بنام خداوند جان و خرد

Insulin Resistance and Diabetes Mellitus

M Siavash
Professor of endocrinology
Isfahan University of medical sciences
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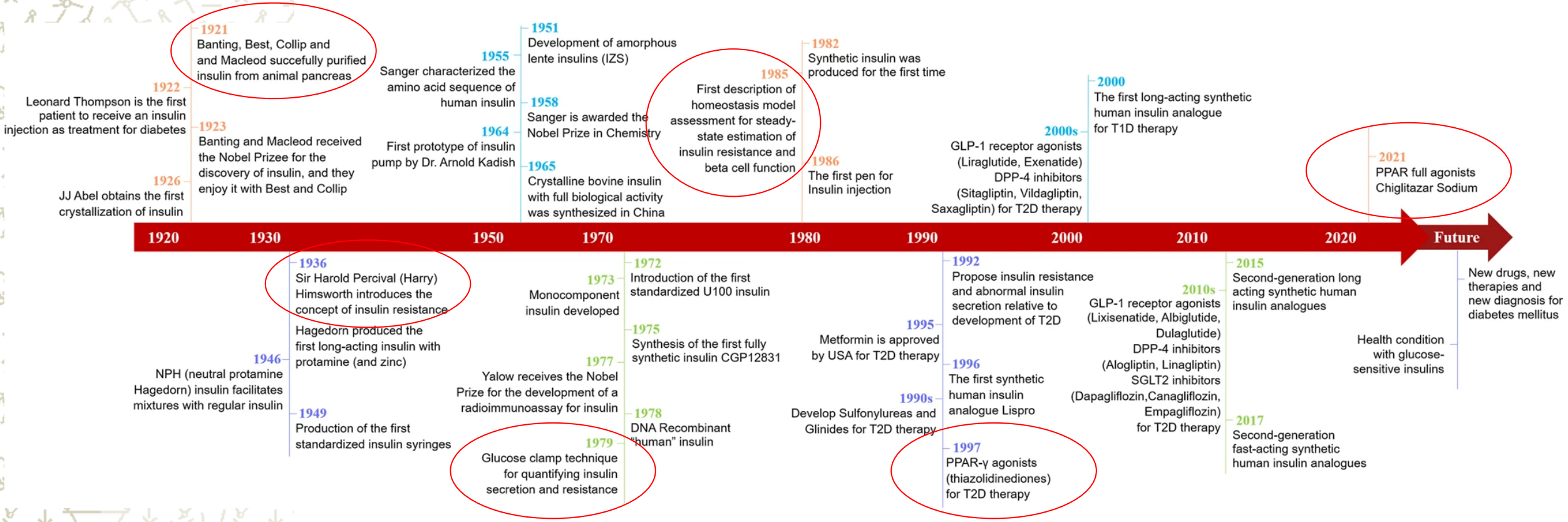
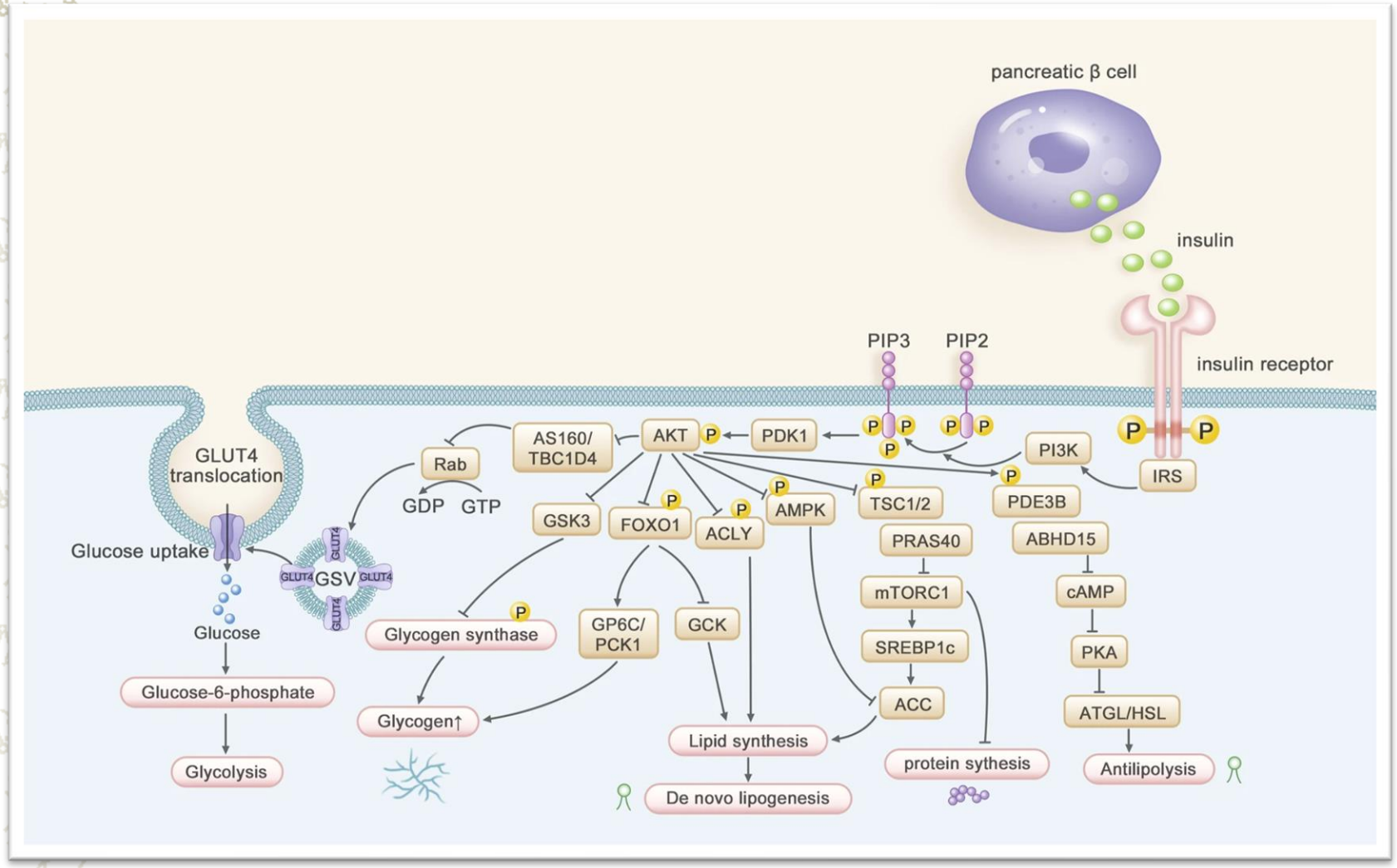
A timeline of key discoveries in our understanding of insulin and insulin resistance



- Genetic studies have shown that modern humans inherited some Neanderthal alleles associated with increased risk of type 2 DM (e.g., variants in SLC16A11)

The insulin signaling pathway including proximal and distal segments



Insulin Resistance

- Insulin resistance is when cells in your muscles, fat, and liver don’t respond well to insulin and can’t easily take up glucose from your blood
- Insulin resistance can defined as a subnormal biological response to normal insulin concentrations.
- As a result, your pancreas makes more insulin to try to overcome your increasing blood glucose levels.
- This is called hyperinsulinemia

Insulin Resistance

- The syndromes of insulin resistance actually make up a broad clinical spectrum, which includes:
- obesity,
- glucose intolerance,
- diabetes, and
- the metabolic syndrome, as well as
- an extreme insulin-resistant state

Insulin Resistance Risk Factors

- overweight or obesity (Excess body fat)
- age 45 or older
- Family history of diabetes
- Low physical inactivity
- health conditions such as high blood pressure and abnormal cholesterol levels
- a history of gestational diabetes
- a history of heart disease or stroke
- polycystic ovary syndrome, also called PCOS
- certain medicines, such as glucocorticoids , some antipsychotics , and some medicines for HIV
- hormonal disorders, such as Cushing’s syndrome and acromegaly
- sleep problems, especially sleep apnea

