NEPRESTANA, SVEOBUHVATNA MEDICINSKA NEGA PACIJENATA SA DIJABETESOM

dijabetes melitus: dijagnoza, klasifikacija i patofiziologija

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Ciljevi

- Opisati patofiziologiju dijabetes melitusa.
- Navesti epidemiologiju i faktore rizika za dijabetes melitus.
- Tretman i uobičajene komplikacije dijabetes melitusa.
- Identifikovati važnost poboljšanja saradnje i koordinacije nege medju interprofesionalnim timom kako bi se poboljšalo pružanje nege za pacijente pogodjene dijabetes melitusom.
- Edukacija o samostalnom vodjenju dijabetesa (*diabetes self-management education - DSME*).
- Samostalnom vodjenju dijabetesa (*diabetes self-management support - DSMS*).

Definicija

- *Dijabetes mellitus* obuhvata grupu sličnih metaboličkih poremećaja koji se fenotipski ispoljavaju hiperglikemijom.

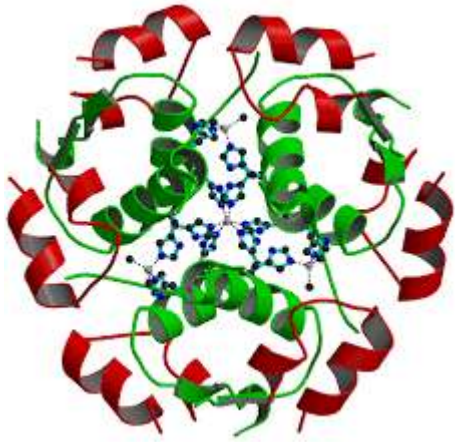
- Zavisno od epidemiologije dijabetes melitusa, faktori koji doprinose hiperglikemiji mogu da obuhvate:
  - Smanjeno lučenje insulina
  - Smanjeno korišćenje glikoze
  - Povećano stvaranje glikoze

INSULIN DISCOVERY

Frederick G. Banting

Charles H. Best

Insulin otkriće



- **Insulin su izolovali** *1921.* Kanadjanin *Frederick Banting i Charles Best*.
- **Primarnu strukturu** mu je biohemijskom analizom otkrio *Frederic Sanger* 1955.
- *Dorothy Hodgkin* 1969. rešila i **njegovu prostornu strukturu.**

Before Insulin

JL on 12/15/22 and 2 mos later

Before insulin was discovered in 1921, everyone with type 1 diabetes died within weeks to years of its onset

Klasifikacija

- DM tip 1 (nema prevencije)
  - Imunski posredovan
  - Idiopatski
- DM tip 2(*self management* je suština Th)
- Drugi specifični tipovi dijabetesa
- Gestacioni dijabetes melitus
  - Medjunarodno udruženje za dijabetes i studijske grupe za trudnoću i *American Diabetes Association – ADA*, preporučuju da se dijabetes koji se dijagnostikuje kod trudnice tokom redovnog pregleda klasifikuje kao „pravi“ dijabetes, a ne kao GDM.

Table 2.1—Staging of type 1 diabetes (12,15)

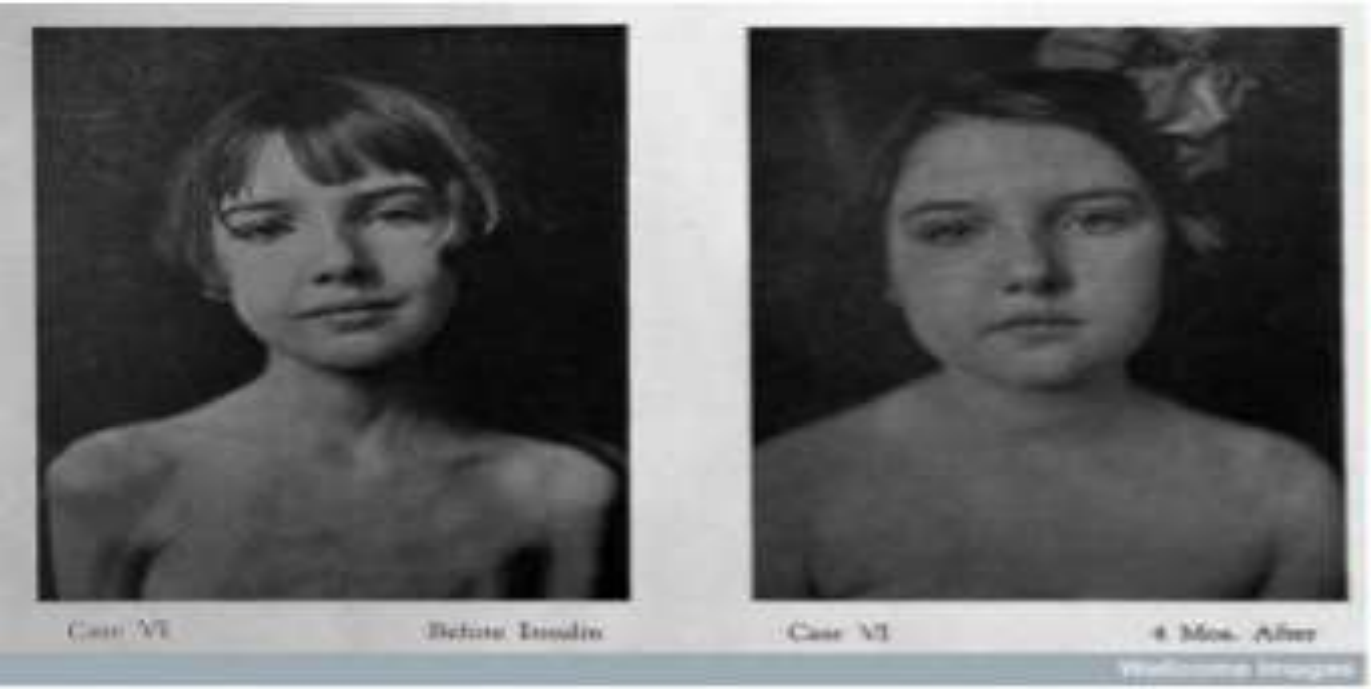
	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Type 1 Diabetes

diabetes due to
absolute deficiency of insulin



Type 2 Diabetes

diabetes due to
insulin resistance and
inadequate compensatory insulin secretory response

Medjunarodni ekspertski komitet

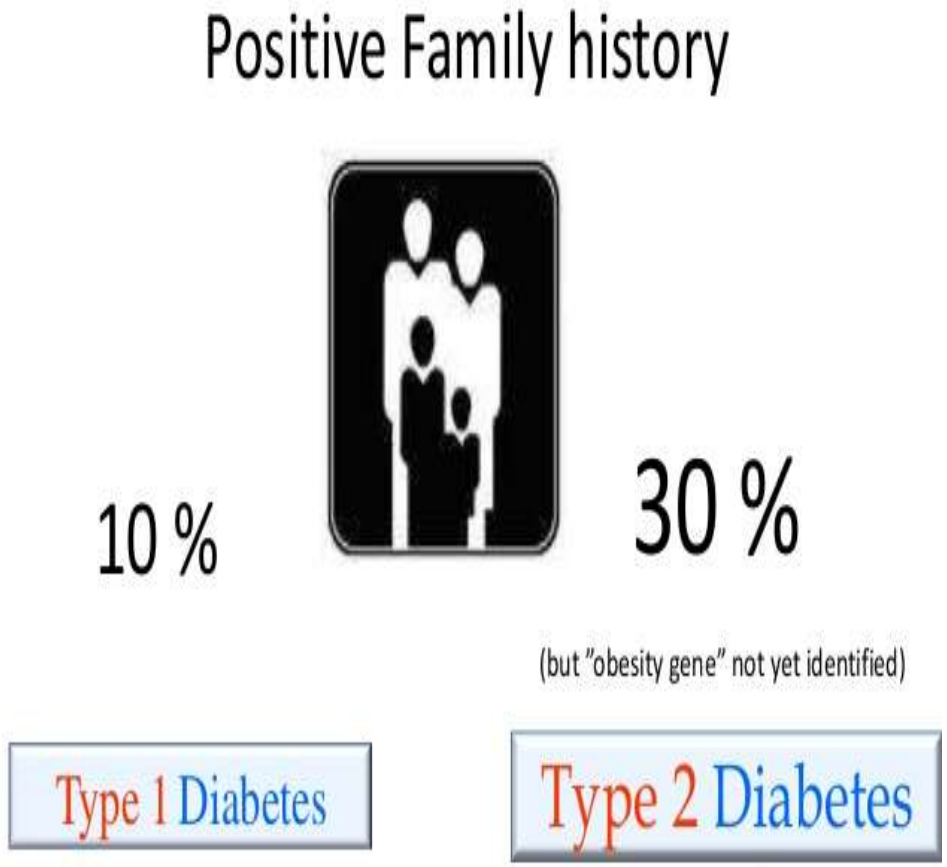
- **Američka asocijacija za dijabetes** (*American Diabetes Association - **ADA***),
- **Evropska asocijacija za studije u dijabetesu** (*European Association for the Study of Diabetes - **EASD***) i
- **Medjunarodna dijabetesna federacija** (*International Diabetes Federation - **IDF***),

Epidemiologija

- Dramatično povećava poslednjih decenija (~ 3% opšte populacije)

- Uzrast <20 godina → prevalenca 0,19%
- Uzrast >20 godina → prevalenca 8,6%
- Uzrast >65 godina → prevalenca 20,1%

- Dijabetes Tip2 – vodeći uzrok:
  - Nefropatije – 44%
  - Neuropatije – 60% netraumatske amputacije donjih ekstremiteta
  - Retinopatije – 28,4%



Dijagnoza

- Podnošljivost glukoze je klasifikovana u tri kategorije:
  - ✓Normalna tolerancija glukoze,
  - ✓DM
  - ✓Narušena tolerancija glukoze
- Tolerancija na glukozu može se proceniti na osnovu:
  - ✓vrednosti glukoze u plazmi izmerene natašte (*fasting plasma glucose –FPG*),
  - ✓Odgovora na oralni test provokacije glukozom,
  - ✓Na osnovu hemoglobina A_{1C} .

Normalna tolerancija glukoze
ADA

- ✓Hemoglobin A_{1C} (HbA_{1C}) < 5,7% ili,
- ✓Glikemija (glukoza u plazmi) natašte < 5,6 mmoll/l ili,
- ✓Glikemija u toku OGTT-aca 75g glukoze u 120 minutu < 11,1 mmol/l ili
- ✓Glikemija u bilo kom slučajnom uzorku krvi (bez obzira na obrok) ≥ mmol/l uz prisustvo tipičnih dijabetesnih simptoma (poliurija, polidipsija, gubitak u telesnoj težini) ≥ 11,1 mmol/l

Dijagnostički kriterijumi za dijabetes prema ADA

- ✓Hemoglobin A_{1C} (HbA1C) ≥ 6,5% ili,
- ✓Glikemija (glukoza u plazmi) natašte ≥ 7,0 mmoll/l ili,
- ✓Glikemija u toku OGTT-aca 75g glukoze u 120 minutu ≥ 11,1 mmol/l ili
- ✓Glikemija u bilo kom slučajnom uzorku krvi (bez obzira na obrok) ≥ mmol/l uz prisustvo tipičnih dijabetesnih simptoma (poliurija, polidipsija, gubitak u telesnoj težini) ≥ 11,1 mmol/l

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Dijagnostički kriterijumi za predijabetes prema ADA

Table 2.5—Criteria defining prediabetes*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

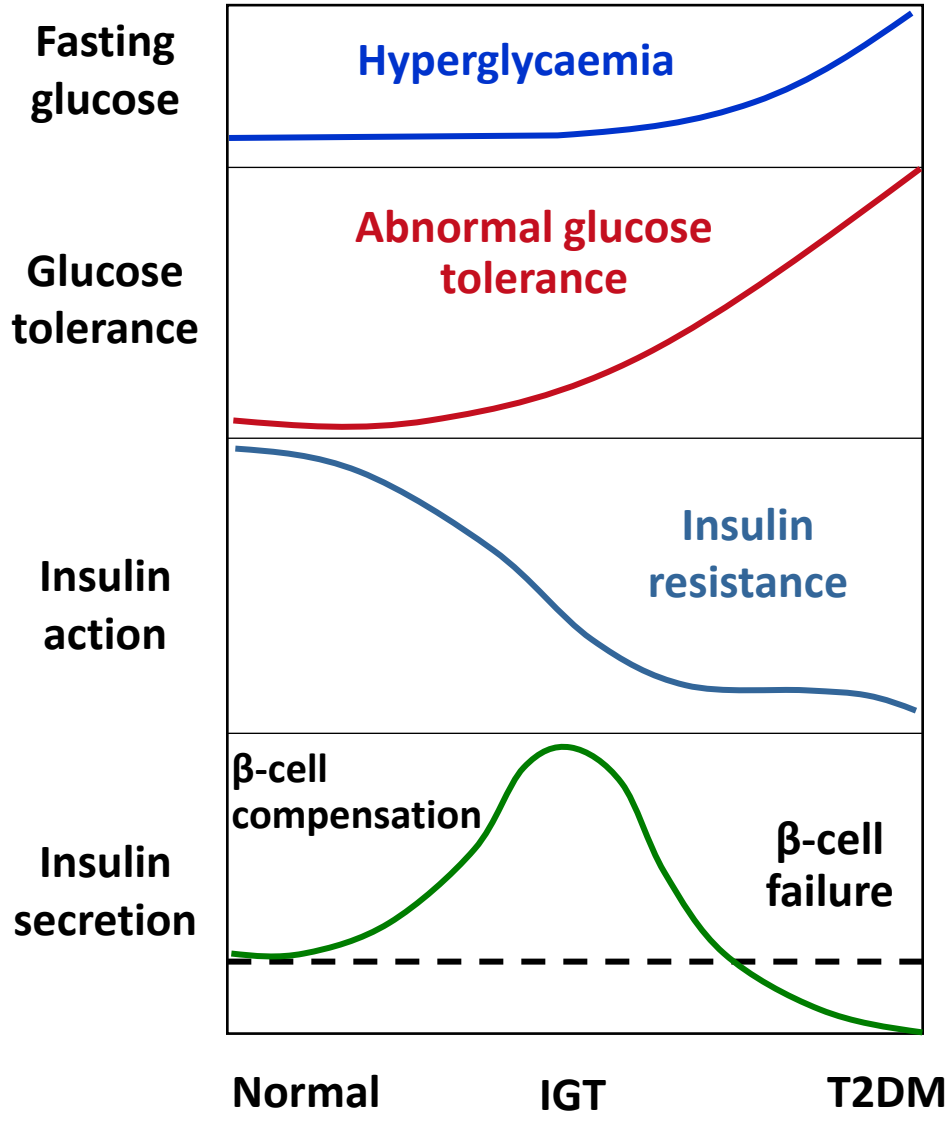
- ✓Hemoglobin A_{1C} (HbA1C) 5,7 - 6,4% ili,
- ✓Glikemija (glukoza u plazmi) natašte 5,6 - 6,9 mmoll/l ili,
- ✓Glikemija u toku OGTT-aca 75g glukoze u 120 minutu 7,8 - 11mmol/l ili

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Narušena (abnormalna) tolerancija glukoze* ADA

- ✓Hemoglobin A_{1C} (HbA_{1C}) ≥ 5,7-6,4% ili,
- ✓Glikemija (glukoza u plazmi) natašte ≥ 5,6-6,9 mmoll/l (hiperglikemija natašte – *impaired fasting glucosae* – IFG) ili,
- ✓Oralni test opterećenja glukozom (*oral glucose tolerance test – OGTT*), mada još validan test za dijagnozu DM, ne koristi se tako često u rutinskoj kliničkoj praksi.

*neki za ovu kategoriju koriste naziv **predijabetes**, **povećan rizik od dijabetesa**, **intermedijarna hiperglikemija** (WHO).



Rano otkrivanje (skrining)

- Široka upotreba FPG ili HbA_{1C} kao testa za rano otkrivanje DM tipa2, preporučuju se:
  1. Brojne osobe koje zadovoljavaju sadašnje kriterijume za DM nemaju simptome dijabetesa ili nisu svesne da imaju ovu bolest;
  2. Epidemiološke studije pokazuju da DM tipa 2 može da postoji i desetak godina pre postavljanja dijagnoze;
  3. Neke osobe sa DM tipa 2 imaju jednu ili više komplikacija specifičnih za DM u vreme postavljanja dijagnoze;
  4. Lečenje DM tipa 2 može pozitivno da promeni tok bolesti, dijagnoza predijabetesa treba da podstakne na prevenciju razvoja dijabetesa.
- ADA predlaže skrining kod svih osoba starijih od 45 godina, svake tri godine, kao i raniji skrining za osobe sa prekomernom telesnom težinom (ITM>25kg/m^2).

