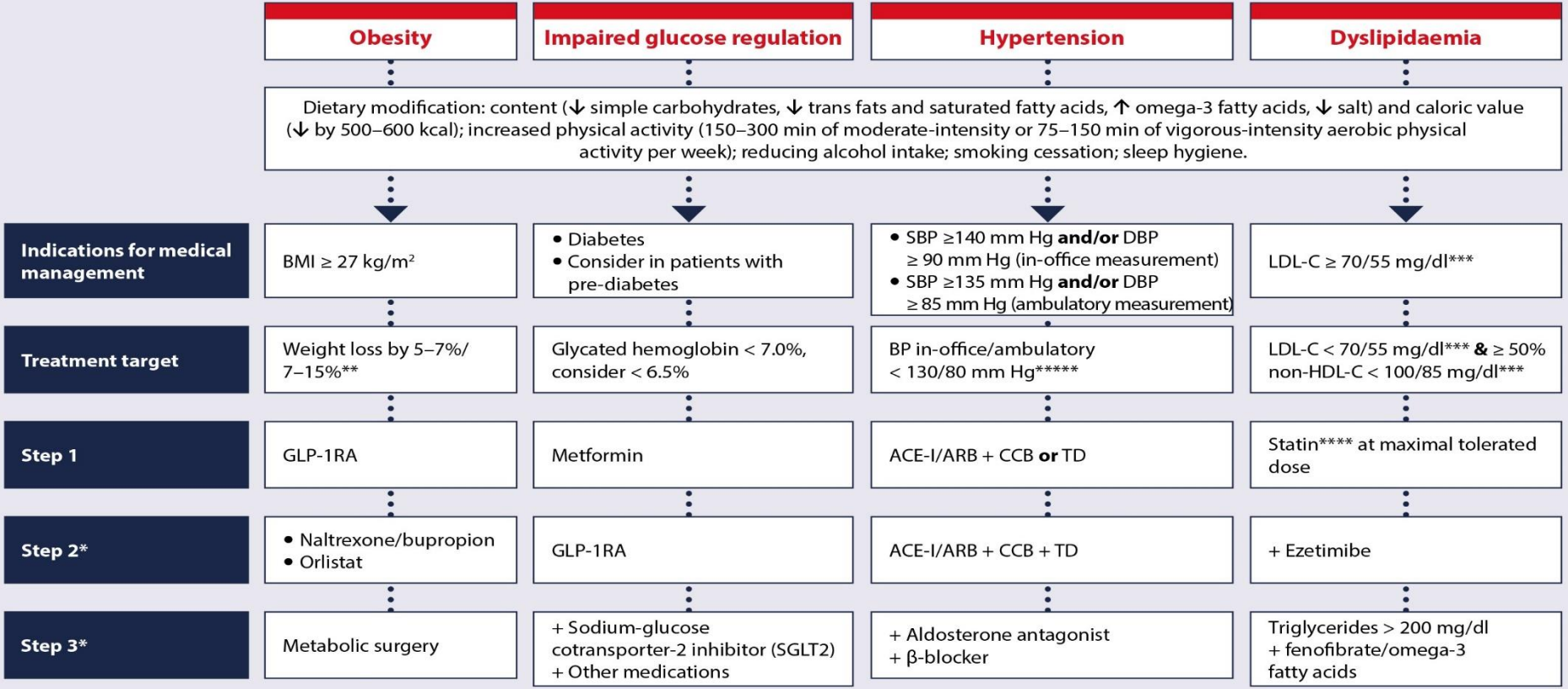
METABOLIC SYNDROME



* Should treatment target fail to be achieved, take the next step. ** In all patients and patients with diabetes, respectively. *** In high risk and very high risk groups, respectively. **** High-potency atorvastatin/rosuvastatin. ***** In patients above 70 years of age < 140/90 mmHg (in-office measurement) and < 135/85 mmHg (ambulatory measurement)