Symptoms of Insulin Resistance

- Insulin resistance no symptoms

- Symptoms of prediabetes:
- Acanthosis nigricans, Skin tags, Increased thirst, Frequent urination, Vaginal and skin infections,….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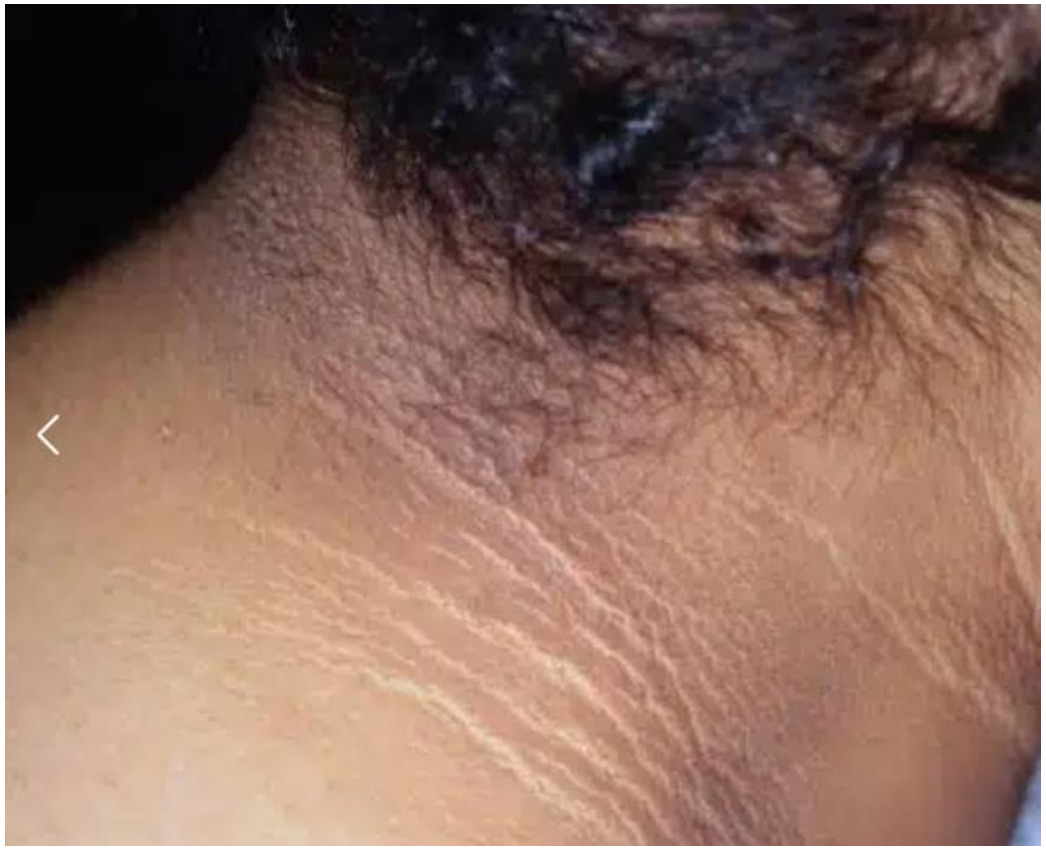
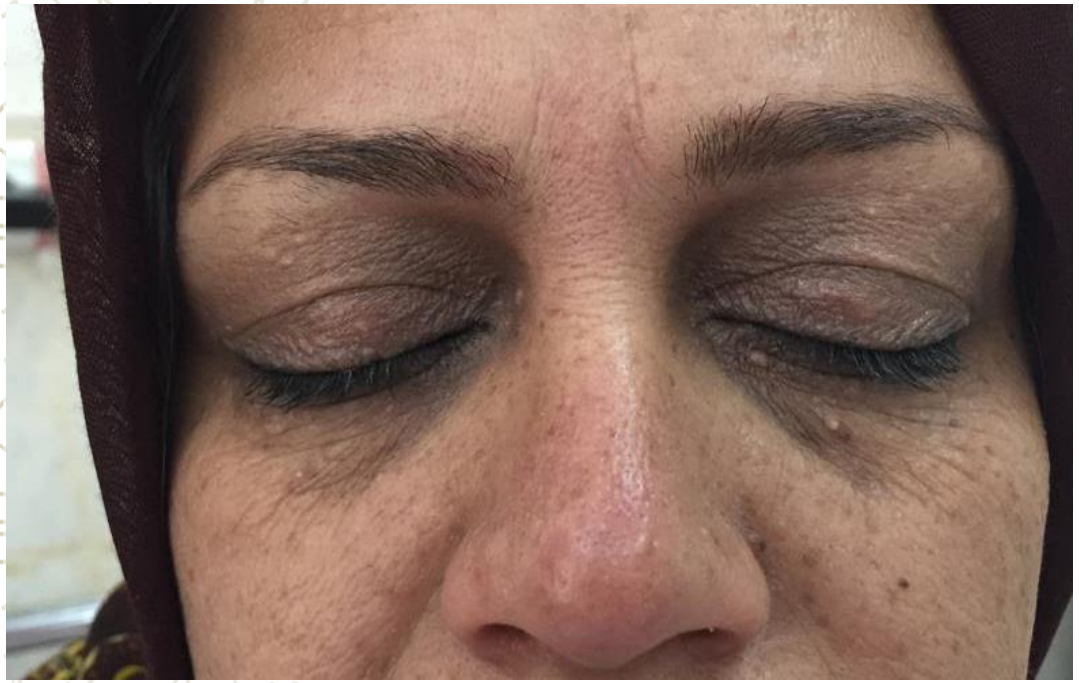




Insulin resistance related diseases in human

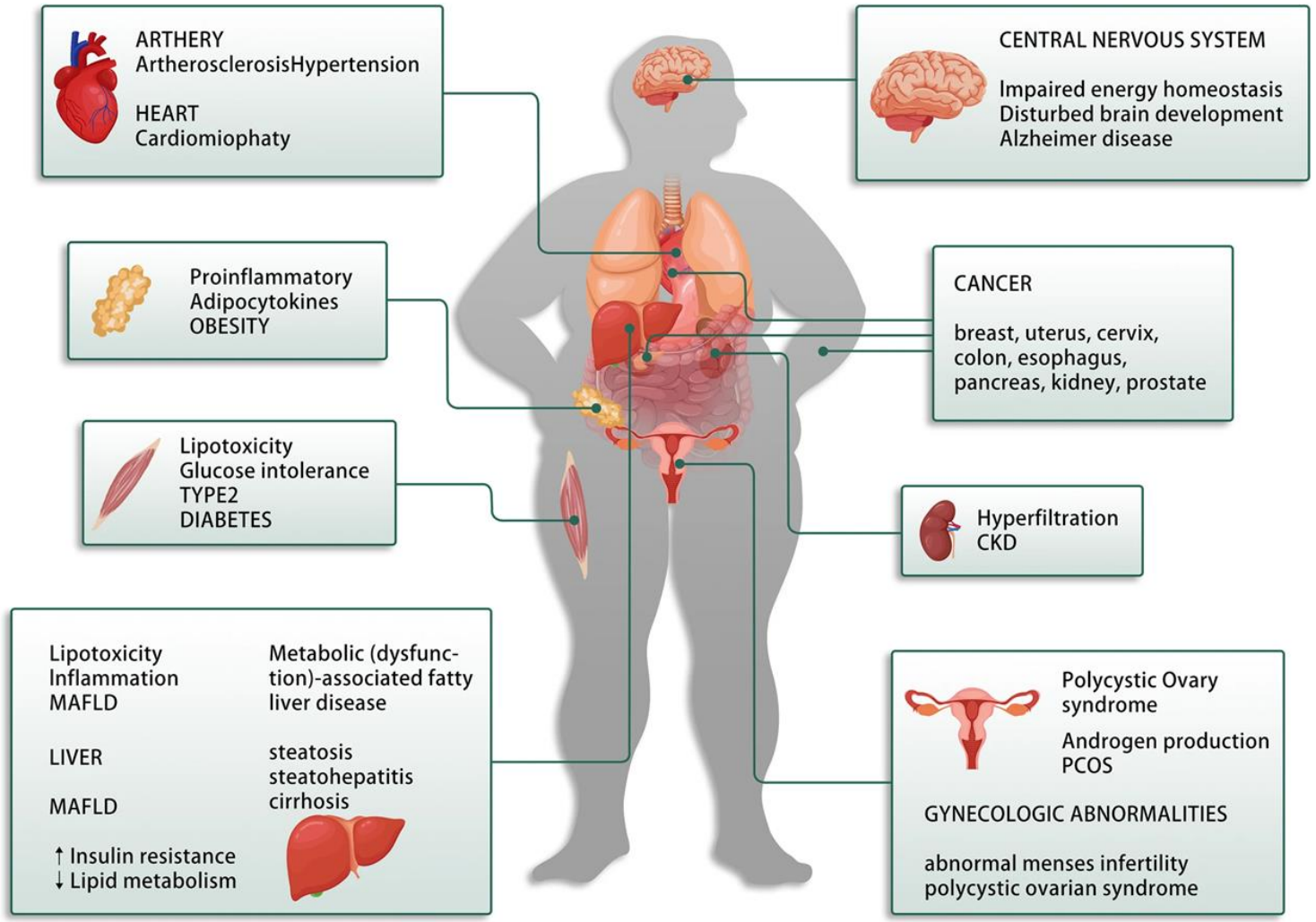
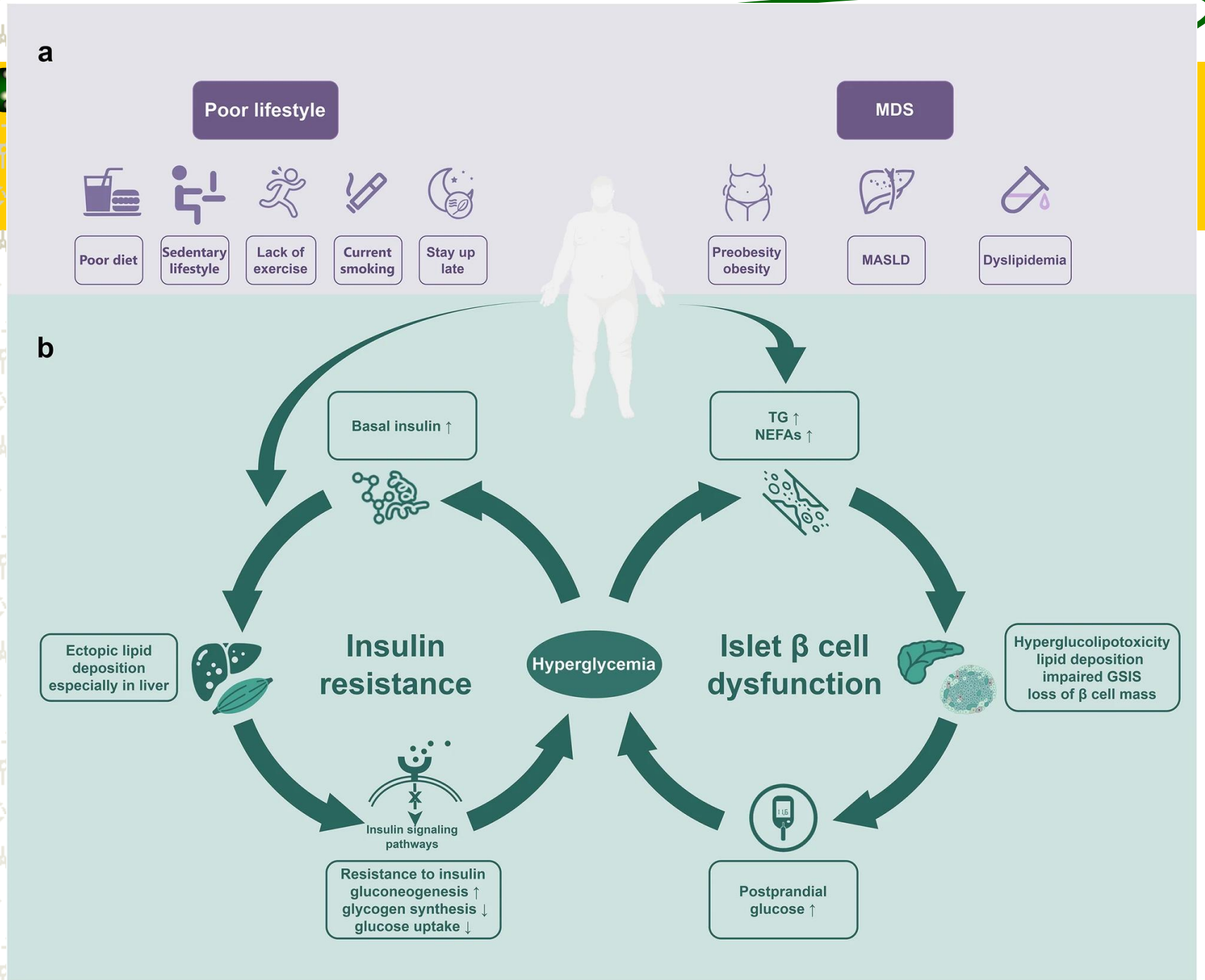