Type 1 Diabetes

2.5 Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or can be considered an option for first-degree family members of a proband with type 1 diabetes. B

2.6 Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes. B

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Prediabetes and Type 2 Diabetes

2.7 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. B

2.8 Testing for prediabetes and/ or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI $25 kg/m2 or $23 kg/m2 in Asian Americans) who have one or more risk factors (Table 2.3).B

2.9 For all people, screening should begin at age 35 years. B

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Prediabetes and Type 2 Diabetes (continued)

2.10 If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i.e., weight gain). C

2.11 To screen for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate (Table 2.2 and Table 2.5). B

2.12 When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/ day) should be assured for 3 days prior to testing. A

2.13 In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. A

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Prediabetes and Type 2 Diabetes (continued)

2.14 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI $85th percentile) or obesity (BMI $95th percentile) and who have one or more risk factor for diabetes. (See Table 2.4 for evidence grading of risk factors.) B

2.15 People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 36 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. E

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (254)

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Faktori rizika za DM tip 2

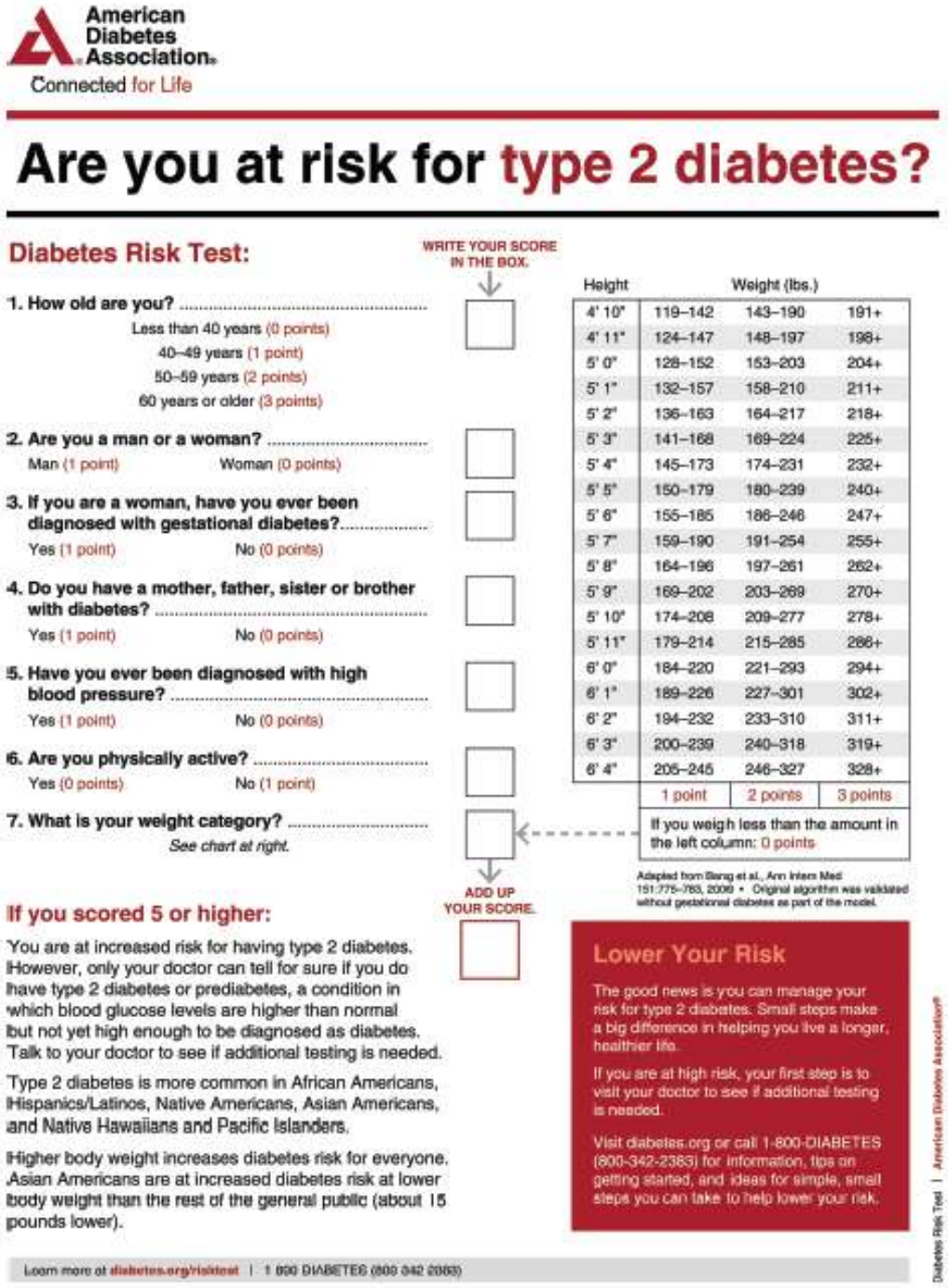
- Porodična anamneza dijabetesa (roditelj ili brat/sestra oboleli od DM tip 2),
- Gojaznost (ITM>25kg/m^2),
- Fizička neaktivnost,
- Rasa/etnička pripadnost,
- Ranije indetifikovana sa IFG, IGT ili HbA_{1C} ≥ 5,7-6,4%,
- Anamnestički podaci o GDM ili rodjenju bebe teže od 4 kg,
- Hipertenzija (TA≥140/90 mmHg),
- Nivo HDL holesterola < 0,90 mmol/l i ili nivo triglicerida > 2,82 mmol/l,
- Sindrom policističnih jajnika ili *acanthosis nigricans*,
- Anamneza kardiovaskularnih bolesti.

Regulacija homeostaze insulina

- Homeostaza glukoze odražava ravnotežu izmedju stvaranja glukoze u jetri i njenog preuzimanja i iskorišćavanja u perifernim tkivima.
- Insulin je najvažniji regulator ove metaboličke kontrole, ali nervni ulaz, metabolički signali i drugi hormoni (glukagon) rezultiraju integrisanom kontrolom snabdevanja i iskorišćavanja glukoze.
- Organi koji regulišu glukozu i lipide komuniciraju pomoću neuronskih i humoralnih mehanizama sa masnim tkivom i mišićima koji proizvode:
  - Adipokine,
  - Miokine,
  - Metabolite koji utiču na funkciju jetre.

diabetes.org/socrisktest

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38



American Diabetes Association.
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you?
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes?
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?
Yes (1 point) No (0 points)

6. Are you physically active?
Yes (0 points) No (1 point)

7. What is your weight category?
See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1 800 DIABETES (800 342 2383)

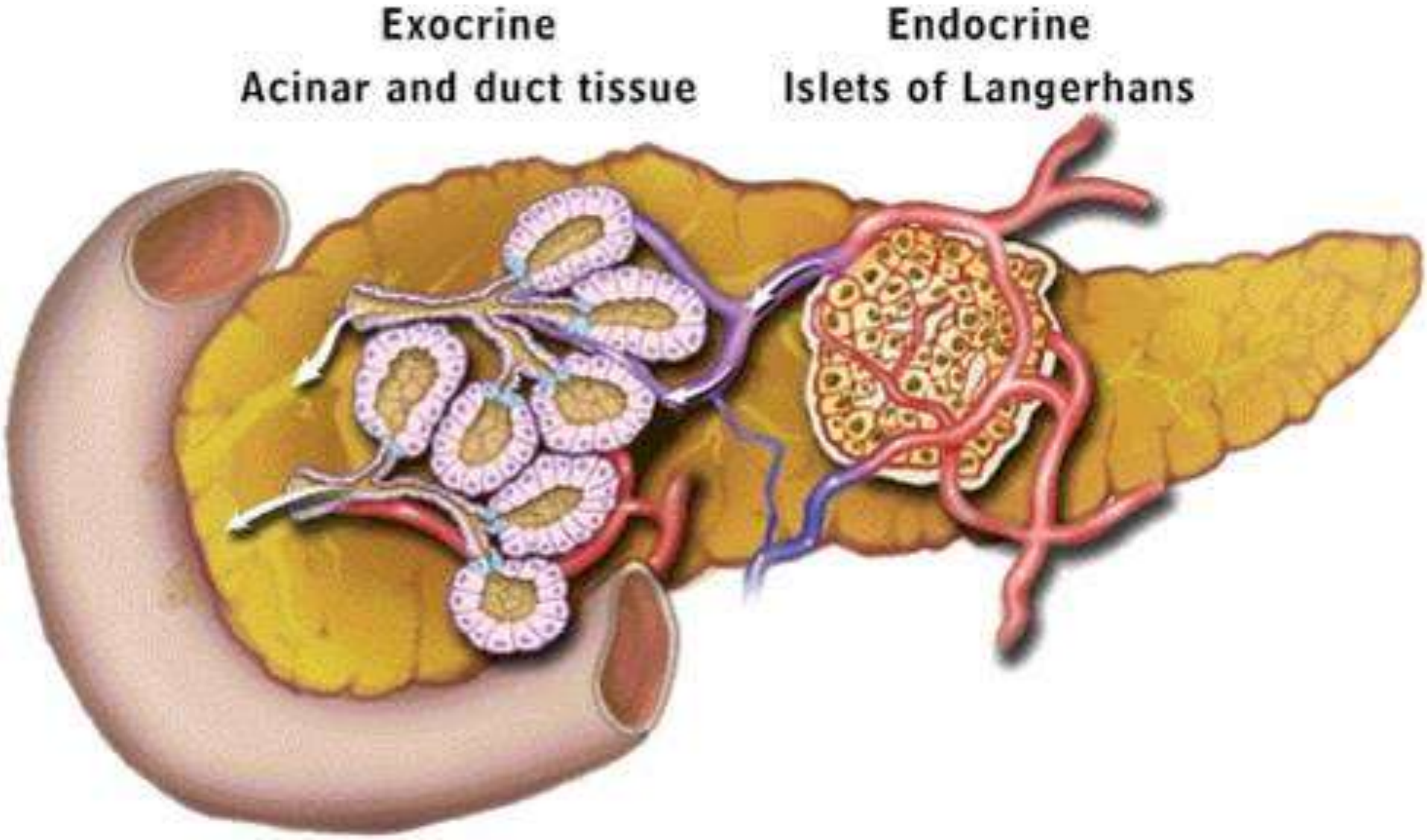
Diabetes Risk Test | American Diabetes Association®

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,**

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

patofiziologija



Endocrine

The pancreas produces hormones that regulate blood sugar

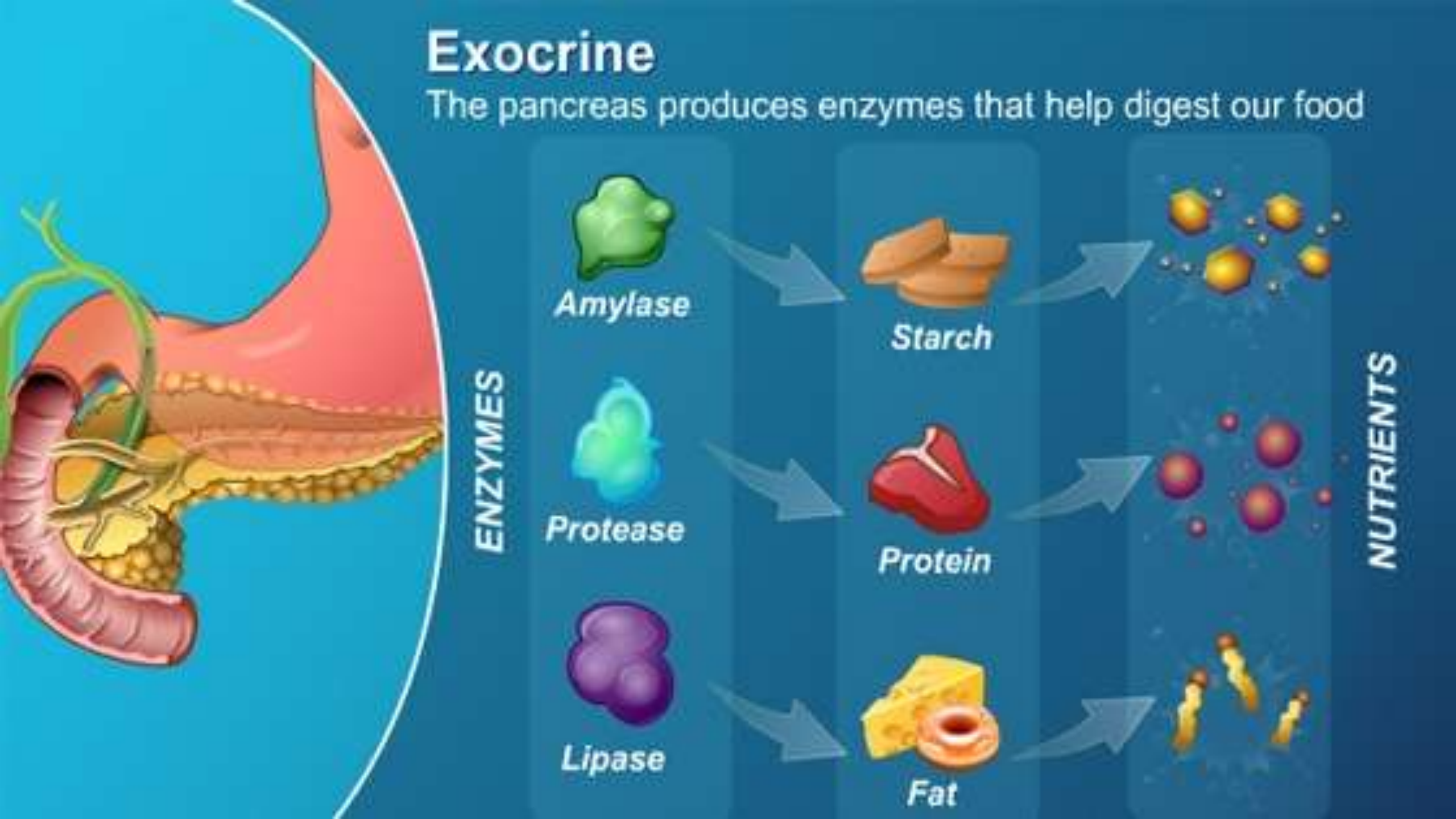
Exocrine

The pancreas produces enzymes that help digest our food

Amylase

Protease

Lipase

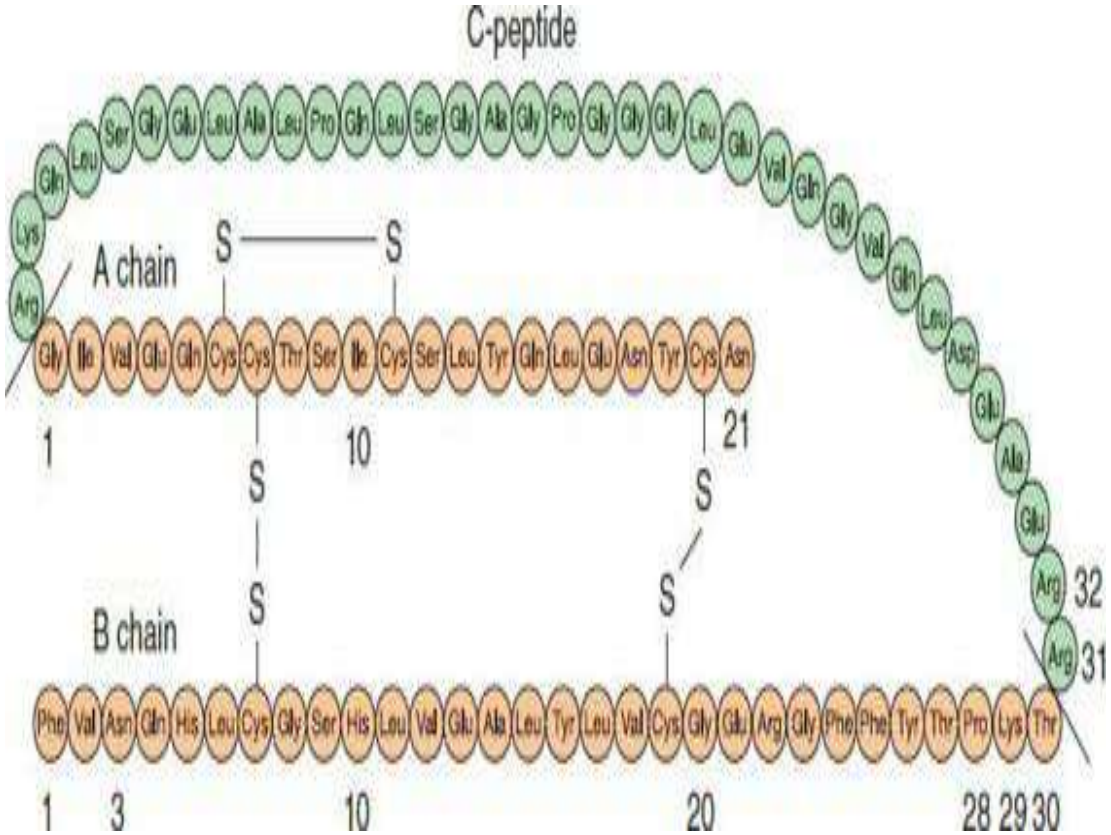

Exocrine
The pancreas produces enzymes that help digest our food
ENZYMES
Amylase
Protease
Lipase
Starch
Protein
Fat
NUTRIENTS