ACE-I – angiotensin-converting-enzyme inhibitors; **ARB** – angiotensin receptor blocker; **BMI** – body mass index; **BP** – blood pressure; **CCB** – calcium channel blocker; **DBP** – diastolic blood pressure; **GLP-1RA** – Glucagon like peptide-1 receptor agonist; **LDL-C** – LDL cholesterol; **non-HDL-C** – non-HDL cholesterol; **SBP** – systolic blood pressure; **TD** – thiazide/thiazide like duretic

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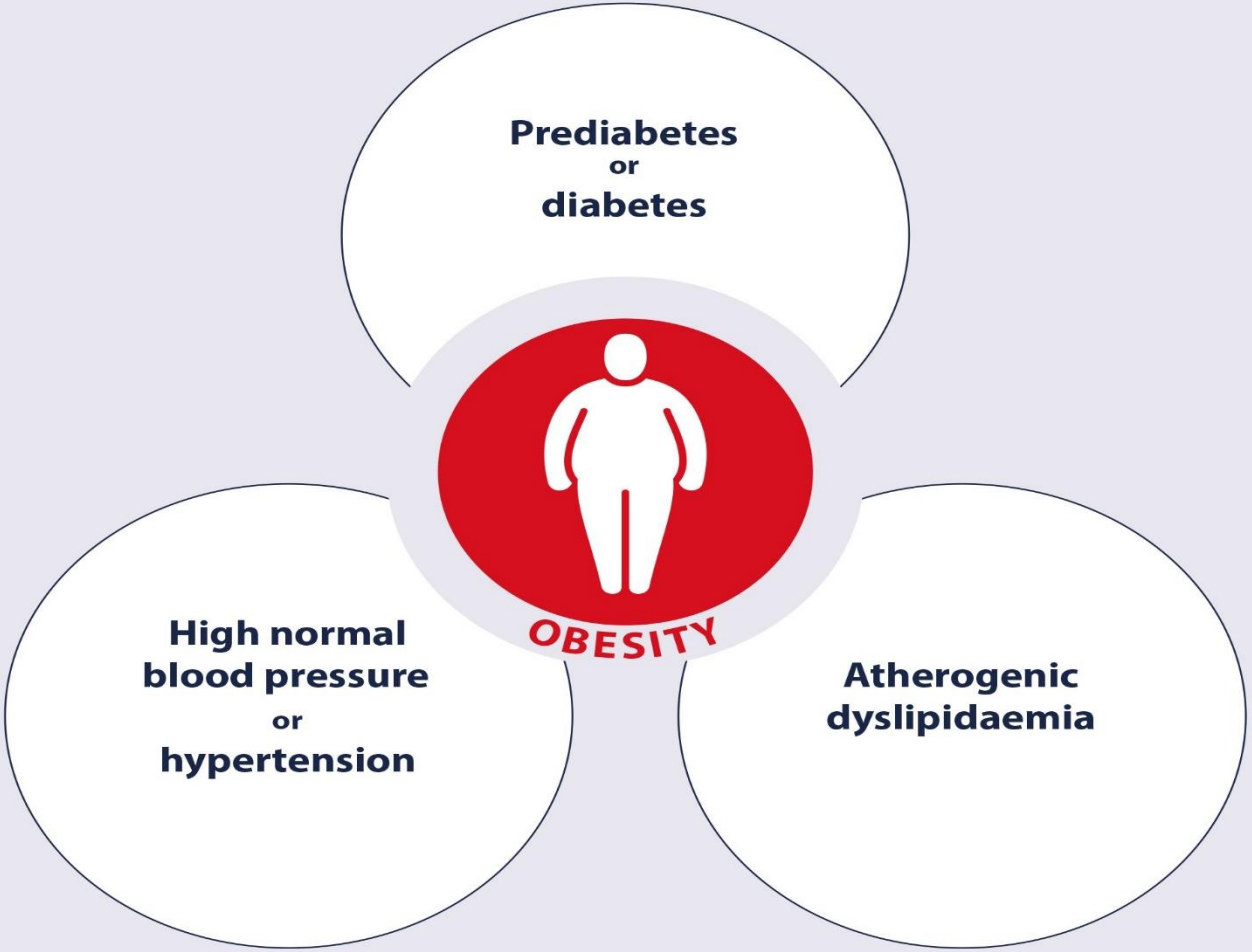
METABOLIC SYNDROME



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