Table 2.6—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) and who have one or more additional risk factors:

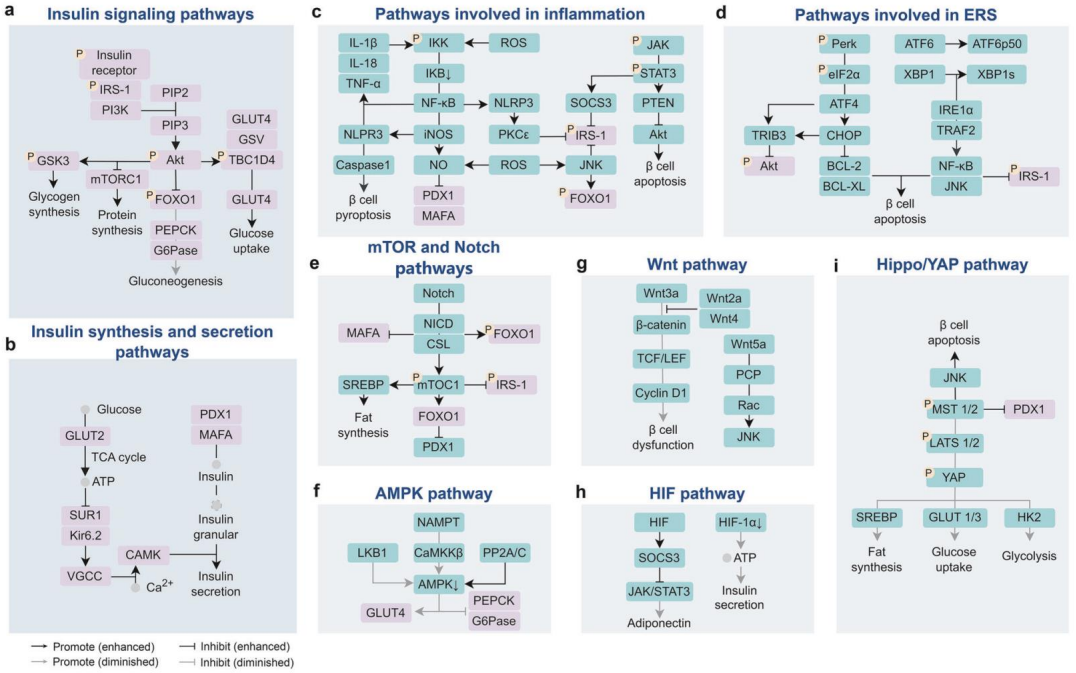
- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- High-risk race, ethnicity, and ancestry (see **Table 2.5**)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, large- or small-for-gestational-age birth weight)

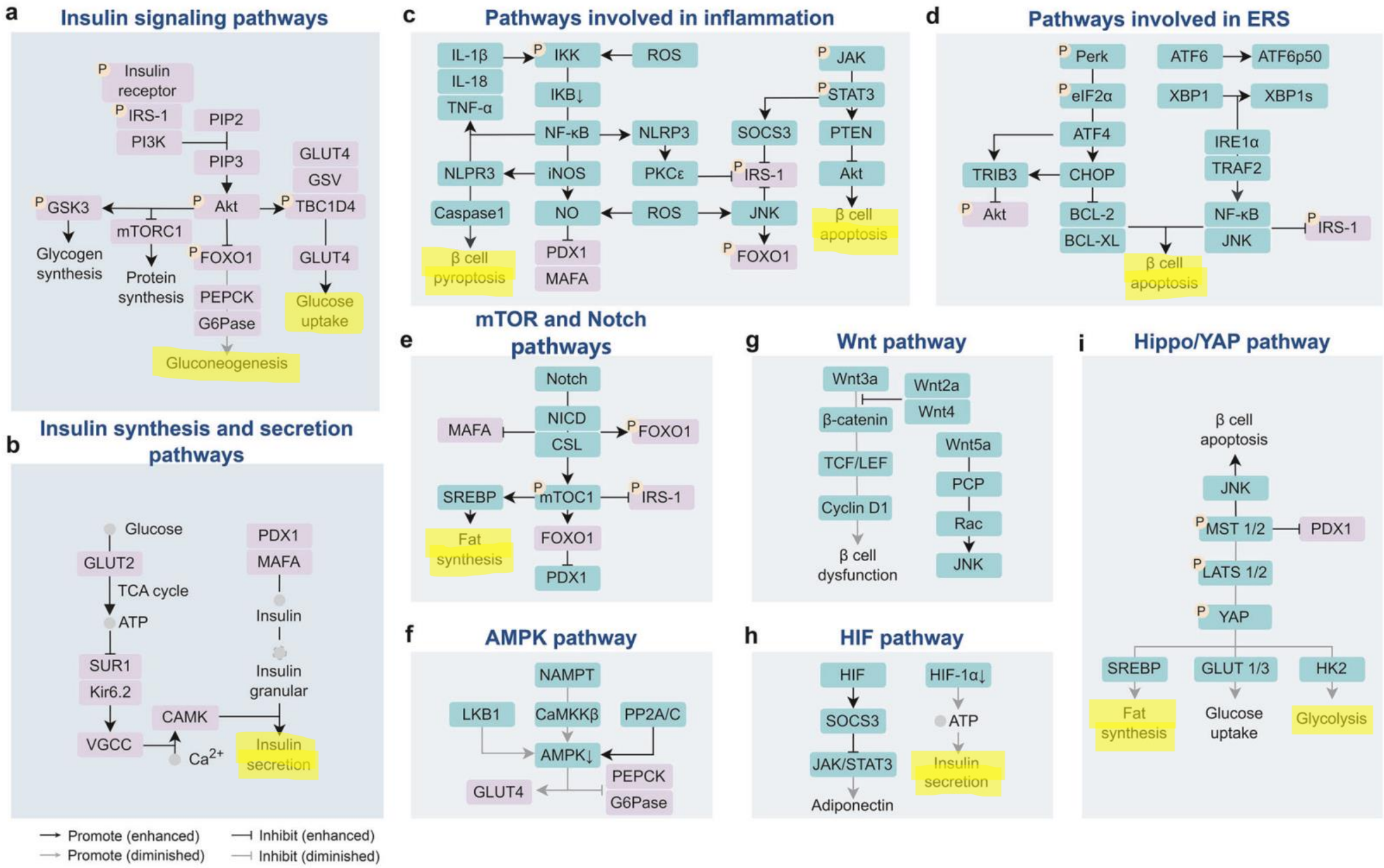
GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2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


a
Poor lifestyle
MDS
Poor diet
Sedentary lifestyle
Lack of exercise
Current smoking
Stay up late
Preobesity obesity
MASLD
Dyslipidemia
b
Basal insulin ↑
TG ↑
NEFAs ↑
Ectopic lipid deposition especially in liver
Insulin resistance
Hyperglycemia
Islet β cell dysfunction
Hyperglucolipotoxicity
lipid deposition
impaired GSIS
loss of β cell mass
Insulin signaling pathways
Resistance to insulin
gluconeogenesis ↑
glycogen synthesis ↓
glucose uptake ↓
Postprandial glucose ↑