Ćelije pankreasnih ostrvaca i njihove sekretorne funkcije

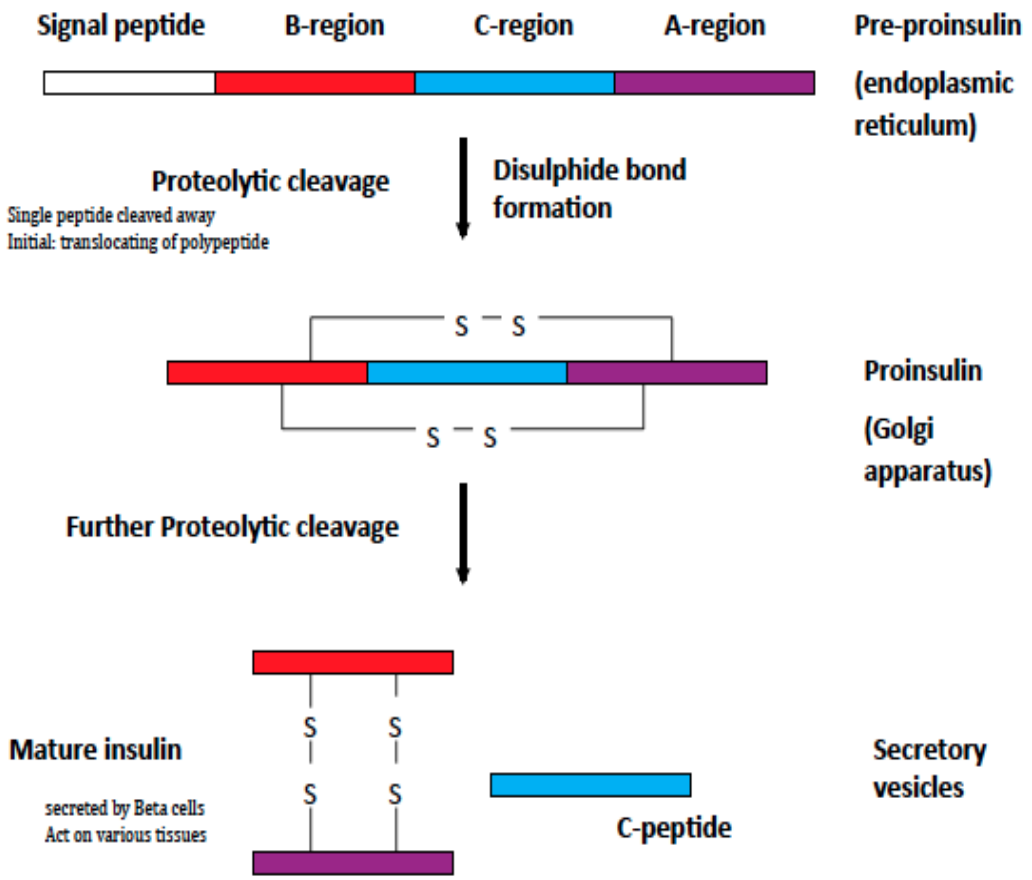
Tip ćelija	Procenat zastupljenosti (%)	Sekretorni produkti
Alfa (A)	**20**	**Glukagon** (hiperglikemijski faktor, koji mobiliše zalihe glikogena)**, proglukagon**
Beta (B)	**75**	**Insulin (**skladišni i anabolički hormon tela)**, C peptid, proinsulin, amilin** (ostrvski amiloidni polipeptid, IAPP; modulira apetit, pražnjenje želuca i lučenje glukagona i insulina)
Delta (D)	**3-5**	**Somatostatin** (univerzalni inhibitor sekretornih ćelija)
Epsilon	**< 1**	**Grelin** (peptid za koji se zna da povećava oslobadjanje hormona rasta hipofize)
F ćelije (PP ć, Gama ć)	**< 0,5**	**Pankreasni polipeptid** (mali protein koji olakšava procese varenja mehanizmom koji još nije razjašnjen)

Struktura insulina

- ✓Polipeptidni hormon
- ✓51 aminokiselina
- ✓Dva lanca
  - ✓A lanac, 21 amino kiselina
  - ✓B lanac, 30 aminokiselina
- ✓Povezani disulfidnim vezama
- ✓U granulama se nalazi 8mg insulina (1mg=28 jedinica insulina (oko 200 jedinica ukupno))



Biosinteza insulina



- Stvara se u beta ćelijama pankreasninih ostrvaca,
- Prvo se sintetiše **prekusorski polipeptid – pre proinsulin,** od 86 aminokiselina sa signalnim peptidom koji ga upućuje u edndoplazmatični retikulum.
- Proteolitičkim odvajanjem aminoterminalnog signalnog polipeptida stvara se **proinsulin** (strukturno sličan faktorima rasta sličnim insulin I I II, koji se vezuju slabim vezama za insulinski receptor) (endoplazmatični retikulum),
- Odvajanje jednog dela proinsulina, od 31 aminokiseline uzrokuje stvaranje C peptida* i insulinske lance A (21 amino-kiselina) i B (30 aminokiselina), koji su spojeni disulfidnim vezama (*Goldgi* aparat).

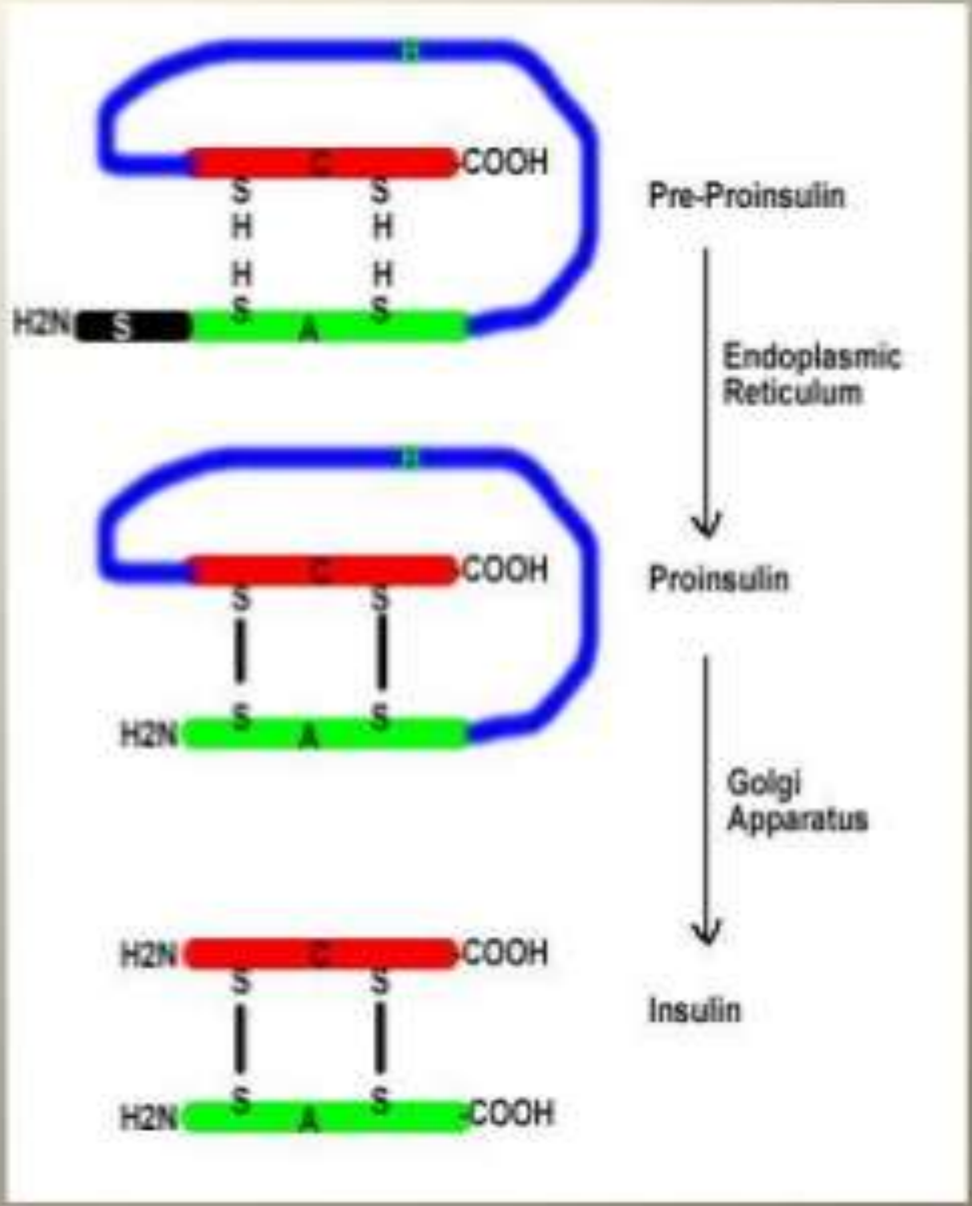
*Kako se c-peptid sporije razgradjuje u jetri od insulina, on je koristan marker insulinske sekrecije i dozvoljava razlikovanje endogenih i egzogenih izvora insulina u slučajevima hipoglikemije.

BIOSYNTHESIS OF INSULIN:

Insulin is synthesized as preproinsulin in pancreatic β-cells. It contains a signal peptide which directs the nascent polypeptide chain to the rough endoplasmic reticulum. Then it is cleaved as the polypeptide is translocated into lumen of the RER, forming proinsulin. Proinsulin is transported to the trans-Golgi network (TGN) where immature granules are formed.

Proinsulin undergoes maturation into active insulin through action of cellular endopeptidases known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. The endopeptidases cleave at 2 positions, releasing a fragment called the C-peptide, and leaving 2 peptide chains, the B- and A- chains, linked by 2 disulfide bonds. The cleavage sites are each located after a pair of basic residues and after cleavage these 2 pairs of basic residues are removed by the carboxypeptidase. The C-peptide is the central portion of proinsulin, and the primary sequence of proinsulin goes in the order "B-C-A"

The resulting mature insulin is packaged inside mature granules waiting for metabolic signals (such as leucine, arginine, glucose and mannose) and vagal nerve stimulation to be exocytosed from the cell into the circulation.



Insulin

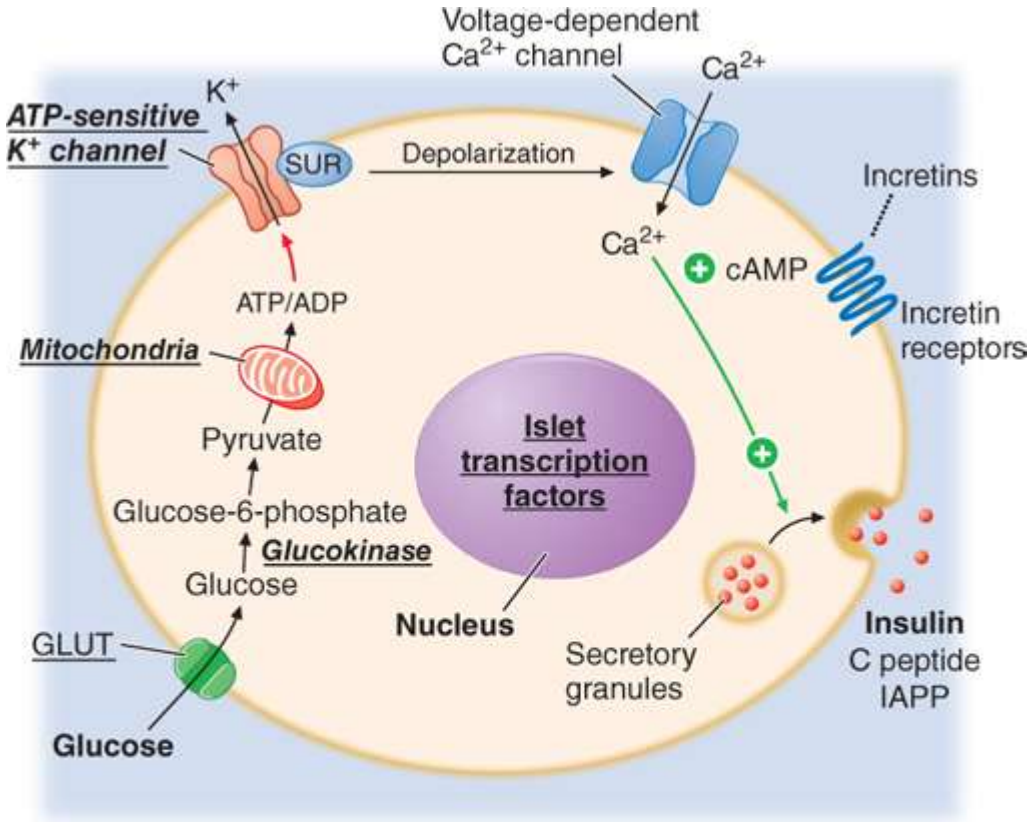
- Stimulišu oslobadjanje insulina:

  - povišenje glikemije
  - adrenalina u stresu
  - gastrointestinalni hormoni
  - oralni antidijabetici/derivati sulfonilurea

- Inhibiraju oslobadjanje insulina:

  - insulina preko autoreceptora
  - somatostatin iz alfa ćelija

Sekrecija insulina



- Glukoza se transportuje pomoću nosača/transportera za glukozu (GLUT1 i GLUT2).
- Fosforilacija glukoze pomoću glukokinaze faktor je kojim se kontroliše i ograničava brzina sekrecije izazvana glukozom.
- Metabolizam glukozo-6-fosfata preko glikolize stvara **ATP**, koji inhibiše aktivnost ATP-osetljivog kalijumskog kanala.

  (ovaj kanal se sastoji od dva različita proteina: jedan za koji se vezuju različiti hipoglikemici (sulfonilurea, meglitinidi) i drugi koji ima ulogu ispravljača kalijumskog kanalića).
- Inhibicija **kalijumskog kanala** dovodi do depolarizacije beta ćelijske membrane, što dovodi otvaranja voltažnih **kalcijumskih kanala**, a posledični ulazak kalcijuma u ćelije dovodi do sekrecije insulina.
- Insulin se **pulsatilno oslobadja**, sa malim sekretornim skokovima svakih 10 min i većim amplitudama na svakih 80-150min.
- **Inkretini** se oslobadjaju iz neuroendokrinih ćelija iz neuroendokrinih ćelija gastriintestinalnog trakta nakon ingestije hrane i potenciraju sekreciju insulina stimulisanu glukozom i istovremeno sprečavaju sekreciju glukagona.

Sekrecija insulina :

- Bazalna
- Stimulisana

Stimulacija

- **GLULOZA**
- **Šećeri (manoza)**
- **Aminokiseline (glukoneogene: leucin, arginin)**
- **Hormoni (***glucagon-like polipeptide 1* **(GLP1),** *glucose dependent insulinotropic polypeptide* **(GIP)**
- **Glukagon**
- **Masne kiseline (visoka koncetracija)**
- **Holecistokinin**
- **Beta adrenergička stimulacija**
- **Lekovi (sulfonilurea, meglitinid, nateglinid, isoproterenol, acetilholin)**

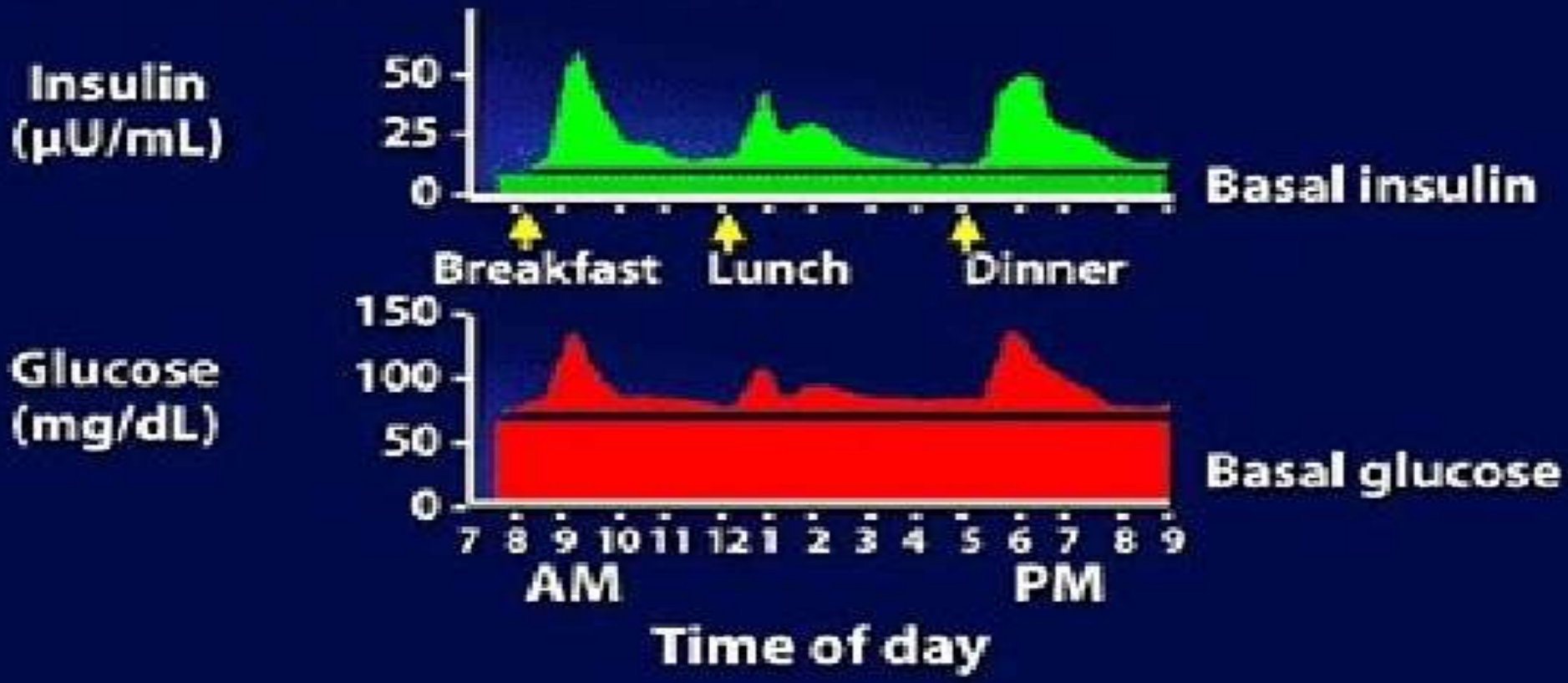
Inhibicija

- **Insulin**
- **Somatostatin**
- **Leptin**
- **Alfa adrenergička stimulacija**
- **Hronično povišen nivo glukoze**
- **Niska koncetracija masnih kiselina**
- **Lekovi (diazoksid, fenitoin, vinblastin, kolhicin)**