Signaling pathways involved in T2D

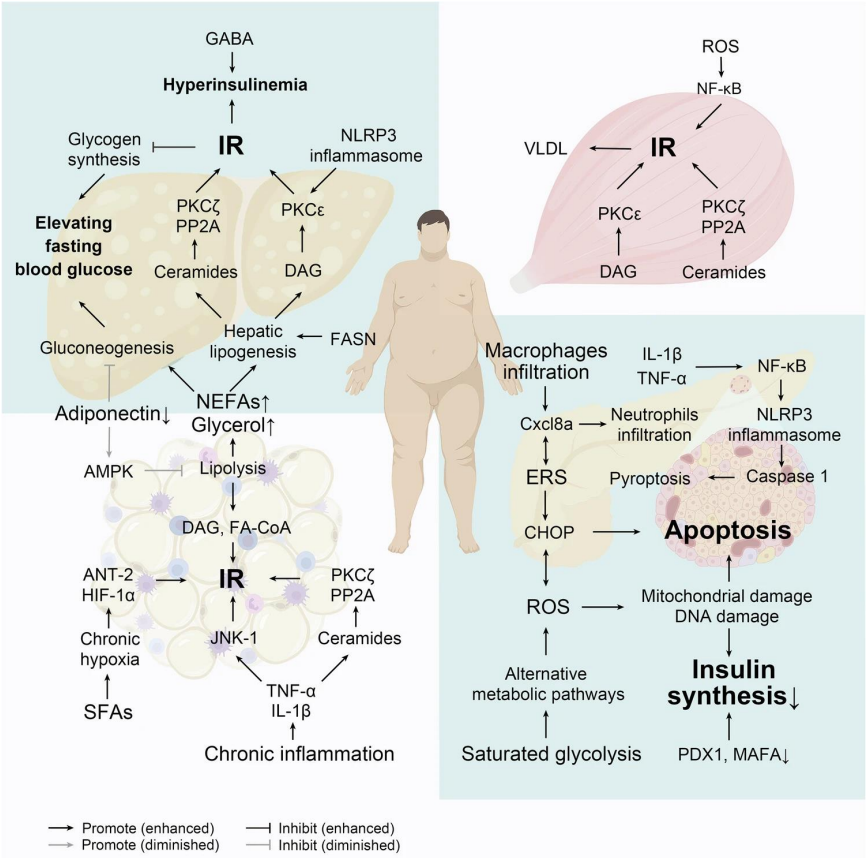
- In T2D, insulin signaling pathways (a) and insulin synthesis and secretion pathways (b) are affected by inflammatory pathways (c), ERS (d), and other pathways such as mTOR and notch pathways (e), AMPK pathway (f), Wnt pathway (g), HIF pathway (h), Hippo/YAP pathway (i)



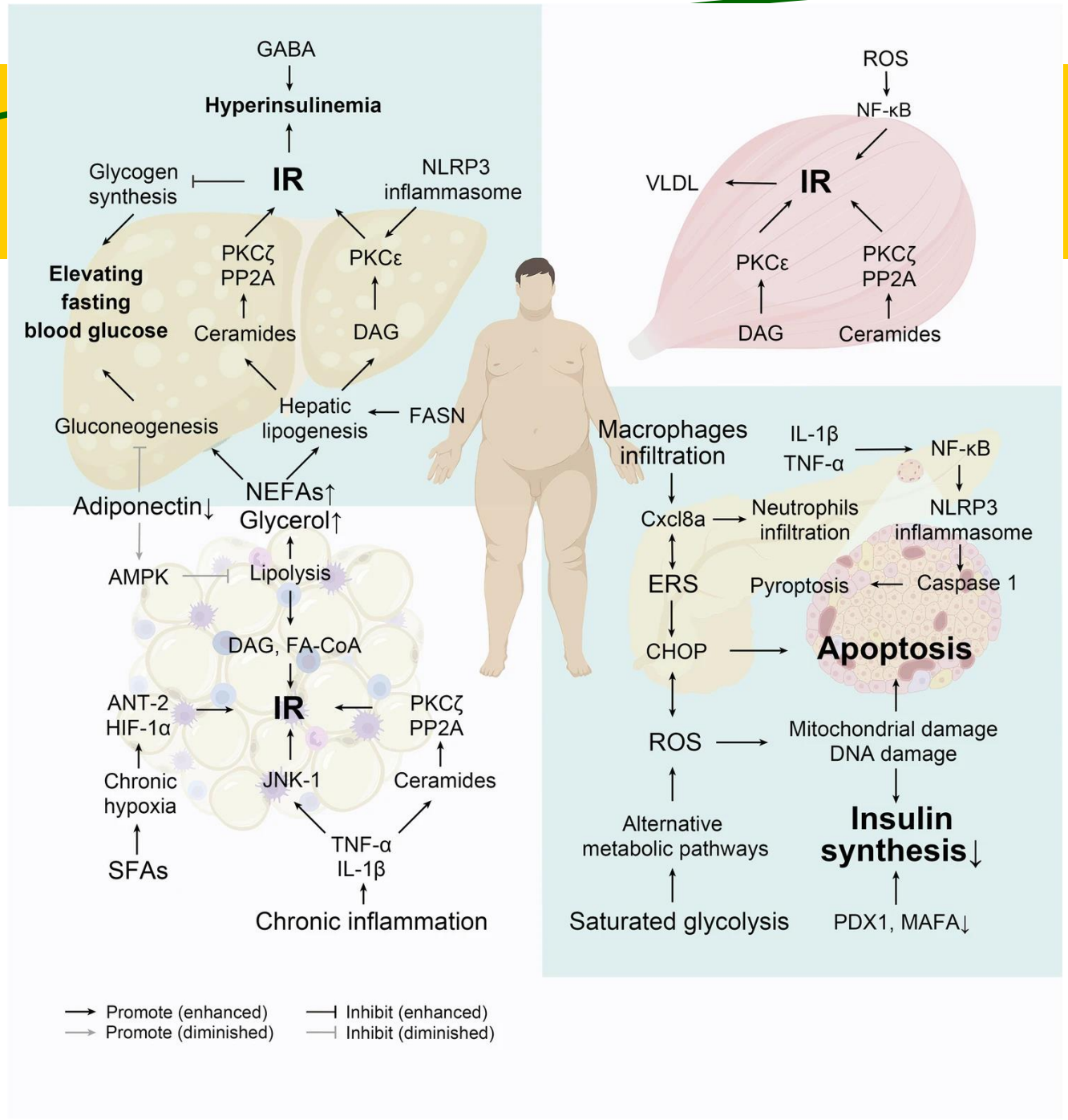

a
Insulin signaling pathways
P Insulin receptor
P IRS-1
PI3K
PIP2
PIP3
P Akt
P GSK3
mTORC1
P FOXO1
P TBC1D4
GLUT4
GSV
GLUT4
Glycogen synthesis
Protein synthesis
PEPCK
G6Pase
Glucose uptake
Gluconeogenesis
b
Insulin synthesis and secretion pathways
Glucose
GLUT2
TCA cycle
ATP
SUR1
Kir6.2
VGCC
Ca2+
CAMK
PDX1
MAFA
Insulin
Insulin granular
Insulin secretion
Promote (enhanced)
Promote (diminished)
Inhibit (enhanced)
Inhibit (diminished)
c
Pathways involved in inflammation
IL-1β
IL-18
TNF-α
P IKK
IKBα
NF-κB
NLRP3
iNOS
NO
PDX1
MAFA
ROS
NLPR3
Caspase1
β cell pyroptosis
PKCε
ROS
P JAK
P STAT3
SOCS3
PTEN
P IRS-1
Akt
JNK
P FOXO1
β cell apoptosis
d
Pathways involved in ERS
P Perk
P eIF2α
ATF4
CHOP
TRIB3
P Akt
BCL-2
BCL-XL
ATF6
ATF6p50
XBP1
XBP1s
IRE1α
TRAF2
NF-κB
JNK
P IRS-1
β cell apoptosis
e
mTOR and Notch pathways
Notch
NICD
CSL
MAFA
P FOXO1
SREBP
P mTOC1
P IRS-1
Fat synthesis
FOXO1
PDX1
g
Wnt pathway
Wnt3a
Wnt2a
Wnt4
β-catenin
TCF/LEF
Cyclin D1
β cell dysfunction
Wnt5a
PCP
Rac
JNK
i
Hippo/YAP pathway
β cell apoptosis
JNK
P MST 1/2
PDX1
P LATS 1/2
P YAP
SREBP
GLUT 1/3
HK2
Fat synthesis
Glucose uptake
Glycolysis
f
AMPK pathway
NAMPT
LKB1
CaMKKβ
PP2A/C
AMPK↓
PEPCK
G6Pase
GLUT4
h
HIF pathway
HIF
SOCS3
JAK/STAT3
Adiponectin
HIF-1α↓
ATP
Insulin secretion

A sketch of pathogenesis of T2D

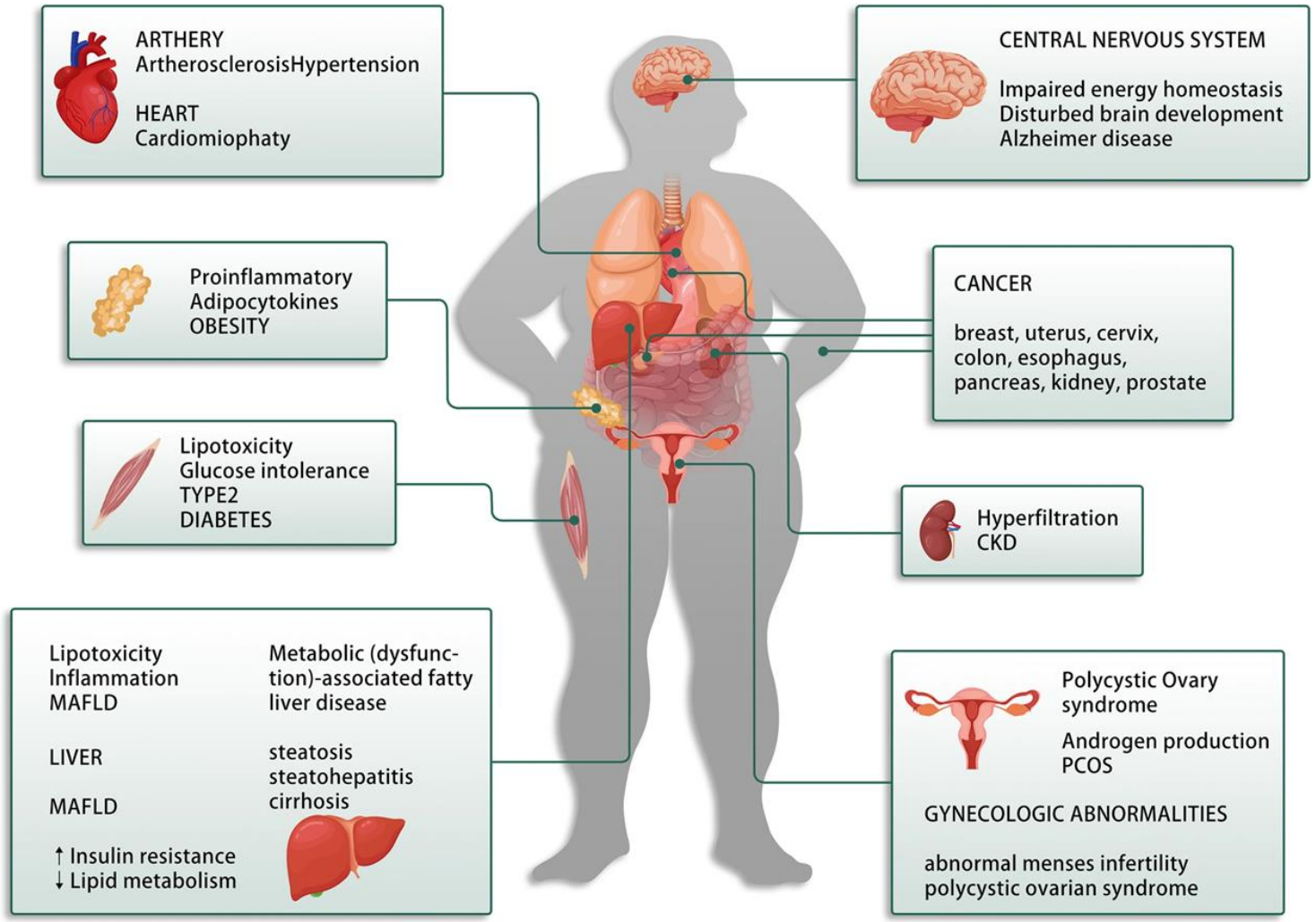
- Under the stimulation of SFAs, hypoxia in adipocytes due to enhanced SFAs metabolism, and the release of inflammatory factors from macrophage infiltration cause chronic inflammation in adipose tissues, leading to adipocyte IR and increased lipolysis.
- NEFAs and glycerol from lipolysis causes increased lipid synthesis, gluconeogenesis, and ectopic fat deposition in the liver, which affects IRS-1/PI3K/Akt2 phosphorylation on the one hand, and increases hepatic release of glucose on the other.
- At the same time, ectopic fat deposition also occurs in the muscle and leads to elevated circulating VLDL, further exacerbating lipid metabolism disorders and IR in the liver.
- Persistent hyperglycemia and excess fatty acids in the circulation due to overnutrition and IR further damage β-cell function and mass by some shared pathways, involving inflammation, ERS, and oxidative stress.



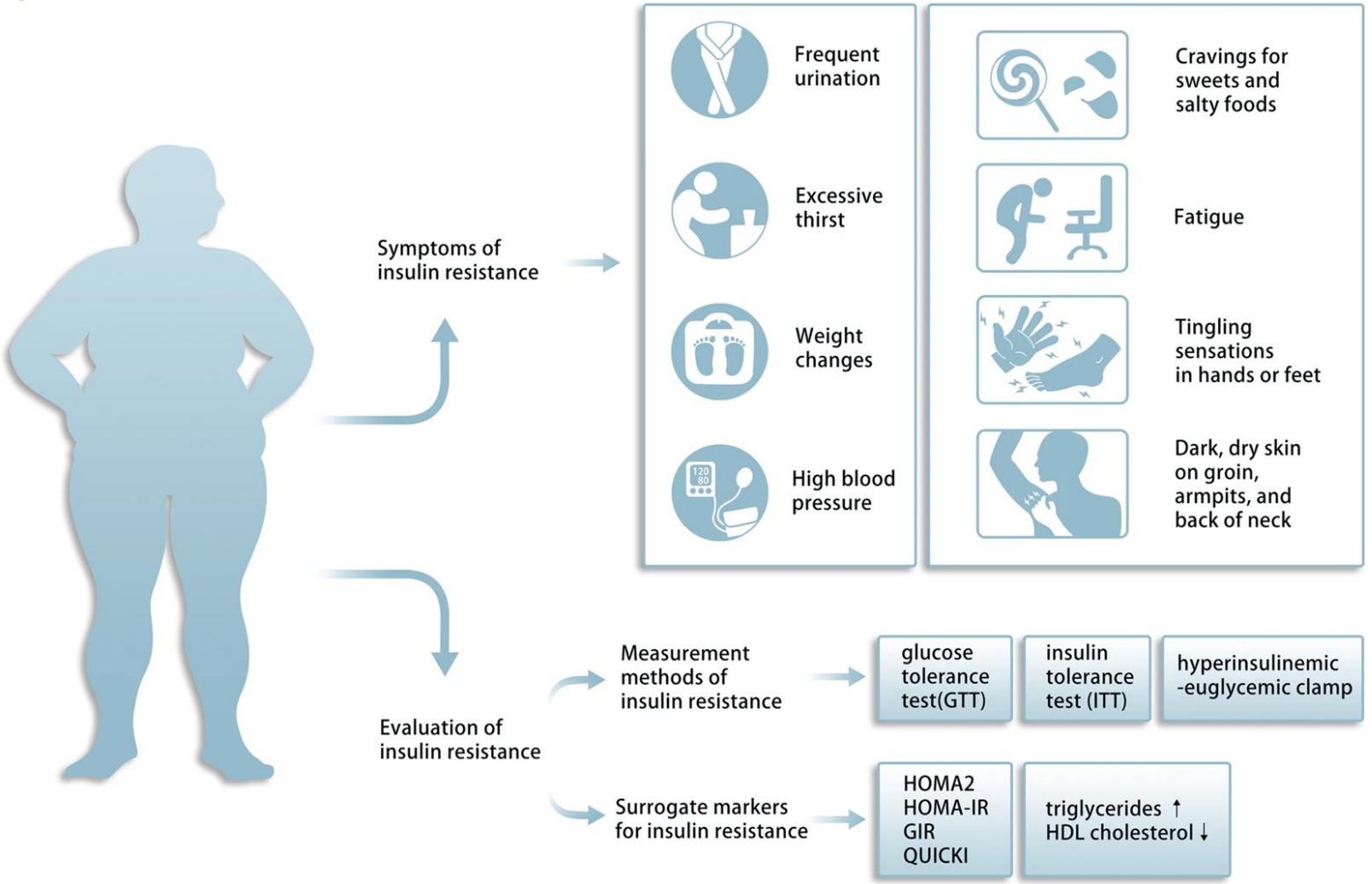
IR insulin resistance, SFAs saturated fatty acid, NEFAs non-esterified fatty acids, TNF-α tumor necrosis factor α, IL-1β interleukin-1β, JNK c-Jun N-terminal kinase, FASN fatty acid synthase, DAG diacylglycerol, FA-CoA Fatty acyl-coenzyme A, ANT-2 adenine nucleotide translocase 2, HIF-1α hypoxia-inducible factor 1 alpha, NLRP3 NOD-like receptor family pyrin domain-containing 3, GABA γ-aminobutyric acid, PP2A protein phosphatase 2A, PKC protein kinase C, AMPK adenosine 5'-monophosphate-activated protein kinase, VLDL very-low-density lipoprotein, ROS reactive oxygen species, NF-κB nuclear factor-kappa B, Cxcl8a neutrophil chemokine (C-X-C motif) ligand 8a, ERS endoplasmic reticulum stress, CHOP C/EBP homologous protein, PDX1 pancreatic and duodenal homeobox factor-1, MAFA MAF bZIP transcription factor A