Normalna insulinska sekrecija

- **Bazalna insulinska sekrecija**
  - **Kontinuirano odvija izmedju obroka i tokom noći u količini 0,5-1U/h kod odraslih osoba (obezbedjuje serumsku koncetraciju insulina 5-15mU/ml)**
  - **Kod većine osoba je konstantna od 10h ujutro do ponoći, od ponoći do 04 h ona opada za oko 50% u odnosu na bazalne vrednosti, od 04h do 10h pre podne raste za oko 50% u odnosu na bazalne vrednosti**
  - **Redukuje hepatičnu produkciju glukoze, ali dopušta dovoljan nivo glukoze za energetske potrebe CNS**
  - **Kod bolesnika sa dijabetesom, primenom insulina srednje dugog i dugog dejstva pokušava se imitirati bazalna insulinska sekrecija.**
- **Stimulisana insulinska sekrecija**
  - **Dešava se kao odgovor na obrok i rezultira insulinskim odgovorom u koncetraciji 60-80 mU/ml, od momenta uzimanja obroka do 30 min nakon obroka**
  - **Nakon toga, koncetracija polako opada na bazalni nivo tokom naredna 2-4h**
  - **Primenom regularnog – kratkodelujućeg insulina pokušava se imitirati stimulisana insulinska sekrecija.**

Physiologic Insulin Secretion: 24-Hour Profile



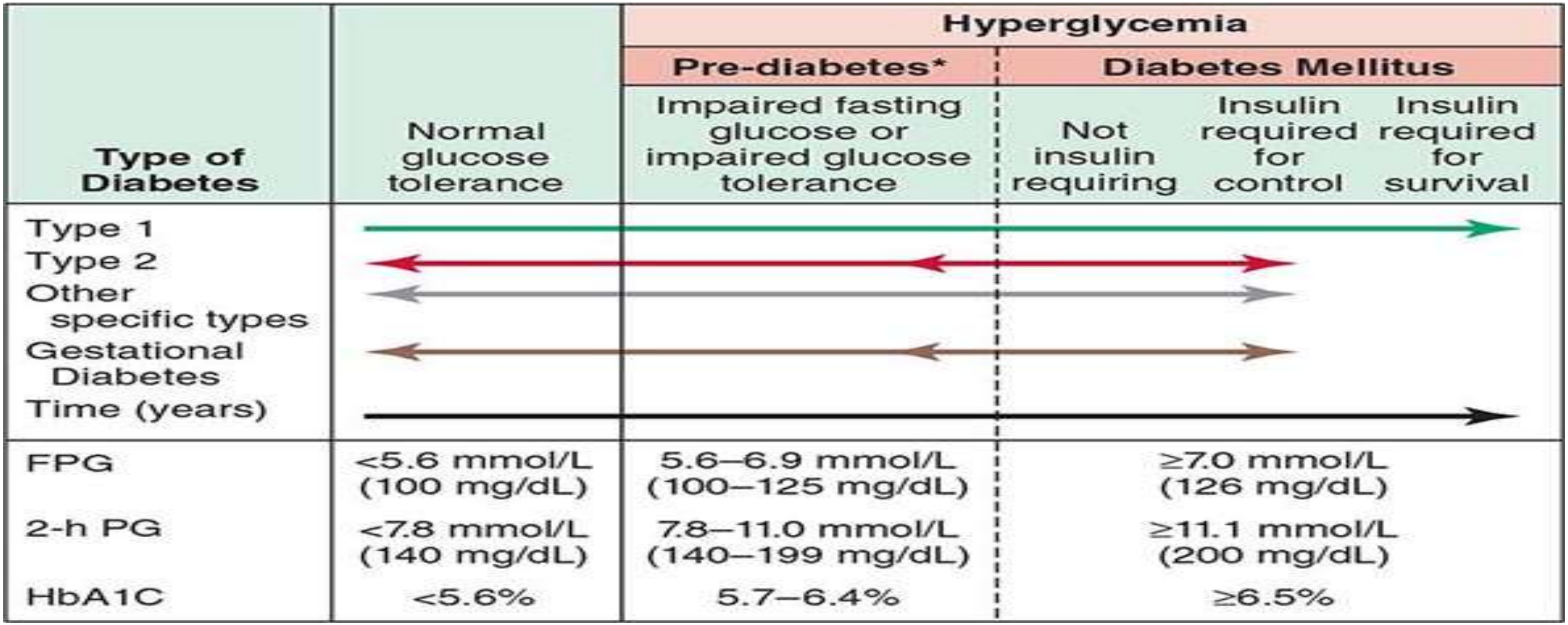
Metabolizam insulina

- Jetra i bubrezi su dva glavna organa koji uklanjaju insulin iz cirkulacije.
- Jetra normalno čisti krv od približno 60% insulina koji se oslobadja iz pankreasa na osnovu svoje lokacije kao krajnjeg mesta protoka krvi u portalnoj veni, pri čemu bubrezi uklanjaju 35-40% endogenog hormona.
- Kod dijabetičara lečenih insulinom koji primaju potkožne injekcije insulina, ovaj odnos je obrnut, pri čemu se čak 60% egzogenog insulina izlučuje putem bubrega, a jetra ne uklanja više od 30-40%.
- Poluvreme cirkulacije insulina je 3-5 minuta.

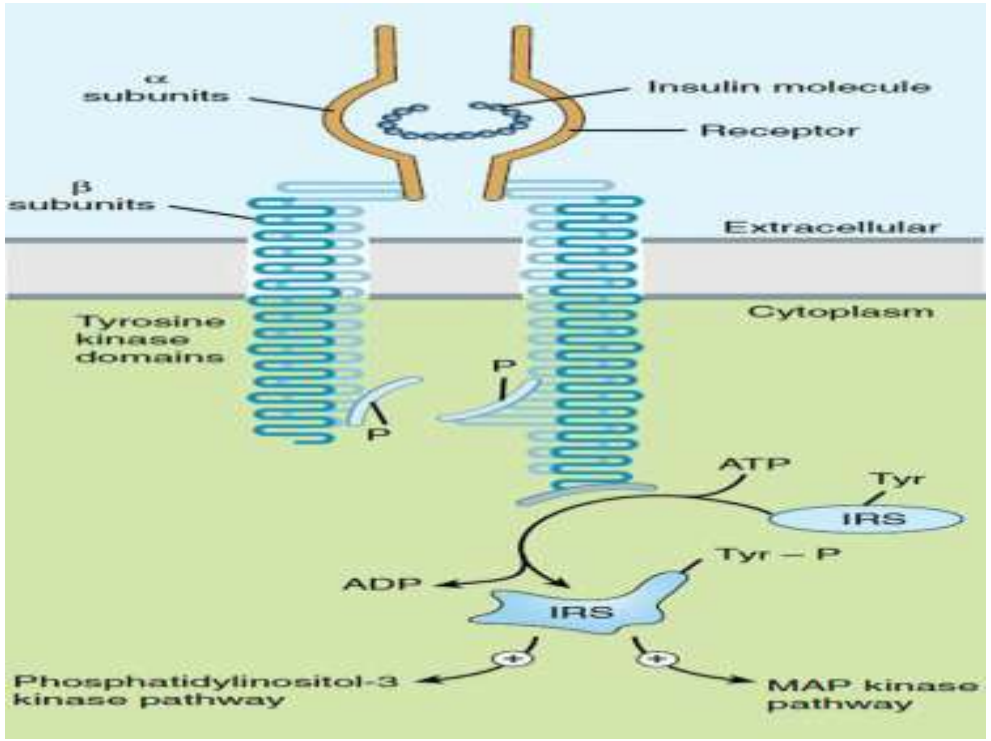
Cirkulacioni insulin

- Bazalne vrednosti insulina u serumu od 5–15 µU/mL (30–90 pmol/L) nalaze se kod normalnih ljudi, sa vršnim porastom na 60–90 µU/mL (360–540 pmol/L) tokom obroka.

Spektar homeostaze glukoze i dijabetes melitusa

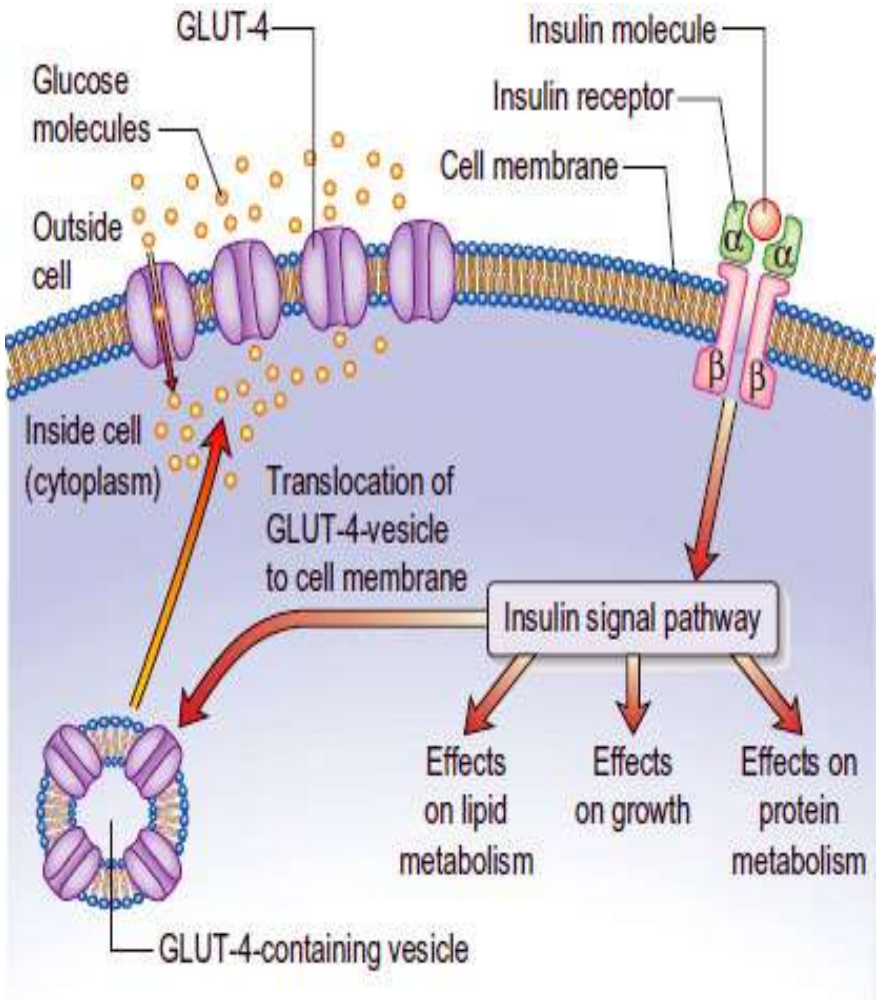


Insulinski receptor – klasa tirozin kinaze receptora



- Veliki transmembranski glikoproteinski kompleks
- 2 kovalentno vezana heterodimera
- Alfa subjedinica – ekstracelularno
- Beta subjedinica – intracelularno, sadrži tirozin kinaze
- Aktiviranje *insulin receptor substrates* – IRS
- *Phosphatidylinositol-3 kinase pathway*
- *Mitogen activated protein kinase pathway (MAP)*
- Pokazano je da je afinitet receptora za insulin veoma veliki, a da maksimalni efekat insulina ispoljava kada je samo 10% receptora “zauzeti” insulinom.

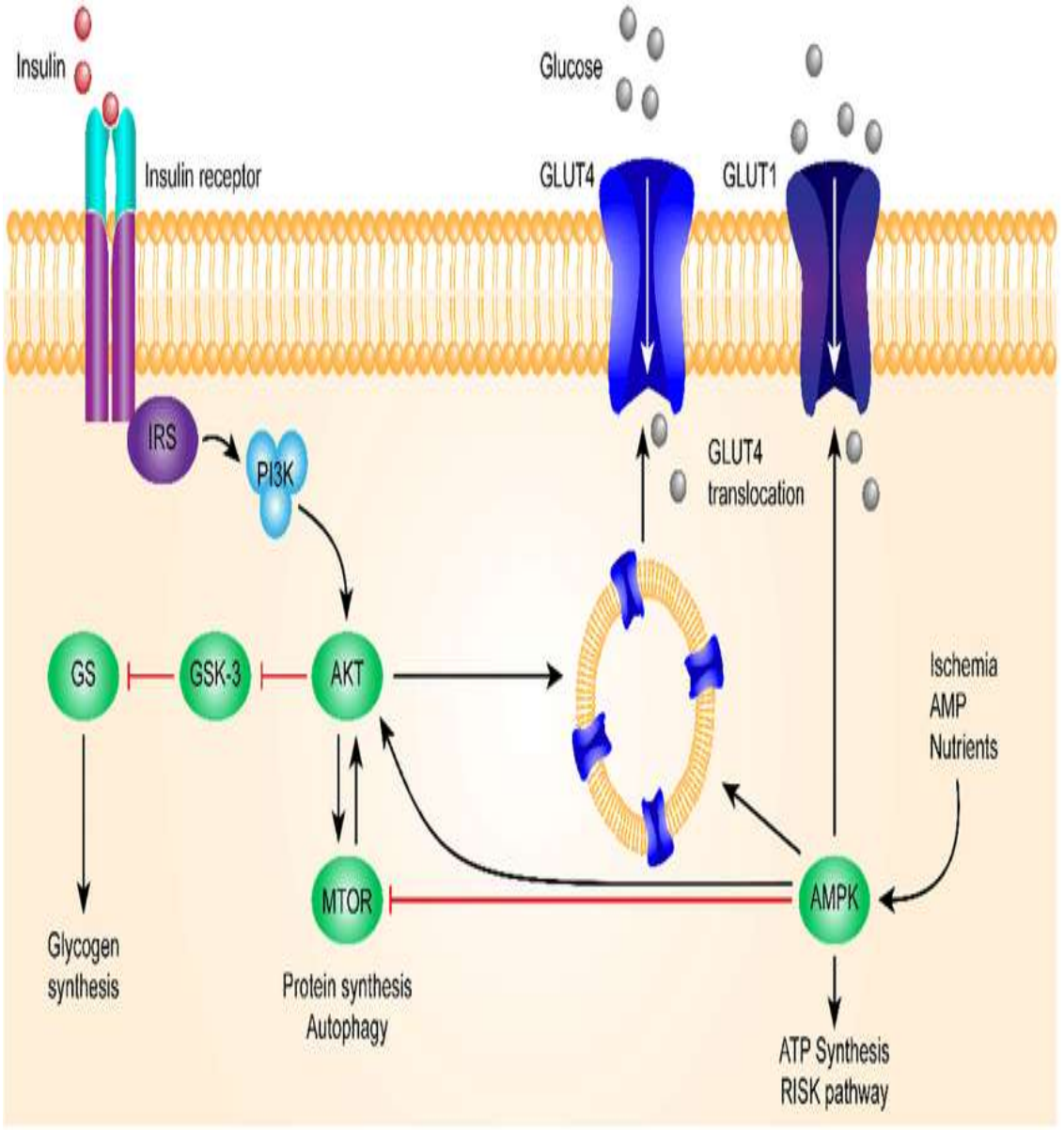
Dejstvo insulina



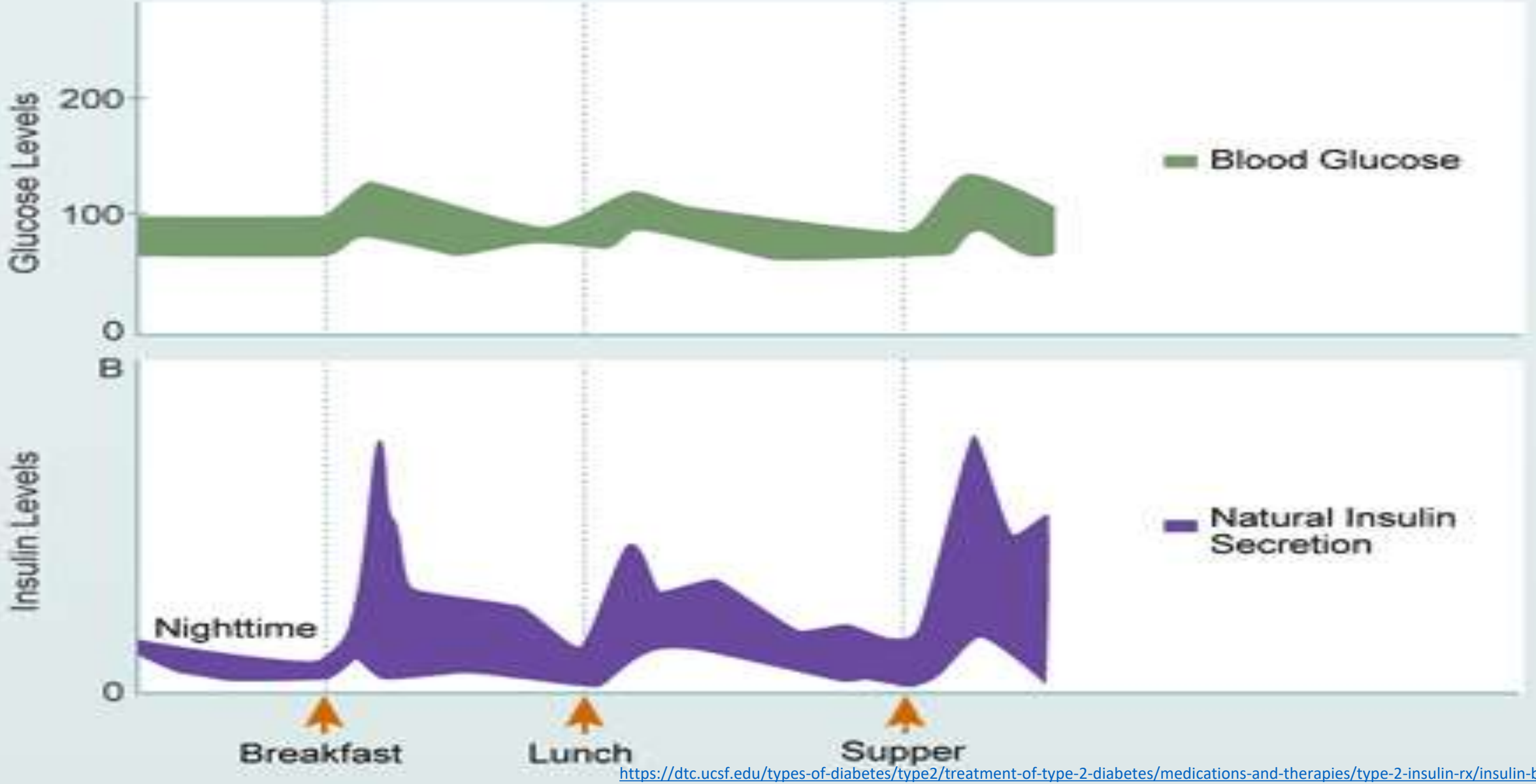
- Kada se insulin sekretuje u portalnu venu, približno se 50% odstranjuje i razgradjuje u jetri.
- Preostli insulin ulazi u sistemsku cirkulaciju i vezuje se za njegove receptora u ciljnim mestima.
- Vezivanje insulina za receptor stimuliše intrizičku aktivnost protein kinaze, koja dovodi do autofosforilacije receptora i aktivacije intacelularnih signalnih molekula (supstrati insulinskog receptora – IRIS).
- Ovi i drugi pomoćni proteini aktiviraju kompleksnu kaskadu reakcija fosforilacije i defosforilacije, što na kraju daje veći broj metaboličkih i mitogenih efekata insulina.
- Aktivacijom fosfatidil-3’-kinaze (PI-3 kinaze) puta, stimuliše se translokacija glukoznih transportera (GLUT4).
- Aktivacija drugih signalnih puteva insulinskog receptora izaziva sintezu glikogena, proteina, lipogenezu i regulaciju različitih gena u ćelijama osetljivim na dejstvo insulina.

Insulinski signalni put

- Insulinski receptor vezuje insulin, ima aktivnost tirozin-protein kinaze i posreduje u metaboličkim funkcijama insulina.
- Vezivanje za insulin stimuliše povezivanje receptora sa nizvodnim medijatorima, uključujući supstrat insulinskog receptora-1 (IRS-1) i PI3K *(phosphoinositol 3-kinase).*
- Receptor insulina može aktivirati PI3K ili direktno, vezivanjem za regulatornu podjedinicu p85, koja proizvodi PIP3, ili indirektno, što dovodi do fosforilacije i aktivacije AKT *(protein kinase B).*
- Nakon toga, AKT fosforiliše Ser9 mesto GSK-3b i inhibira njegovu aktivnost.
- PI3K/AKT/GSK-3b signalni put je uključen u transdukciju signalizacije insulina, a GSK-3b je regulisan i kontrolisan insulinom u ovom signalnom putu, koji je povezan sa regulacijom sinteze glikogena.

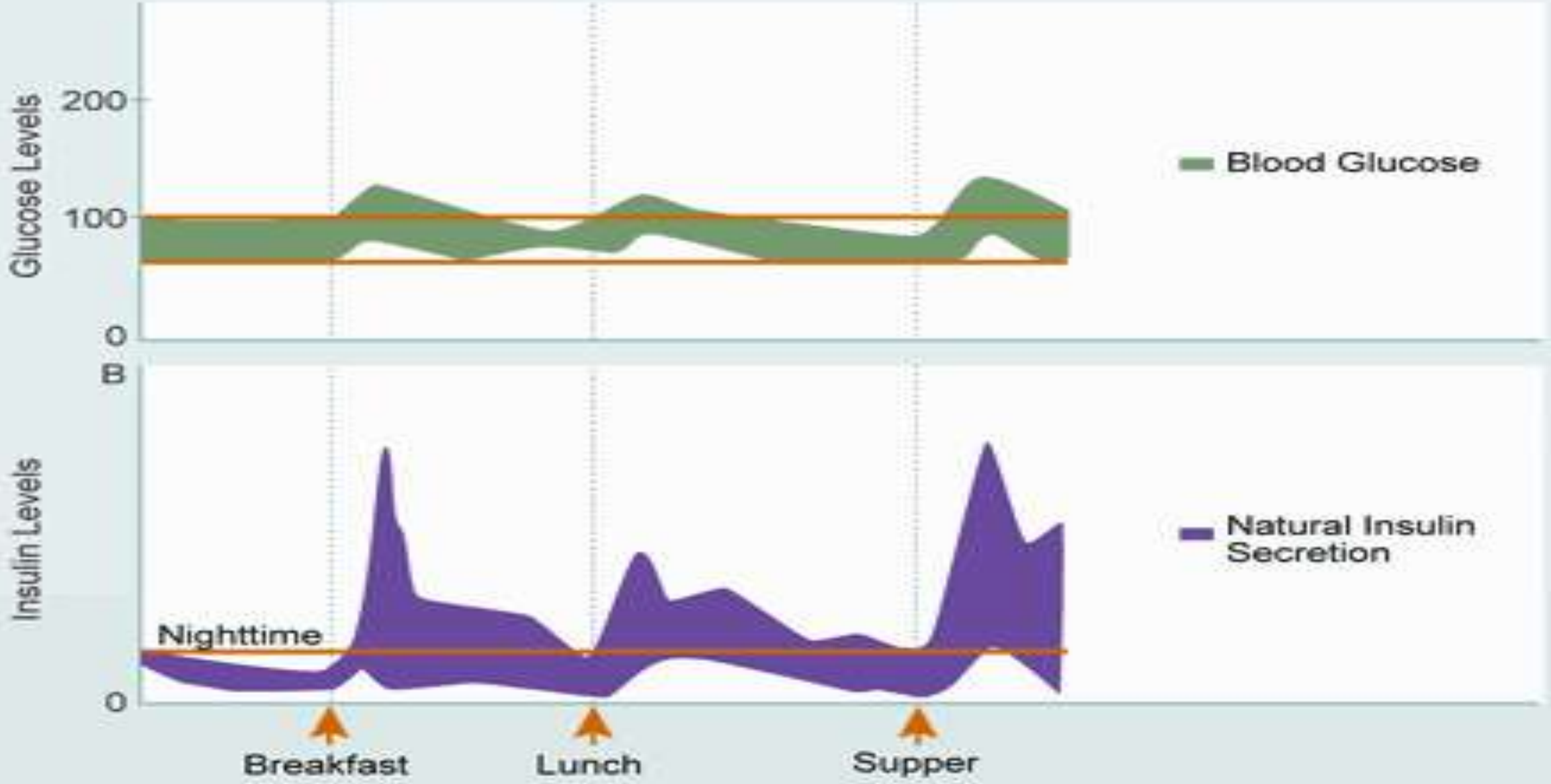


Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours

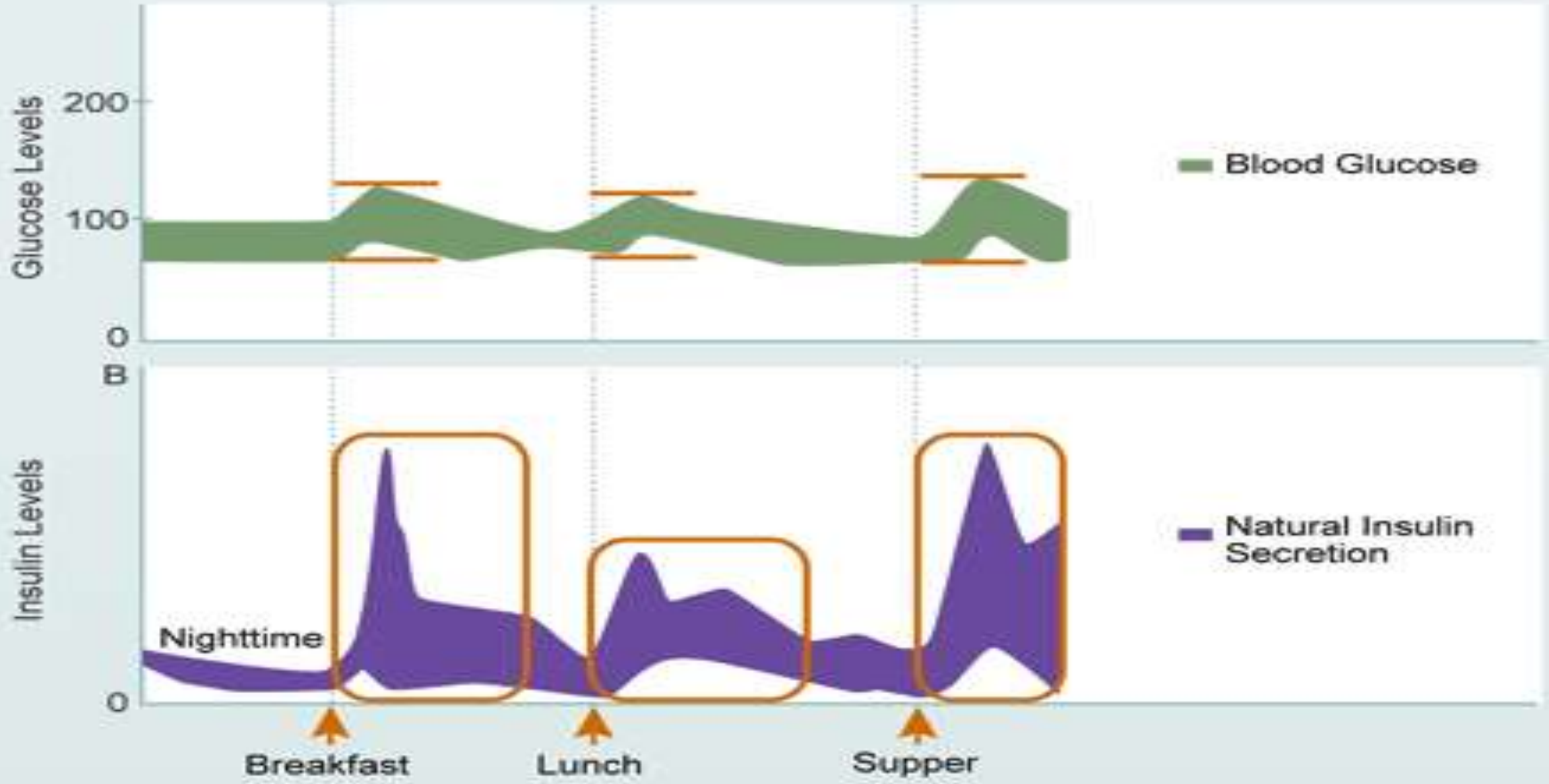


https://dtc.ucsf.edu/types-of-diabetes/type2/treatment-of-type-2-diabetes/medications-and-therapies/type-2-insulin-rx/insulin-basics/

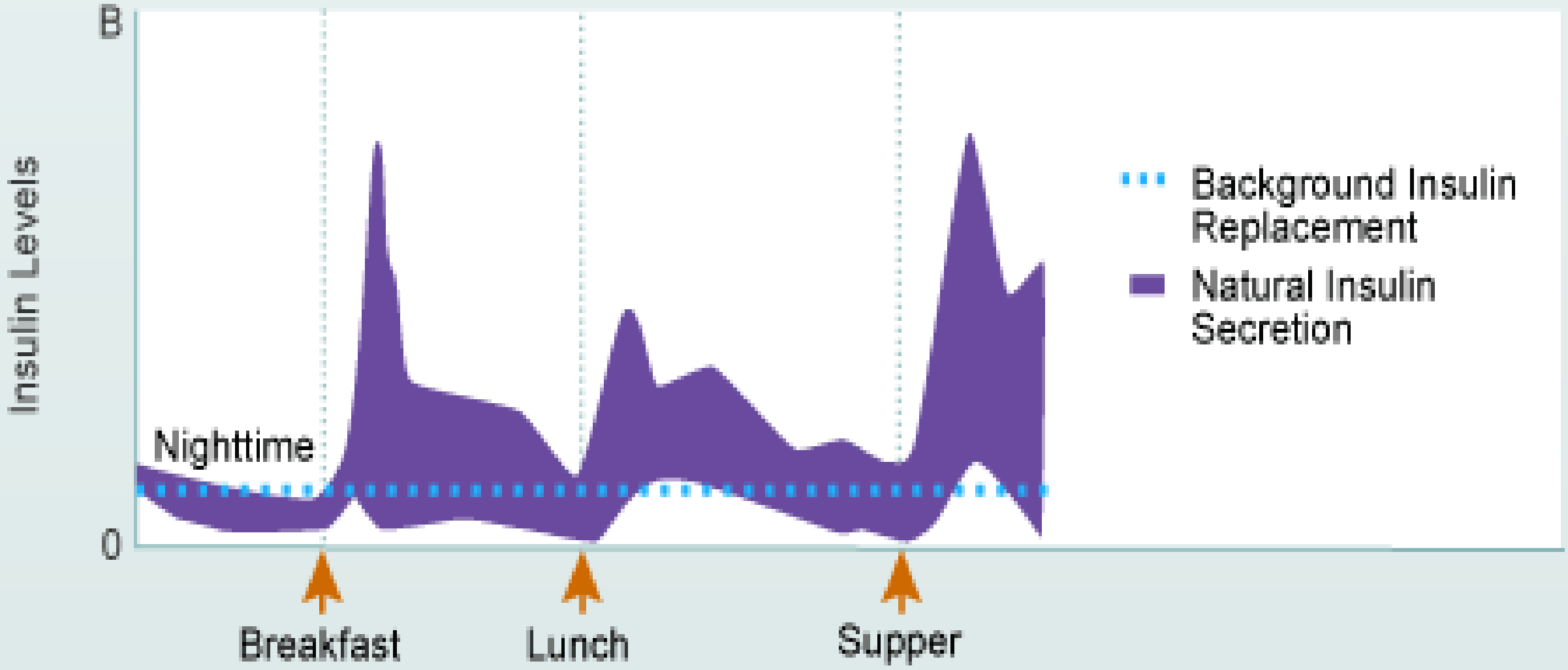
Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours



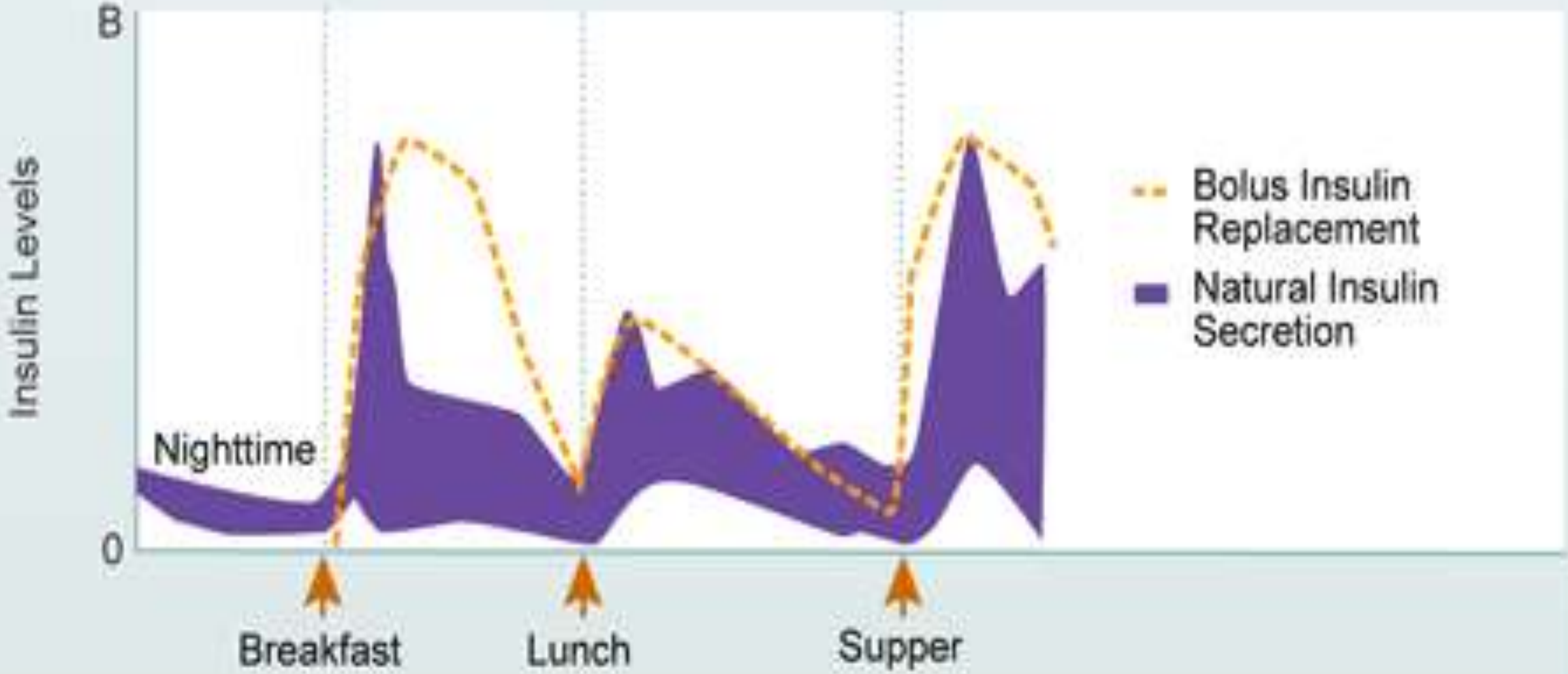
Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours



Background or Basal Insulin Replacement Compared with Natural, Non-diabetic Insulin Secretion



Mealtime or Bolus Insulin Replacement Compared with Natural, Non-diabetic Insulin Secretion



Intensive Insulin Replacement Compared with Natural, Non-diabetic Insulin Secretion

Dejstvo insulina	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

Effect on liver:

- Reversal of catabolic features of insulin deficiency
  - Inhibits glycogenolysis
  - Inhibits conversion of fatty acids and amino acids to keto acids
  - Inhibits conversion of amino acids to glucose
- Anabolic action
  - Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
  - Increases triglyceride synthesis and very-low-density lipoprotein formation

Effect on muscle:

- Increased protein synthesis
  - Increases amino acid transport
  - Increases ribosomal protein synthesis
- Increased glycogen synthesis
  - Increases glucose transport
  - Induces glycogen synthase and inhibits phosphorylase

Effect on adipose tissue:

- Increased triglyceride storage
  - Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
  - Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
  - Intracellular lipase is inhibited by insulin

Poremećaji metabolizma u dijabetes melitusu

Disfunkcija	Uzrok	Simptomi
<u>Metabolizam ugljenih hidrata usled</u>: **Nedovoljnog iskorišćavanja glukoze,** **Povećanja glukoneogeneze** **Smanjenja degradacije glikogena**	**Hiperglikemija** **Glukozurija**	**Polidipsija** **Poliurija** **Pruritus genitalis** **Znojenje**
<u>Metabolizam lipida usled:</u> **Inhibicije sinteze masti** **Povećanja lipolize** **Povećanja sinteze ketonskih tela**	**Hiperlipidemija** **Hiperketonemija** **Ketonurija** **Ketoacidoza**	**Nauzeja** **Povraćanje** **Gubitak telesne mase** **Zadah na aceton**
<u>Metabolizam proteina usled:</u> **Povećanja degradacije proteina** **Povećanja glukoneogeneze** **Smanjenja sinteze proteina**	**Hipergrglikemija** **Glikozurija** **Aminoacidurija** **Povećanje neproteinskog azota u krvi**	**Slabostgubitak telesne mase** **Gubitak mišićne mase**

Glukagon: hemija i metabolizam

- Glukagon se sintetiše u alfa ćelijama Langerhansovih ostrvaca pankreasa.
- Glukagon je peptid — identičan kod svih sisara — koji se sastoji od jednog lanca od 29 aminokiselina, sa molekulskom težinom od 3485.
- Selektivnim proteolitičkim cepanjem se veliki molekul prekursora od približno 18 000 MW pretvara u glukagon.
- Jedan od intermedijera prekursora sastoji se od peptida od 69 aminokiselina koji se zove glicentin, koji sadrži umetnutu sekvencu glukagona između peptidnih ekstenzija.
- Glukagon se u velikoj meri razgradjuje u jetri i bubrezima, kao I u plazmi i na mestima receptora tkiva.
- Njegov poluživot u plazmi je izmedju 3 i 6 minuta, što je slično kao kod insulina.

Farmakološki efekti glukagona

- Metabolički efekti
  - Prvih šest aminokiselina na amino terminalu molekula glukagona vezuju se za specifične receptore povezane sa Gs proteinom na ćelijama jetre.
  - Ovo dovodi do povećanja cAMP-a, što olakšava katabolizam uskladištenog glikogena i povećava glukoneogenezu i ketogenezu.
  - Neposredni farmakološki rezultat infuzije glukagona je podizanje glukoze u krvi na račun uskladištenog glikogena u jetri.
  - Nema efekta na glikogen skeletnih mišića, verovatno zbog nedostatka glukagonskih receptora na skeletnim mišićima.
  - Farmakološke količine glukagona izazivaju oslobadjanje insulina iz normalnih beta ćelija pankreasa, kateholamina iz feohromocitoma i kalcitonina iz ćelija karcinoma medularnog karcinoma.
- Kardijalni efekti
  - Glukagon ima snažan inotropni i hronotropni efekat na srce, posredovan cAMP mehanizmom.
  - Proizvodi efekat veoma sličan onom kod agonista b-adrenoceptora bez potrebe za funkcionalnim b receptorima.
- Uticaj na glatke mišiće
  - Velike doze glukagona izazivaju duboko opuštanje creva.
  - Za razliku od gore navedenih efekata peptida, ovo dejstvo na creva može biti posledica drugih mehanizama osim aktivacije adenil ciklaze.

Glukagon - kliničke upotrebe

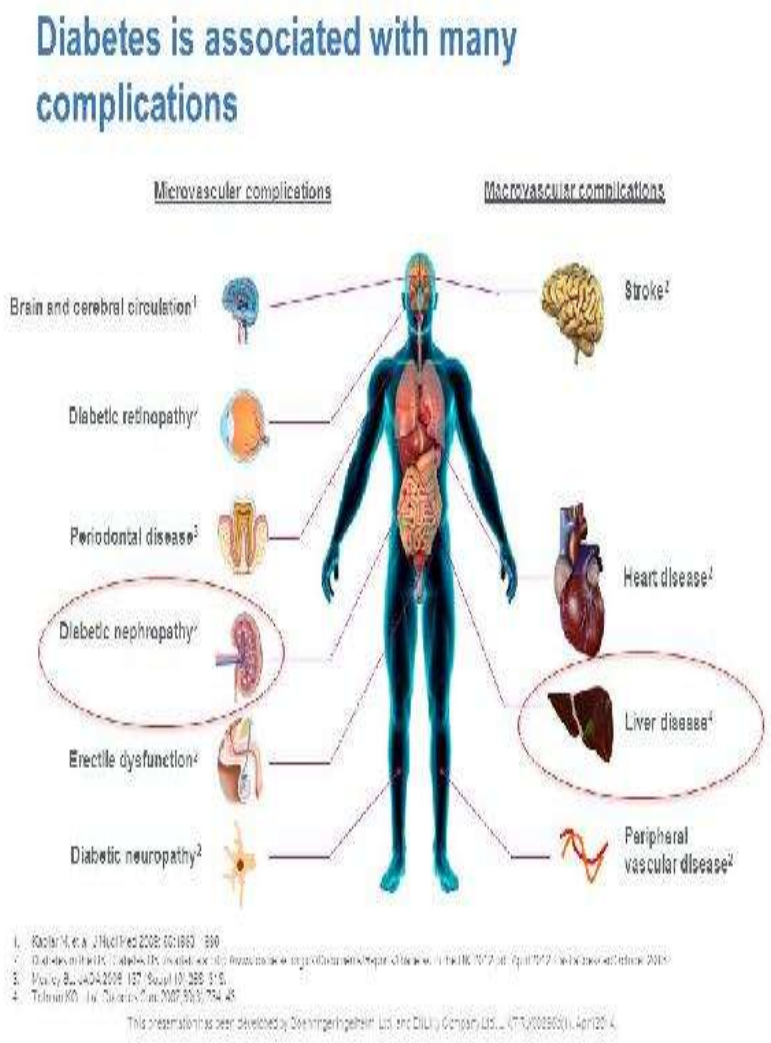
- Glavna klinička upotreba glukagona je za hitno lečenje teških hipoglikemijskih reakcija usled insulinske terapije kada osoba nije u stanju da se samoleči oralnom glukozom (nesvesnost) i intravenski tretman glukozom nije moguć.
- Rekombinantni glukagon je trenutno dostupan u bočici od 1 mg za parenteralnu (iv, im, subkutanu) upotrebu ili dozi od 3 mg nazalnog praha za inhalaciju.
- Glavni neželjeni efekat je prolazna mučnina i povremeno povraćanje, stoga je važno pacijente koji su u nesvesti staviti na bok nakon primene leka.
- Intravenski glukagon se obično koristi u proceduri endoskopske retrogradne holangio-pankreato-grafije da bi se olakšalo opuštanje sfinktera *Oddi*.
- Glukagon se ponekad koristi u lečenju predoziranja beta blokatorima zbog sposobnosti leka da poveća proizvodnju cAMP u srcu nezavisno od funkcije beta-receptora.
- Glukagon ne treba davati pacijentima sa feohromocitomom kod kojih može izazvati oslobadjanje kateholamina i povećanje krvnog pritiska; takodje, ga ne treba davati pacijentima sa insulinomom gde može izazvati povratnu hipoglikemiju.

Akutne komplikacije dijabetesa

- Dijabetesna ketoacidoza
- Laktatna acidoza
- Dijabetesno neketogeno hiperosmolarno stanje
- Hipoglikemija u dijabetesu

HRONIČNE KOMPLIKACIJE DIJABETESA

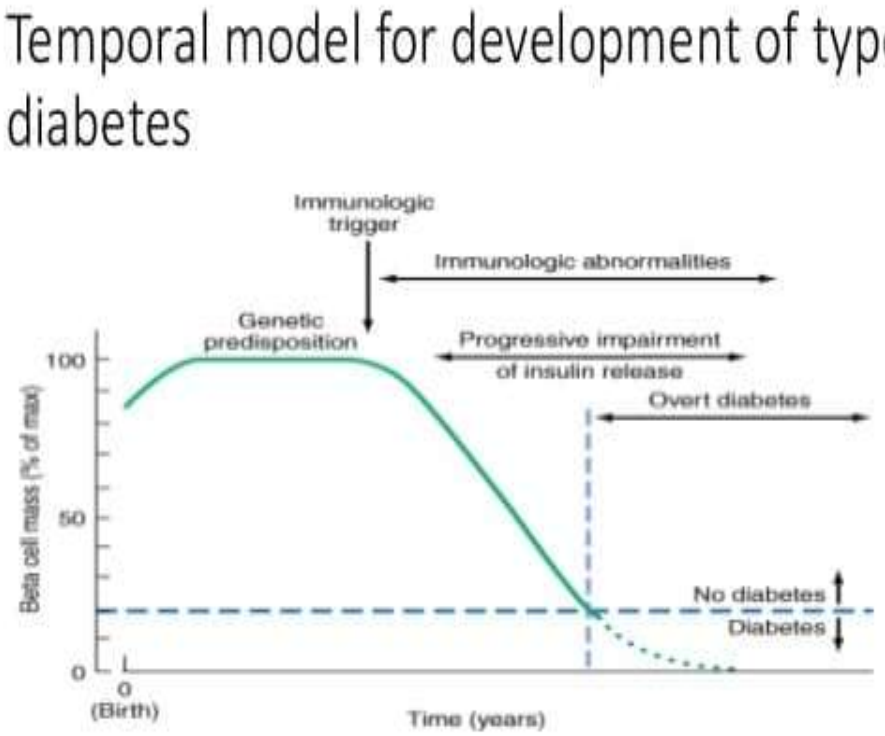
- **Mikrovaskularne**
  - Oboljenja oka
    - Retinopatija (neproliferativna, proliferativna)
    - Makularni edem
    - Katarakta
    - Glaukom
  - Neuropatija
    - Senzitivna i motorna (mono i polineuropatija)
    - Autonomna
  - Nefropatija



- **Makrovaskularne**
  - Bolest koronarnih arterija
  - Periferna vaskularna bolest
  - Cerebrovaskularna bolest

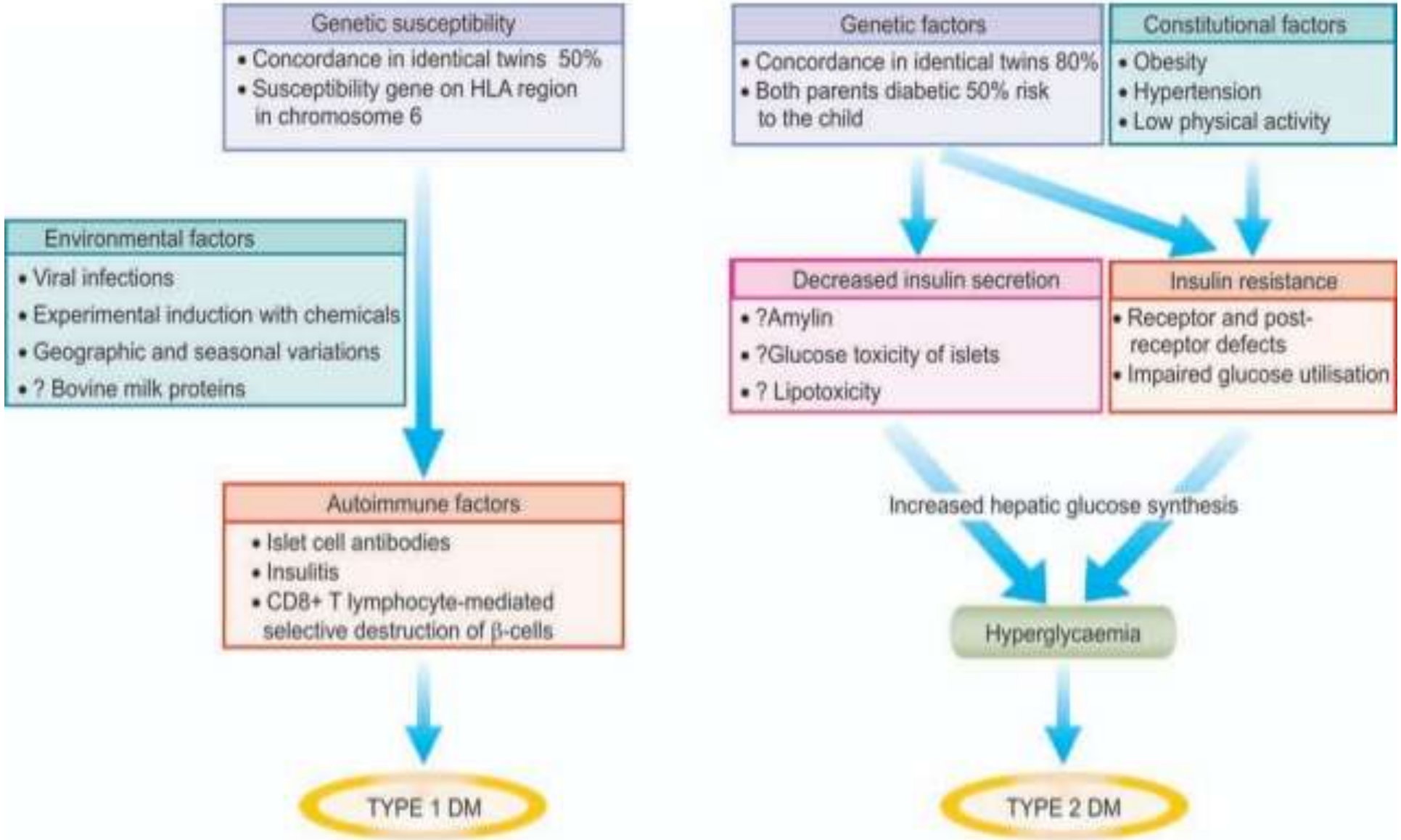
- **Druge**
  - Gastrointestinalne (gastropareza, dijareja)
  - Genitourinarne (uropatije, seksualne disfunkcije)
  - Kožne

Patogeneza DM tip 1



- Rezultat interakcije genetskih, ekoloških i imunskih faktora, koji na kraju dovedu do uništenja beta ćelija pankreasa i nedostatka insulina.
- Incidencija DM tip 1 povećava se brzinom od 3-4% iz nejasnih razloga.
- Alfa ćelije (stvaraju glukagon), delta ćelije (stvaraju somatostatin) ili PP ćelije (stvaraju pankreasni polipeptid) funkcionalno i embrionalno slične beta ćelijama i prikazuju iste proteine ko beta ćelije, su neobjašnjivo poštedjene od autoimunskog razaranja.
- *Honey moon* period može da se javi u toku jedne ili dve godine od početka dijabetesa i povezan je sa smanjenim potrebama za insulinom.