GABA
Hyperinsulinemia
IR
Glycogen synthesis
NLRP3 inflammasome
Elevating fasting blood glucose
PKCζ PP2A
PKCε
Ceramides
DAG
Gluconeogenesis
Hepatic lipogenesis
FASN
Adiponectin↓
NEFAs↑ Glycerol↑
AMPK
Lipolysis
DAG, FA-CoA
ANT-2 HIF-1α
IR
PKCζ PP2A
Chronic hypoxia
JNK-1
Ceramides
SFAs
TNF-α IL-1β
Chronic inflammation
ROS
NF-κB
VLDL
IR
PKCε
PKCζ PP2A
DAG
Ceramides
Macrophages infiltration
IL-1β TNF-α
NF-κB
Cxcl8a
Neutrophils infiltration
NLRP3 inflammasome
ERS
Pyroptosis
Caspase 1
CHOP
Apoptosis
ROS
Mitochondrial damage DNA damage
Alternative metabolic pathways
Insulin synthesis↓
Saturated glycolysis
PDX1, MAFA↓
Promote (enhanced)
Promote (diminished)
Inhibit (enhanced)
Inhibit (diminished)

Insulin resistance related diseases in human



Ex vivo diagnosis methods for insulin resistance



Diagnosis and Test

$$\text{HOMA index} = \text{insulin (mU/L)} \times [\text{glucose (mmol/L)}/22.5]$$

$$\text{QUICKI} = \frac{1}{\log \text{insulin (mU/L)} + \log \text{glucose (mg/dL)}}$$

$$\text{McAuley index} = e^{[2.63 - 0.28 \ln (\text{insulin (mU/L)}) - 0.31 \ln (\text{triglycerides (mmol/L)})]}$$

$$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/dL}) \times \text{fasting glucose (mg/dL)}/22.5$$

$$\text{TyG index} = \text{Ln}[\text{TG(mg/dL)} \times \text{FPG(mg/dL)}/2]$$

$$\text{TyG-BMI} = \text{TyG index} \times \text{BMI}$$

$$\text{TyG-WC} = \text{TyG index} \times \text{WC}$$

$$\text{Visceral adiposity index} = [\text{WC}/39.68 + (1.88 \times \text{BMI})] \times (\text{TG}/1.03) \times (1.31/\text{HDL}) \quad \text{for men}$$

Management and Treatment

- **Eating a healthy diet**: Avoiding eating excessive amounts of carbohydrates and eating less unhealthy fat, sugar, red meats and processed starches. Eating a diet of more vegetables, fruits, whole grains, fish and lean poultry

- **Physical activity**: A single session of moderate-intensity exercise can increase glucose uptake by at least 40%

- **Losing excess weight**: One study revealed that losing 7% of your excess weight can reduce the onset of Type 2 diabetes by 58%

Therapeutic strategy of insulin resistance

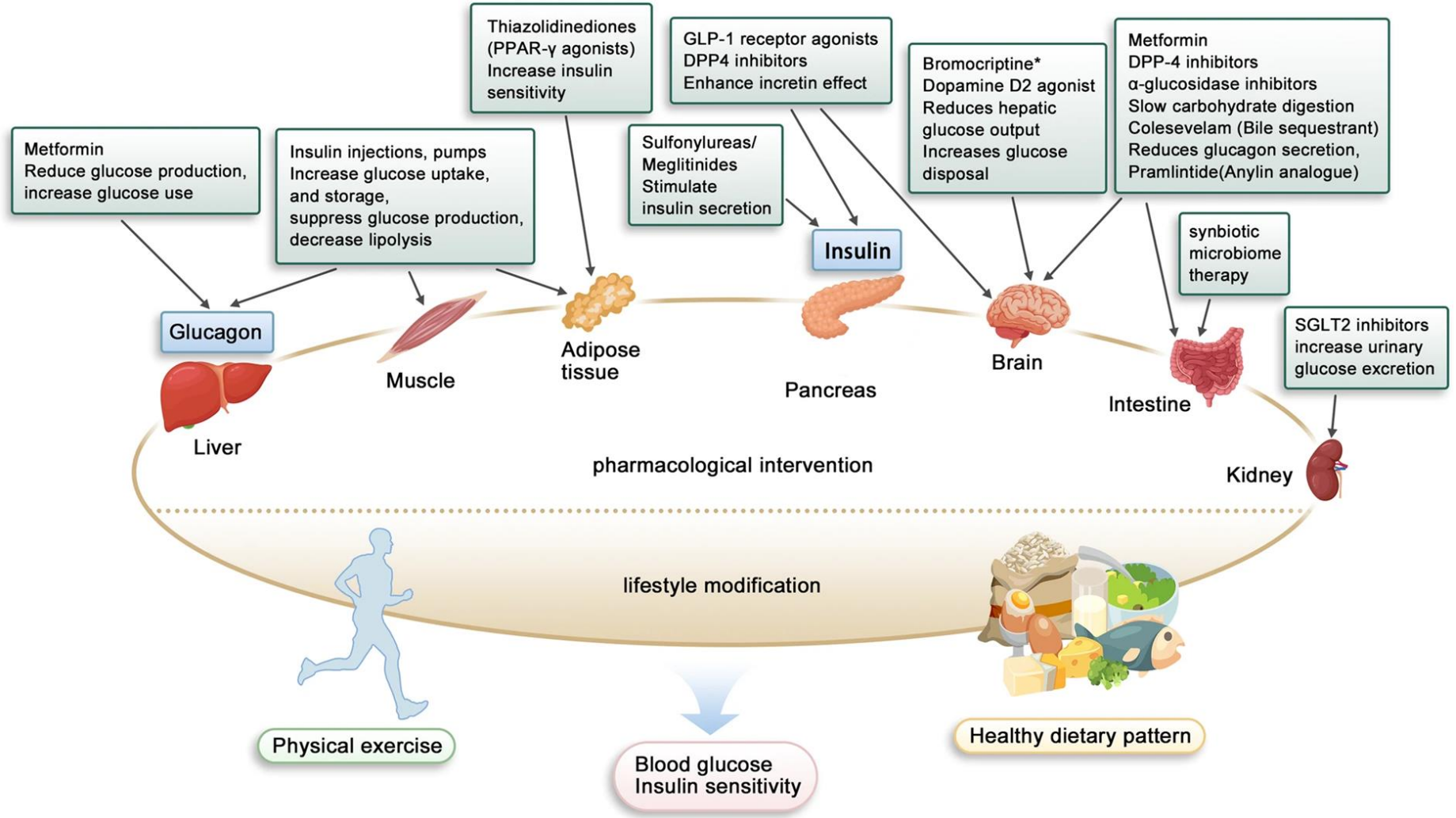


Table 1. Clinical medication for improving insulin resistance

Type	Listed drugs	Mechanism
Biguanides	Metformin	The exact mechanism of metformin is still unclear and may be related to increased insulin receptor tyrosine kinase activity, enhanced glycogen synthesis, and recruitment of the GLUT4 glucose transporter.
Thiazolidinediones	Pioglitazone Rosiglitazone	It mainly activates peroxisome proliferator-activated receptor γ (PPAR-γ) to enhance the sensitivity of adipose muscle and liver to insulin.
GLP-1 receptor agonists	Liraglutide Exenatide Semaglutide Dulaglutide	GLP1 receptor agonists (GLP-1RAs) can affect IR by increasing the expression of glucose transporters in insulin-dependent tissues, reducing inflammation and oxidative stress, and regulating lipid metabolism.
DPP-4 inhibitors	Saxagliptin Vildagliptin Alogliptin Linagliptin Gemigliptin Teneligliptin Trelagliptin	It can decrease the degradation of GLP-1 by inhibiting the activity of DPP4, thereby exerting a role in the treatment of type 2 diabetes.
Sulfonylureas	Glimepiride	It promotes insulin receptor activation, thereby increasing the amount of glucose transporters, which in turn increases insulin sensitivity and improves insulin resistance.
PPAR full agonists	Chiglitazar Sodium	Chiglitazar Sodium is a peroxisome proliferator-activated receptor (PPAR) full agonist that simultaneously activates three subtypes of PPAR receptors (α, γ, and δ). It can induce the expression of downstream target genes related to insulin sensitivity, fatty acid oxidation, energy conversion and lipid transport, and inhibit the phosphorylation of PPARγ receptors associated with insulin resistance.