Schematic mechanisms involved in pathogenesis of two main types of diabetes mellitus



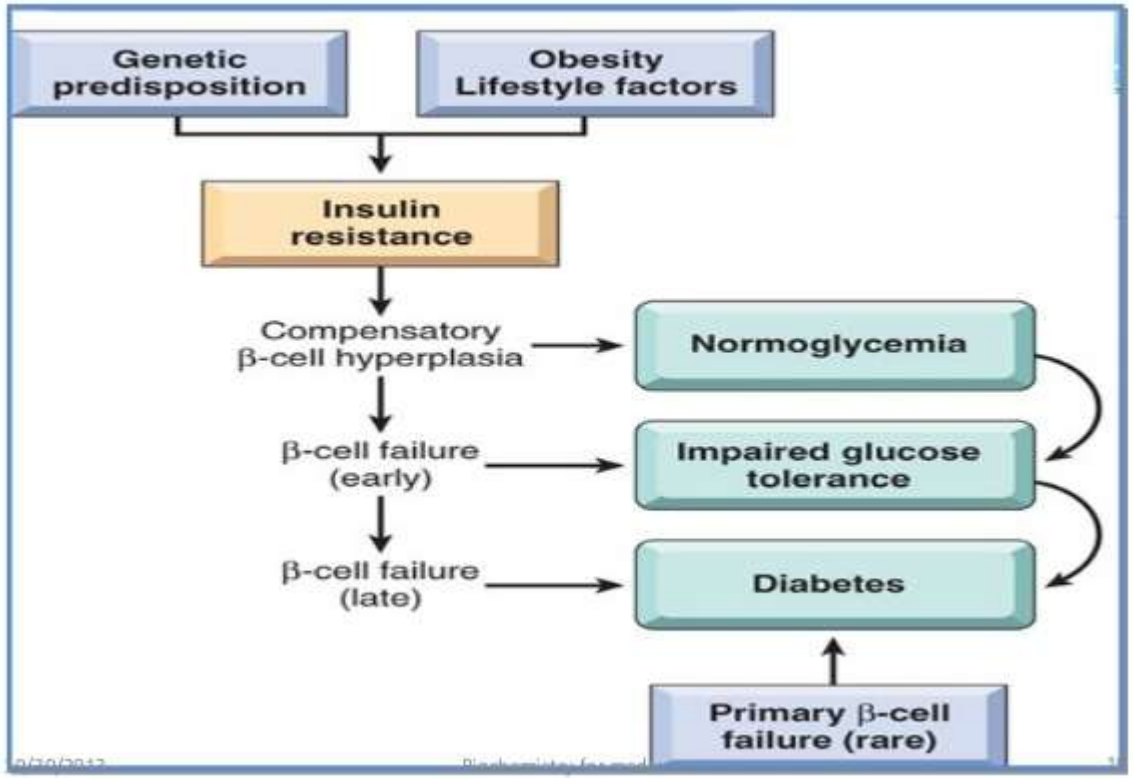
A, PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

B, PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

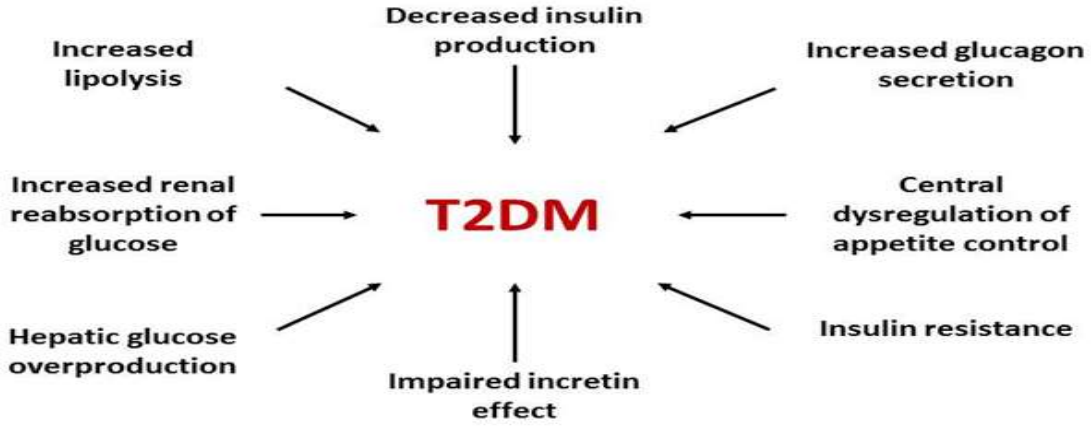
Patogeneza DM tip 2

DM tipa 2 karakteriše se sa četiri patofiziološka poremećaja:

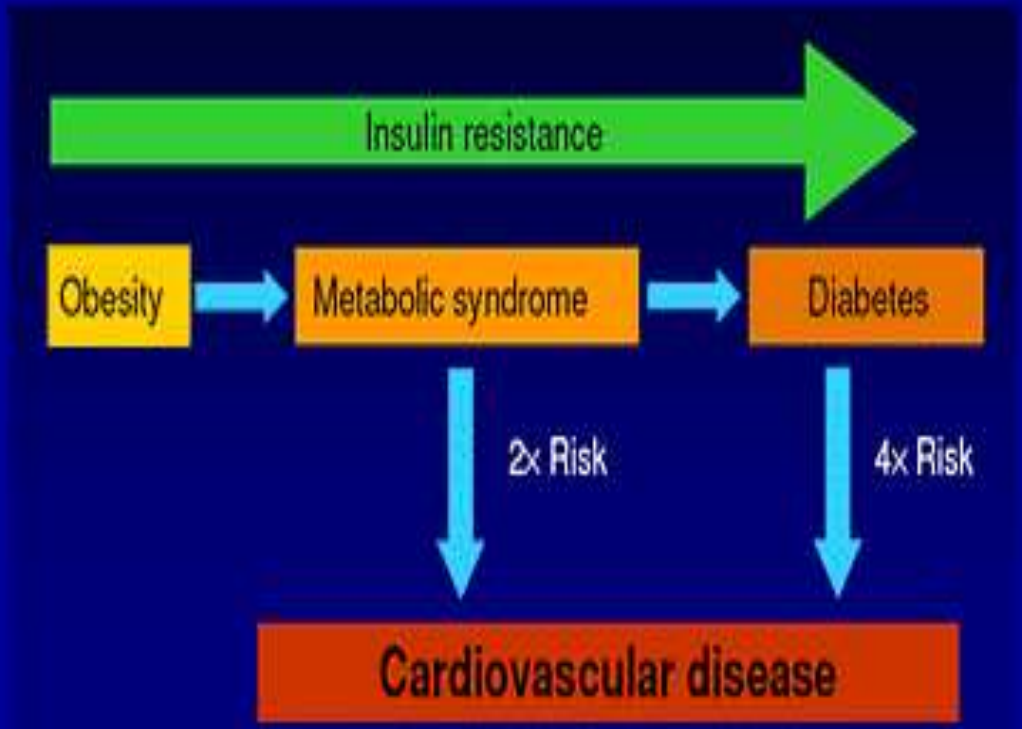
- ✓**Smanjenim lučenjem insulina,**
- ✓**Perifernom insulinskom rezistencijom,**
- ✓**Preteranim stvaranjem glukoze u jetri,**
- ✓**Abnormalnim metabolizmom masti.**



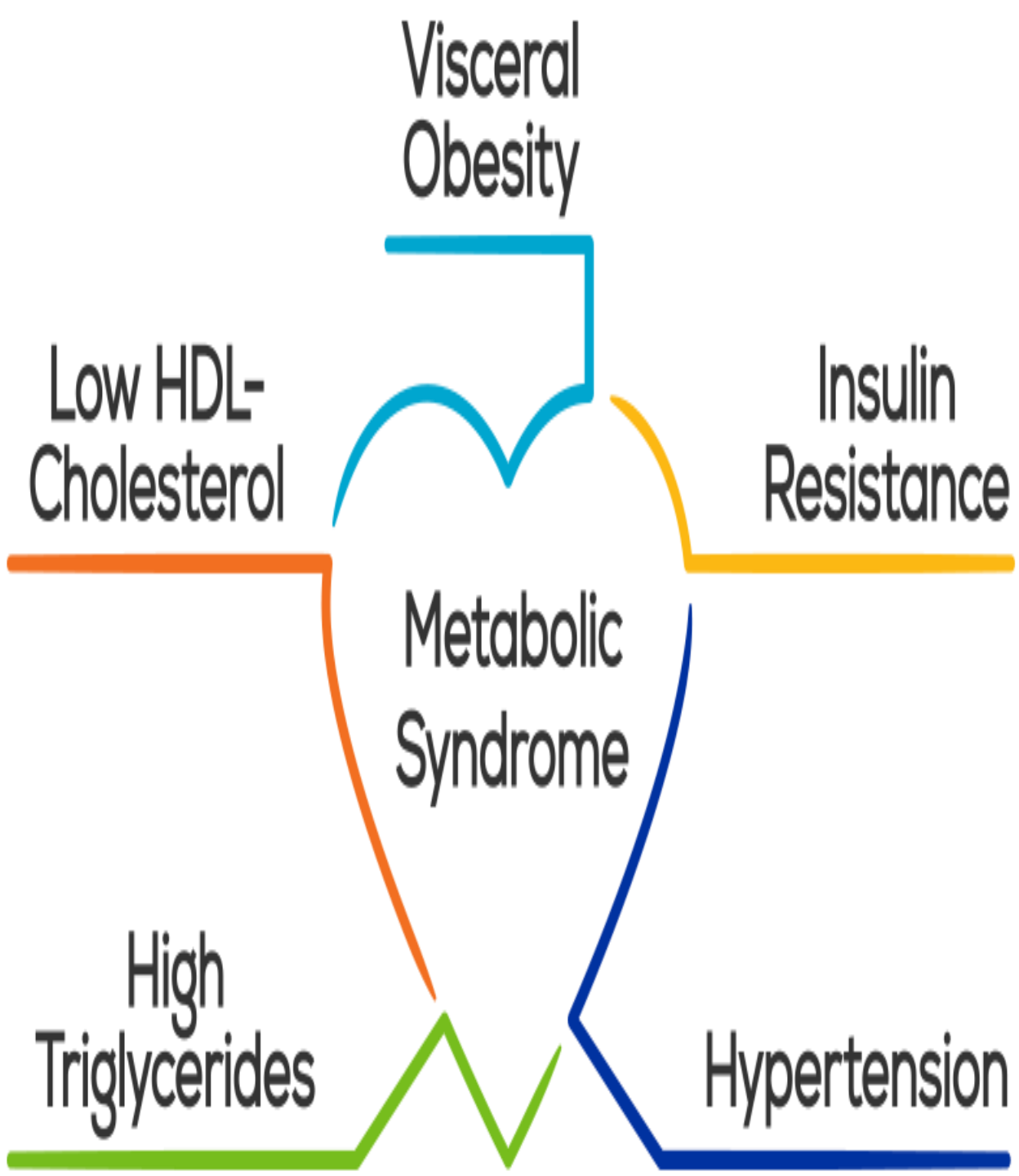
- **Gojaznost**, naročito visceralna i centralna, naročito česta u DM tip 2
- **Adipociti** luče veći broj bioloških produkata (leptin, faktor tumorske nekroze alfa, slobodne masne kiseline) koji menjaju procese kao što su lučenje insulina, dejstvo insulina i telesna masa, a mogu da doprinesu insulinskoj rezistenciji.



Obesity, Metabolic Syndrome, and Type 2 Diabetes

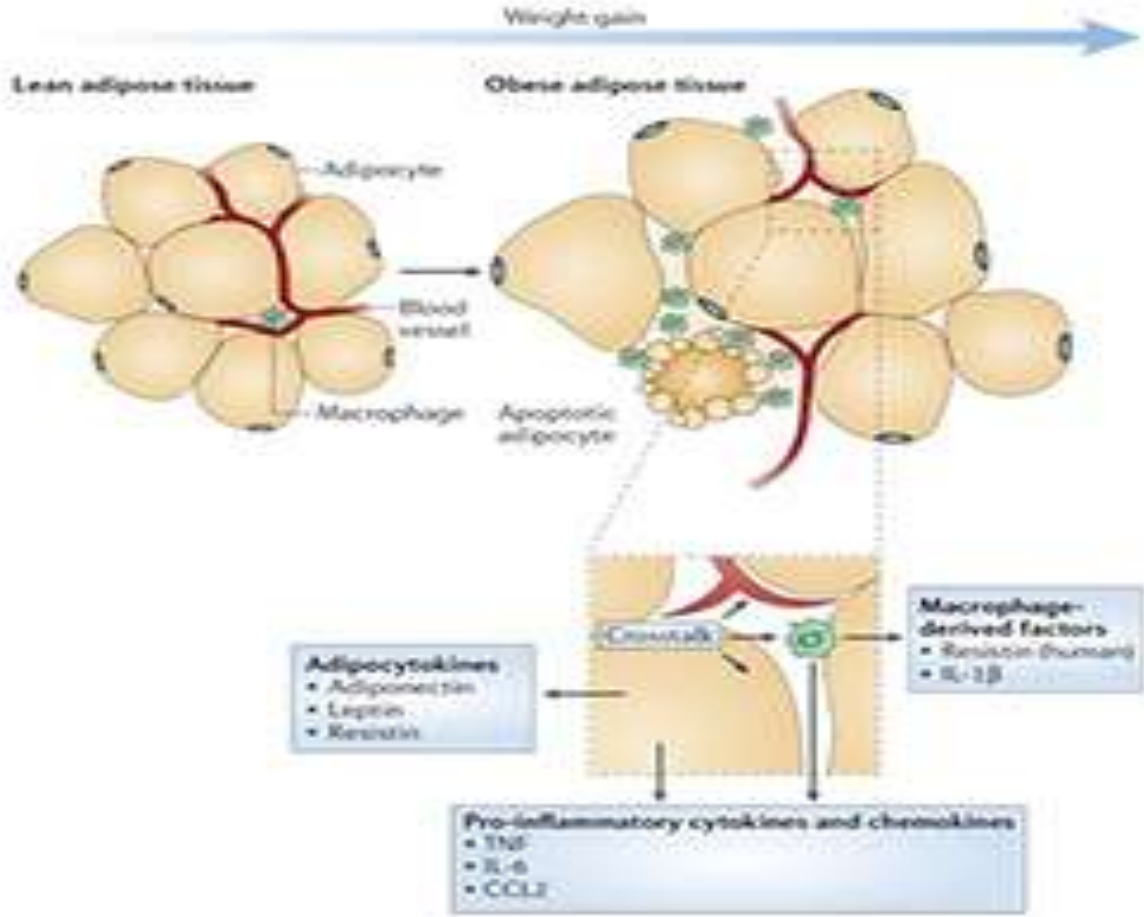


Luscher TF, et al. *Circulation*. 2003;108:1655-1661.
Reilly MP and Rader DJ. *Circulation*. 2003;108:1546-1551.



How is Adipose Tissue Related to Inflammation in the Body?