Selected preclinical studies for insulin resistance

Table 3. Selected preclinical studies for insulin resistance

Intervention	Model	Method	Results	Reference
Propranolol and L-D-ISOPROT	Swiss albino mice of high fructose and high fat diet (HFrHFD) model	The mice were injected with propranolol (30 mg/kg/d, i.p.) and low-dose isoproterenol (5 mg/kg/day, i.p.) for 4 weeks after the 13th week of HFrHFD feeding.	Propranolol and l-d- Isopropionic acid can reduce IR of HFrHFD mice by up-regulating β -inhibin 2 signaling activity.	[505]
Sarsasapogenin (ZGY)	High-fat diet (HFD) C57BL/6 J mice; LPS-induced acute adipose tissue inflammation model	ZGY treatment (80 mg/kg/d, ig, lasting for 18 days) can significantly inhibit the acute adipose tissue inflammation of LPS-treated mice. In obese mice fed with high-fat diet, taking ZGY orally (80 mg-kg/d for 6 weeks) can reduce the infiltration of macrophages, improve IRand reduce the inflammation of adipose tissue.	ZGY can improve IR and reduce fat inflammation in HFD mice, which may be related to the inhibition of IKK/NF-κB and JNK inflammatory signaling pathway.	[506]
PPARα/γ dual Agonist: Propane-2-sulfonic acid octadec-9-enyl-amide (N15)	High fat diet and streptozotocin (STZ)-induced diabetic mice	The mice were received single daily oral treatment with N15 (50 or 100 mg/kg, respectively) for 6 weeks.	The anti-IR effect of N15 may be depended on PPARγ pathway.	[507]
Valdecoxib (VAL)	HFD-fed mice	HFD - fed mice were orally administered VAL (5 mg/kg, once every 2 days) for 8 weeks.	VAL can inhibit inflammation and endoplasmic reticulum stress through AMPK-regulated HSPB1 pathway, thus improving skeletal muscle IR under hyperlipidemia.	[501]
D-chiro-Inositol (DCI)	HFD-fed mice	HFD-fed mice were intragastrically administered with 50 mg of DCI/(kg of body weight (bw))/day for 8 weeks.	DCI decreased the hepatic glucose output and the expression levels of PEPCK and G6Pase through PKCε-IRS/PI3K/AKT signaling pathway in insulin-resistant mice.	[508]
Sitagliptin	HFD-fed SD rat	Rats were given Sitagliptin(100 mg/kg/d) by gavage for 8 consecutive days.	Sitagliptin can significantly inhibit lipid accumulation in blood and liver of rats and improve insulin resistance.	[509]
Muscular resistance, hypertrophy and strength training	HFD-fed Swiss mice	Weight-bearing stair climbing training;Muscle resistance exercise; hypertrophy training and strength training.	Muscle resistance training program can reduce weight, obesity index, adipocyte area and low-grade chronic inflammation, and improve insulin resistance.	[510]
Sodium-glucose cotransporter (SGLT) 2 inhibitor: empagliflflozin	HFD induced obese mice.	HFD with 0.003% empagliflflozin (3 mg/kg bodyweight). And HFD with 0.01% empagliflflozin (10 mg/kg bodyweight).	SGLT2 inhibitor empagliflozin enhances fat utilization and browning by M2 or replacing macrophages activation, and reduces obesity-induced inflammation and insulin resistance.	[511]
Heat shock protein (HSP) 70	HFD-fed C57BL/6 mice	Mice were administered intranasally under isoflurane anesthesia, 10 μl (10 and 40 μg) of the appropriate solution was injected into one nostril, and the mice were supine for 1–2 min, three times a week for 26 days.	4 μg HSP70 significantly improved insulin sensitivity, and 10 μg HSP70 showed a trend of improvement.	[512]
Insulin and exenatide	Male Tg2576 mice	Daily treatment of 0.43 $\times 10^{-3}$ IU NovoRapid insulin + 0.075 μg exenatide + 5 μg BSA per mouse was used. The treatment was given 6 days a week for 8 months	Compared with the control mice, the expression of insulin receptor cascade related genes in AD-like mice treated with insulin and exenatide was normalized.	[513]
GLP-1 receptor agonists: exendin-4	Senescence-accelerated mouse (SAMP8)	A proper amount of exendin-4 and L-form of peneracin were respectively dissolved in PBS solution containing 0.001% methylcellulose (MC), and an equal amount of peptide drug and osmin solution were gently mixed. The mice were injected with sodium pentobarbital intraperitoneally and then with exendin-4 and L-penetratin intranasally.	After intranasal administration with L-form of peneracin, the distribution of exendin-4 in the whole brain increased significantly. Through intranasal injection of L-form of peneracin, the delivery of exendin-4 and insulin to the brain may contribute to insulin signal transduction in hippocampus.	[502]
Lactobacilllus reuteri strain	HFD-fed mice	The mice were gavaged daily with 10^9 CFU of L. reuteri CNCM I-5022 for 12 weeks.	Lactobacillus reuteri improved HOMA-IR and glucose clearance and exhibited better insulin sensitivity in HFD-fed mice.	[503]
Sterilized bififidobacteria	HFD-fed mice	Mice were orally administered with bifidobacteria (200 mg·kg^{-1}, 400 mg·kg^{-1}) daily for 4 weeks.	Oral glucose tolerance and IR test showed that Bifidobacterium sterilization could improve glucose tolerance and reduce insulin resistance.	[514]
Exercise training combined with Bififidobacterium longum OLP-01	Male C57BL/6 J db/db mice	The mice administered orally at a dosage of 1.03 g per kg per day (1.03 × 10^{10} CFU per kg per day) using a stomach tube. The mice were supplemented with strength training.	Exercise and OLP-01 treatment show that they can reduce blood sugar, increase insulin sensitivity, reduce body fat, improve physical activity and protect liver injury, but have no adverse effects.	[504]

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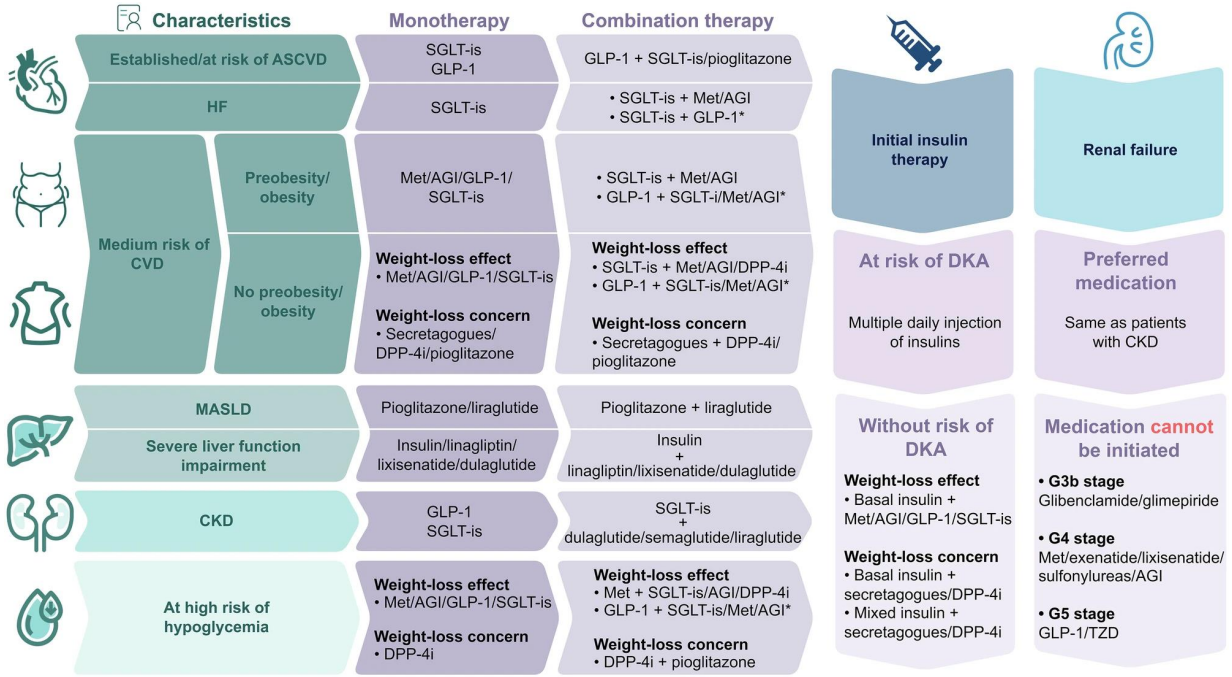
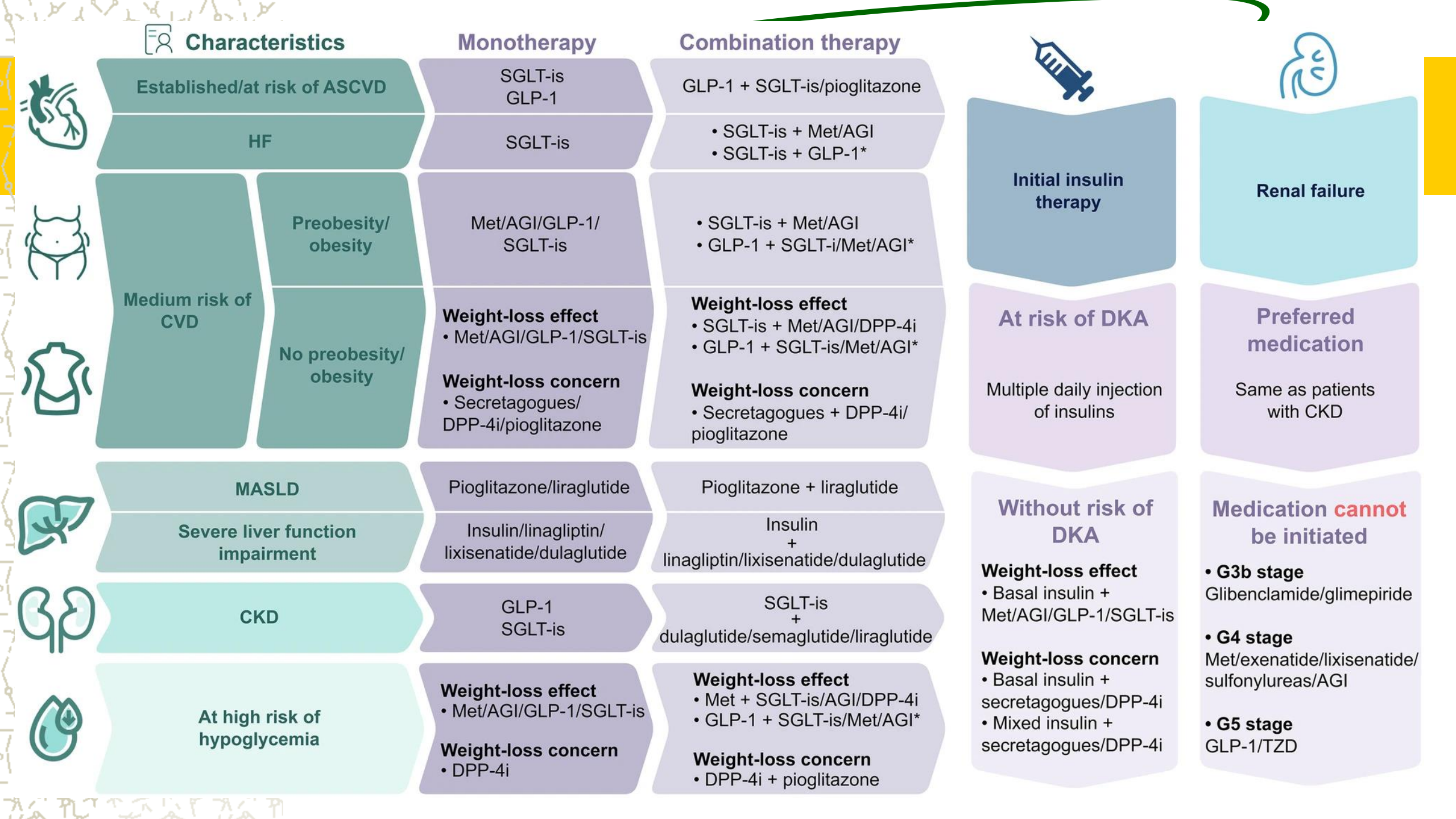
Vicious cycle of hyperglycemia