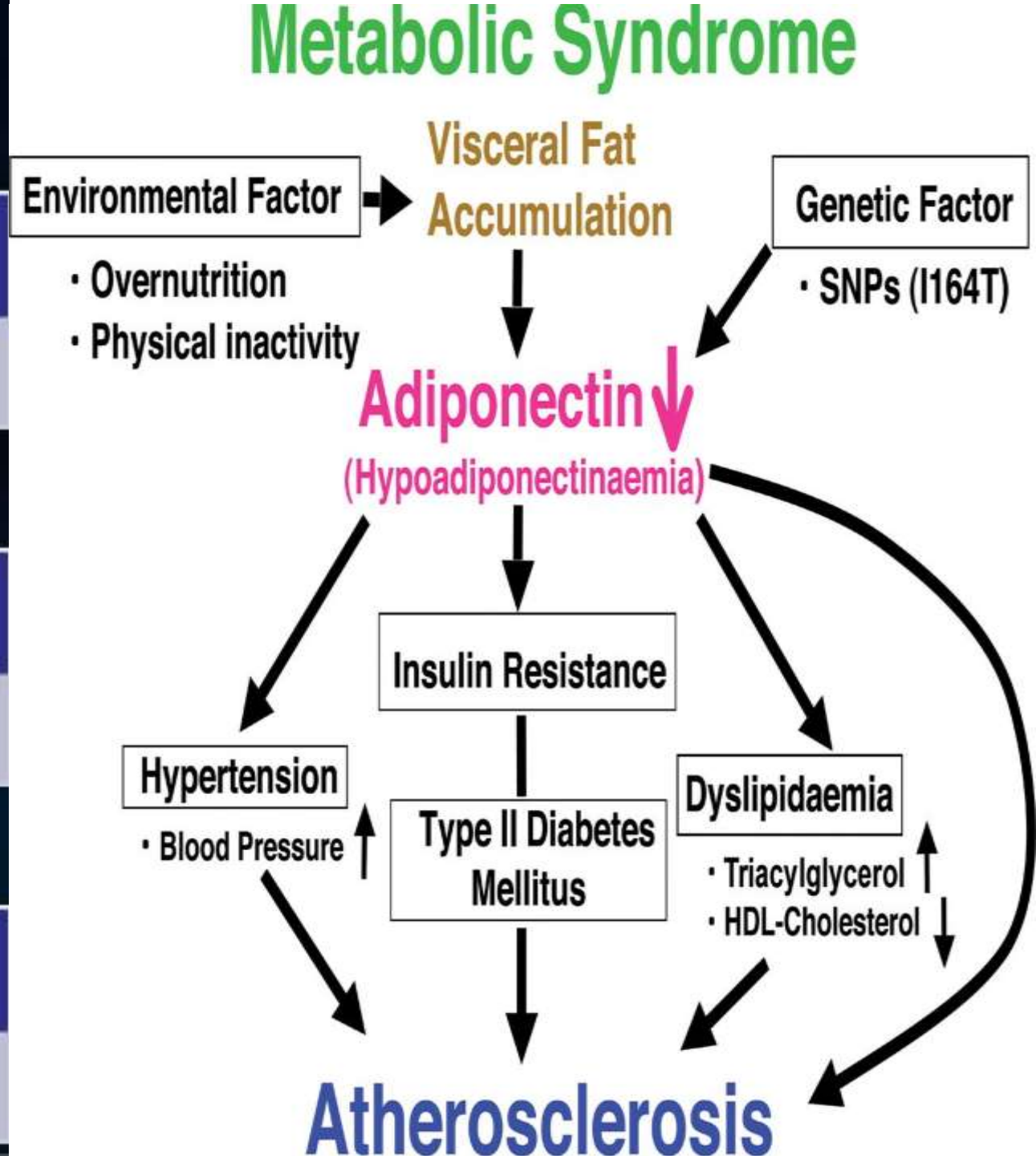
- Obese adipose tissue can be proinflammatory
- Increased levels of adipocytokines can[a,b]
  - Increase levels of inflammatory cytokines, including: TNF-α, IL-1, IL-6
  - Induce proliferation of Th1 cells and decrease proliferation of regulatory T cells
- Similar cytokines are part of the inflammatory milieu of RA[b]
  - It has been suggested, but not confirmed, that adipocytokines expressed by obese adipose tissue can impact severity of RA



Reprinted by permission from Macmillan Publishers Ltd: Tilg H, Moschen AR. *Nat Rev Immunol*. 2006;6:772-783. Copyright 2006.

a. Hauner H. *Proc Nutr Soc*. 2005;64:163-169; b. Gremese E, et al. *Front Immunol*. 2014;5:576.

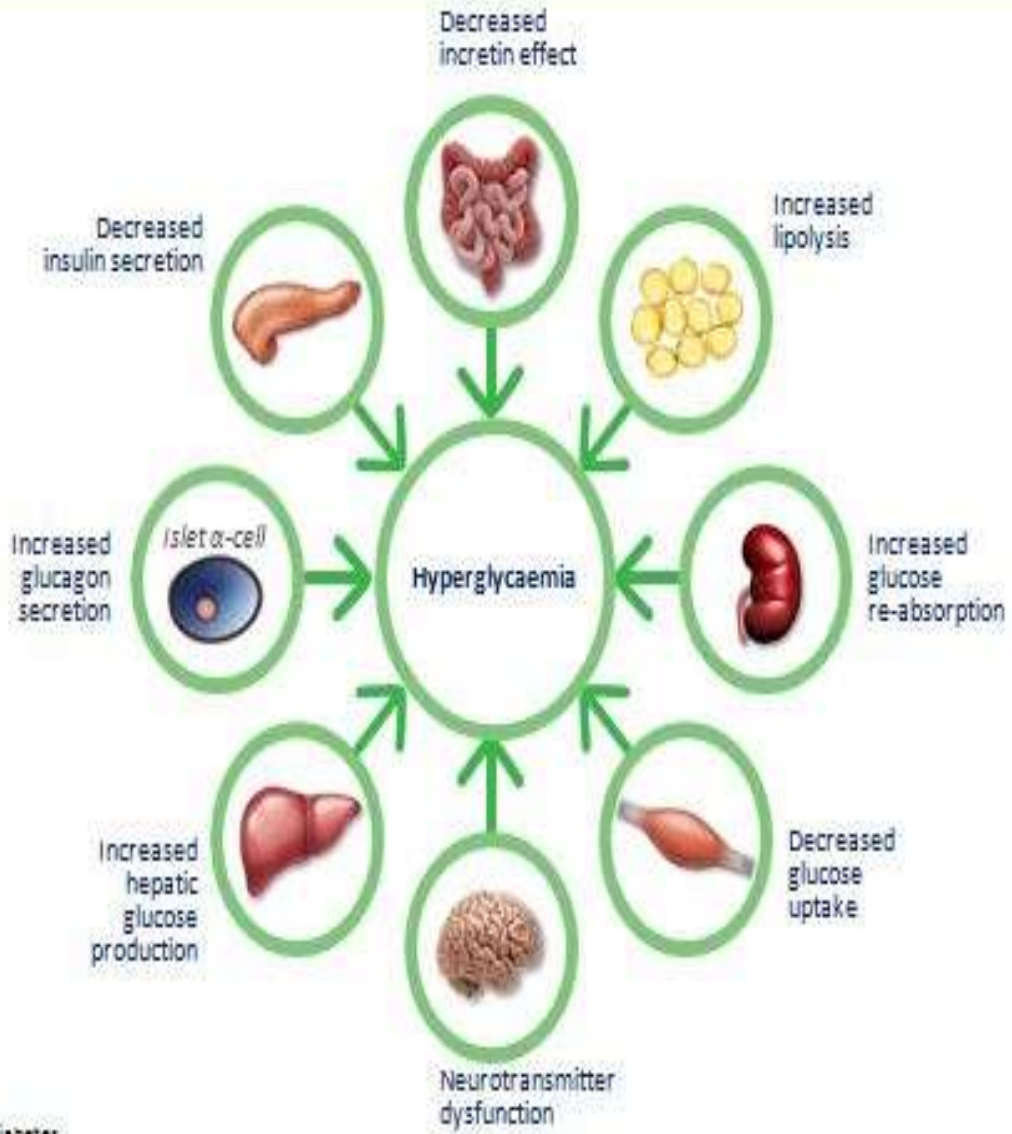

Defect in Type 2 DM
One Hormone Theory
Insulin Deficiency
Two Hormone Theory
Insulin Deficiency
Glucagon Excess
Three Hormone Theory
Insulin Deficiency,Glucagon Excess
Decreased Incretin effect


Metabolic Syndrome
Environmental Factor
Visceral Fat Accumulation
Genetic Factor
• Overnutrition
• Physical inactivity
• SNPs (I164T)
Adiponectin
(Hypoadiponectinaemia)
Insulin Resistance
Hypertension
• Blood Pressure
Type II Diabetes Mellitus
Dyslipidaemia
• Triacylglycerol
• HDL-Cholesterol
Atherosclerosis

The Deadly Quartet

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

Theory of 'Ominous Octet'
Management of Multiple Targets in T2D[1,2]



T2D, Type 2 Diabetes.
1. Adapted from: DeFronzo RA. *Diabetes*. 2009;58:773–795; 2. Adapted from: Tahrani AA, et al. *Lancet*. 2011;378:182–197.

“Zlosutni oktet”

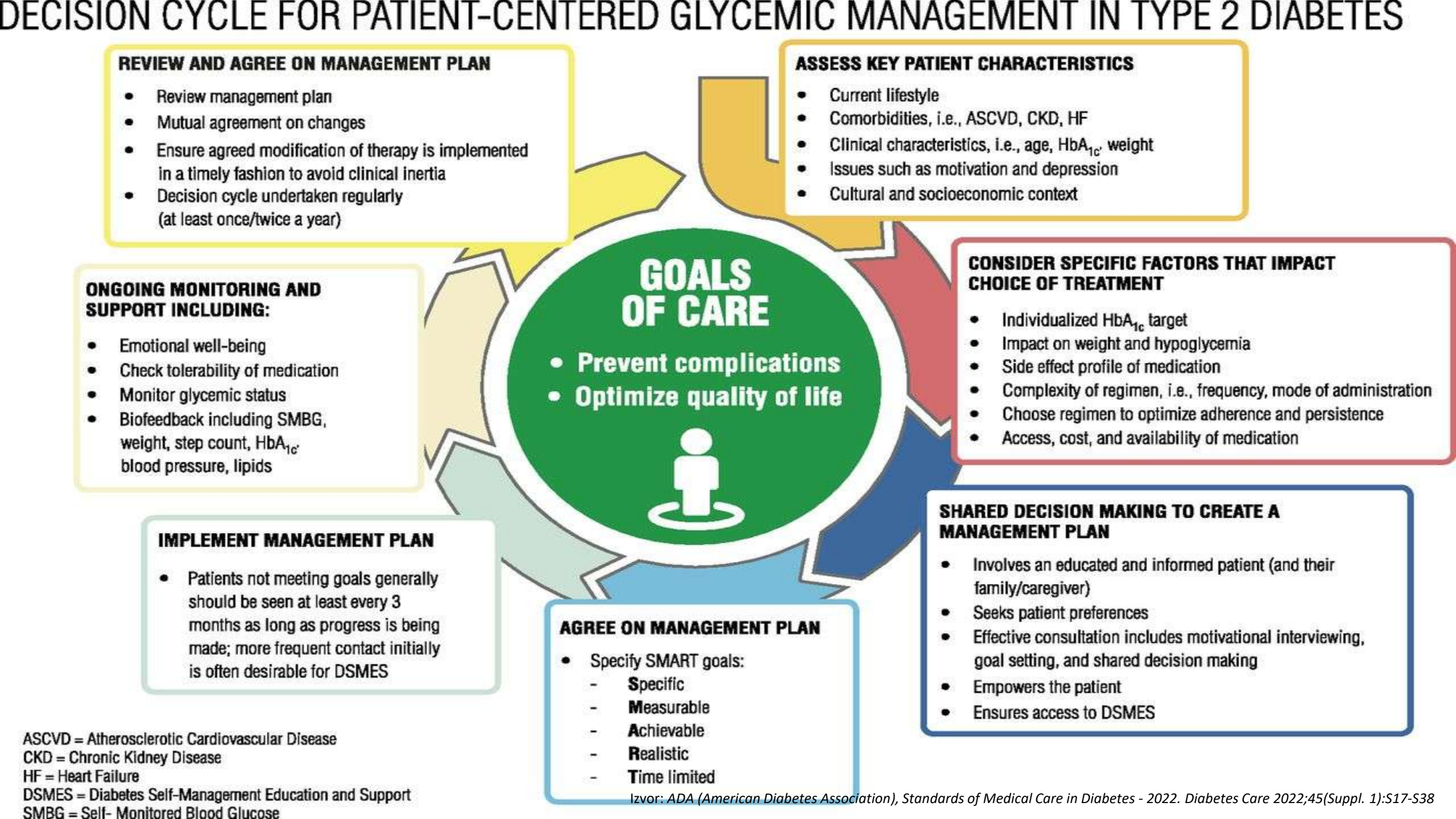
Ralph A. DeFronzo. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes 2009 Apr; 58(4): 773-795. https://doi.org/10.2337/db09-9028

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;

Pristup pacijentu: *Diabetes mellitus*

1. Anamneza
2. Fizikalni pregled
3. Klasifikacija DM svakog pacijenta
4. Laboratorijska procena (ispitivanje)

DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self- Monitored Blood Glucose

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

1. Anamneza

- **Kompletna medicinska istorija bolesti**, sa posebnim osvrtom na aspekte važne za DM:
  - telesna masa, porodična anamneza DM, komplikacije dijabetesa, faktori rizika za razvoj KVB, pušenje, fizička aktivnost, konzumiranje alkohola.

- **Simptomi hiperglikemije**:
  - poliurija, polidipsija, gubitak težine, umor, slabost, oštećenje vida, česte superficijalne infekcije (vaginitis, gljivične infekcije kože), sporo zarastanje kožnih lezija, posle manjih povreda.

2. Fizikalni pregled

- Kompletana fizikalni pregled,
- Aspekti važni za DM:
  - indeks telesne mase,
  - fundoskopija,
  - ortostatski krvni pritisak,
  - periferni pulsevi,
  - mesta ubrizgavanja insulina.
- Pregledati zube i desni: bolesti paradoncijuma.

3. Klasifikacija svakog bolesnika

DM tip 1:

- Početak bolesti pre 30 godine,
- Mršava gradja tela,
- Potrebe za insulinom kao početnom terapijom,
- Sklonost ka razvoju ketoacidoze,
- Povećani rizik od drugih autoimunskih bolesti, kao što je autoimunska bolest štitaste žlezde, insuficijencija nadbubrežne žlezde, perniciozna anemija, celijakija, vitiligo.

DM tip 2:

- Oboljevanje od dijabetesa posle navršene 30 godine života,
- Obično su gojazne (80% su gojazne, ali starije osobe mogu biti i mršave)
- Inicijalno im nije potrebna insulinska terapija,
- Mogu da imaju povezana stanja, kao što su insulinska rezistencija, hipertenzija, kardiovaskularna bolest, dislipidemija ili sindrom policističnih jajnika.

3. Laboratorijska procena (ispitivanja)

- Laboratorijskom procenom treba da se utvrdi da li bolesnik zadovoljava dijagnostičke kriterijume za DM.
- Stepen glikemijske kontrole.
- Standardno laboratorijsko ispitivanje.
- Laboratorijski testovi za stanja/poremećaje povezane sa DM (mikroalbuminurija, dislipidemija, disfunkcija štitaste žlezde)

Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		✓
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		✓
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes – 2022. *Diabetes Care* 2022;45(Suppl. 1):S46-S59

COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES

BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
SOCIAL LIFE ASSESSMENT	**Social network**			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g.., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;45(Suppl. 1):S46-S59

COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES

PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;44(Suppl. 1):S46-S59

COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES

LABORATORY EVALUATION	■ A1C, if the results are not available within the past 3 months	✓	✓	✓
	■ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics+	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA obstructive sleep apnea;PAD, peripheral arterial disease

*At 65 years of age or older

+May be needed more frequently in patients with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see Table 11.1)

#May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications)

^In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent

**Should be performed at every visit in patients with sensory loss, previous foot ulcers, or amputations

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;45(Suppl. 1):S46-S59

Table 2.6—Most common causes of monogenic diabetes (166)

	Gene	Inheritance	Clinical features
MODY	*GCK*	AD	GCK-MODY: higher glucose threshold (set-point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (171)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;45(Suppl. 1):S17-S38

Gestational Diabetes Mellitus

2.26a In women who are planning pregnancy, screen those with risk factors B and consider testing all women for undiagnosed diabetes. E

2.26b Before 15 weeks of gestation, test women with risk factors B and consider testing all women E for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria, if not screened preconception.

2.26c Women identified as having diabetes should be treated as such. A

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Gestational Diabetes Mellitus (continued)

2.26d Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify women who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus diagnosis. B Treatment may provide some benefit. E

2.26e Screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). B

2.27 Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. A

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Gestational Diabetes Mellitus (continued)

2.28 Screen women with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. B

2.29 Women with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. B

2.30 Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. A

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

GDM diagnosis (Table 2.7) can be accomplished with either of two strategies:

1. The “one-step” 75-g OGTT derived from the IADPSG criteria, or
2. The older “two-step” approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive, based on the work of Carpenter and Coustan’s interpretation of the older criteria.

Izvor: *ADA (American Diabetes Association), Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38*

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [244]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis (240).

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2022. Diabetes Care 2022;45(Suppl. 1):S17-S38