- Poor lifestyle and/or metabolic dysfunction syndrome leads to elevated triglycerides, non-esterified fatty acids (a). Excessive lipids is deposited in non-adipose tissue, blocking the insulin signaling pathways, then resulting in insulin resistance, especially in the liver which increase the liver's glucose production and weakens uptake of glucose, thereby increasing blood glucose and basal insulin levels, and the elevated insulin promotes lipid deposition, further aggravating insulin resistance and forming a vicious circle; elevated glucose and lipids produce hyperglucolipotoxicity to islet β cells and lipid deposition in islets, damaging the secretion function and number of pancreatic β cells, and further increasing blood glucose (b).

Personalized choice of hypoglycemic agents for patients with newly diagnosed T2D.

- This figure is modified according to Zhang et al.211 T2D type 2 diabetes, MASLD metabolic associated steatotic liver disease, ASCVD atherosclerotic coronary heart disease, HF heart failure, CKD chronic kidney disease, CVD cardiovascular disease, DKA diabetic ketoacidosis, Met metformin, AGI α-glucosidase inhibitors, GLP-1 glucagon-like peptide-1, SGLT-is sodium-glucose cotransporter inhibitors, DPP-4i dipeptidyl peptidase-4 inhibitors, TZD thiazolidinediones. *These regimens are considered in patients with affordability and willingness for injection therapy




Characteristics
Monotherapy
Combination therapy
Established/at risk of ASCVD
SGLT-is
GLP-1
GLP-1 + SGLT-is/pioglitazone
HF
SGLT-is
• SGLT-is + Met/AGI
• SGLT-is + GLP-1*
Medium risk of CVD
Preobesity/ obesity
Met/AGI/GLP-1/ SGLT-is
• SGLT-is + Met/AGI
• GLP-1 + SGLT-i/Met/AGI*
No preobesity/ obesity
Weight-loss effect
• Met/AGI/GLP-1/SGLT-is
Weight-loss concern
• Secretagogues/ DPP-4i/pioglitazone
Weight-loss effect
• SGLT-is + Met/AGI/DPP-4i
• GLP-1 + SGLT-is/Met/AGI*
Weight-loss concern
• Secretagogues + DPP-4i/ pioglitazone
MASLD
Pioglitazone/liraglutide
Pioglitazone + liraglutide
Severe liver function impairment
Insulin/linagliptin/ lixisenatide/dulaglutide
Insulin + linagliptin/lixisenatide/dulaglutide
CKD
GLP-1
SGLT-is
SGLT-is + dulaglutide/semaglutide/liraglutide
At high risk of hypoglycemia
Weight-loss effect
• Met/AGI/GLP-1/SGLT-is
Weight-loss concern
• DPP-4i
Weight-loss effect
• Met + SGLT-is/AGI/DPP-4i
• GLP-1 + SGLT-is/Met/AGI*
Weight-loss concern
• DPP-4i + pioglitazone
Initial insulin therapy
At risk of DKA
Multiple daily injection of insulins
Without risk of DKA
Weight-loss effect
• Basal insulin + Met/AGI/GLP-1/SGLT-is
Weight-loss concern
• Basal insulin + secretagogues/DPP-4i
• Mixed insulin + secretagogues/DPP-4i
Renal failure
Preferred medication
Same as patients with CKD
Medication cannot be initiated
• G3b stage
Glibenclamide/glimepiride
• G4 stage
Met/exenatide/lixisenatide/ sulfonylureas/AGI
• G5 stage
GLP-1/TZD

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

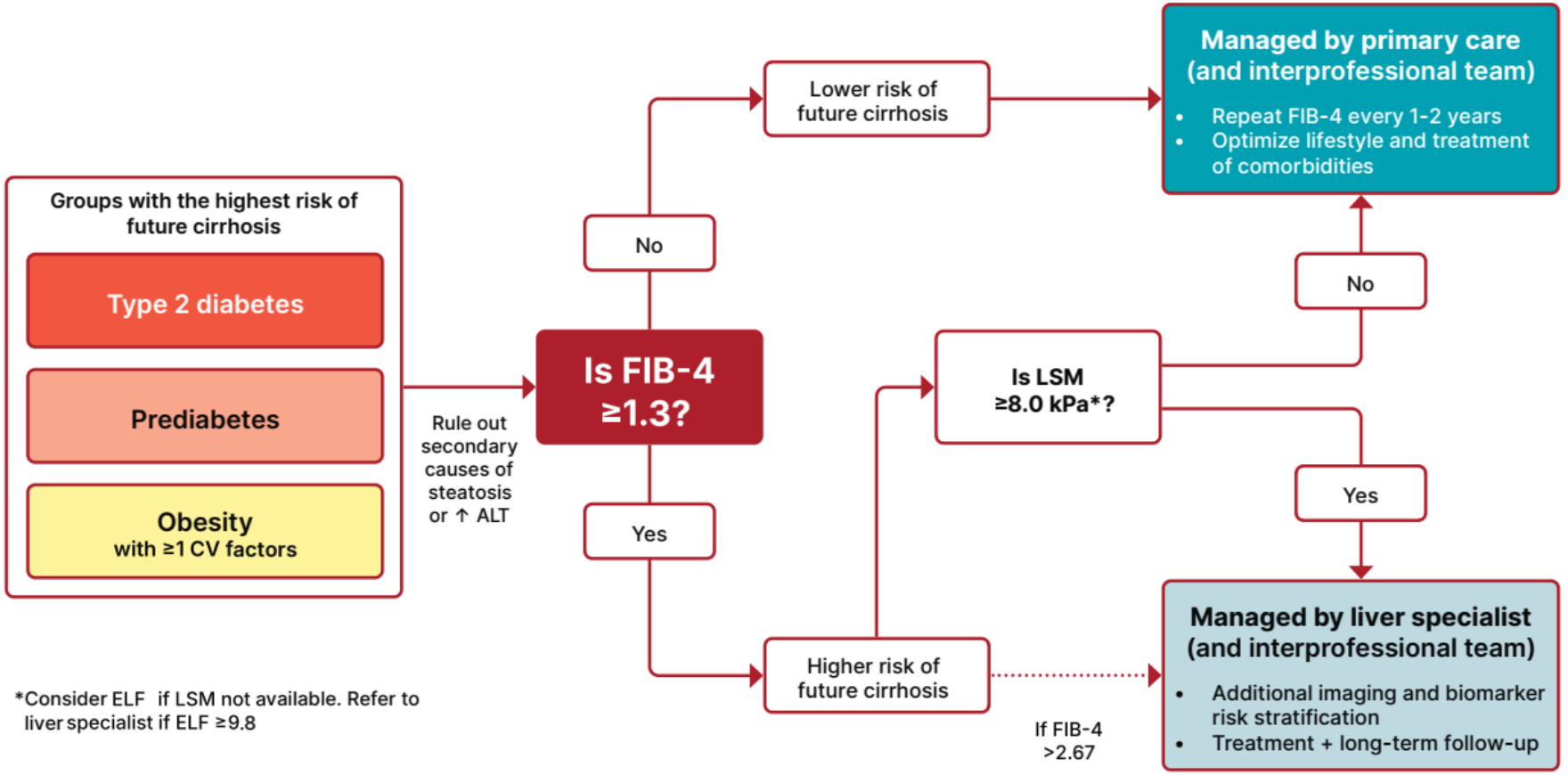
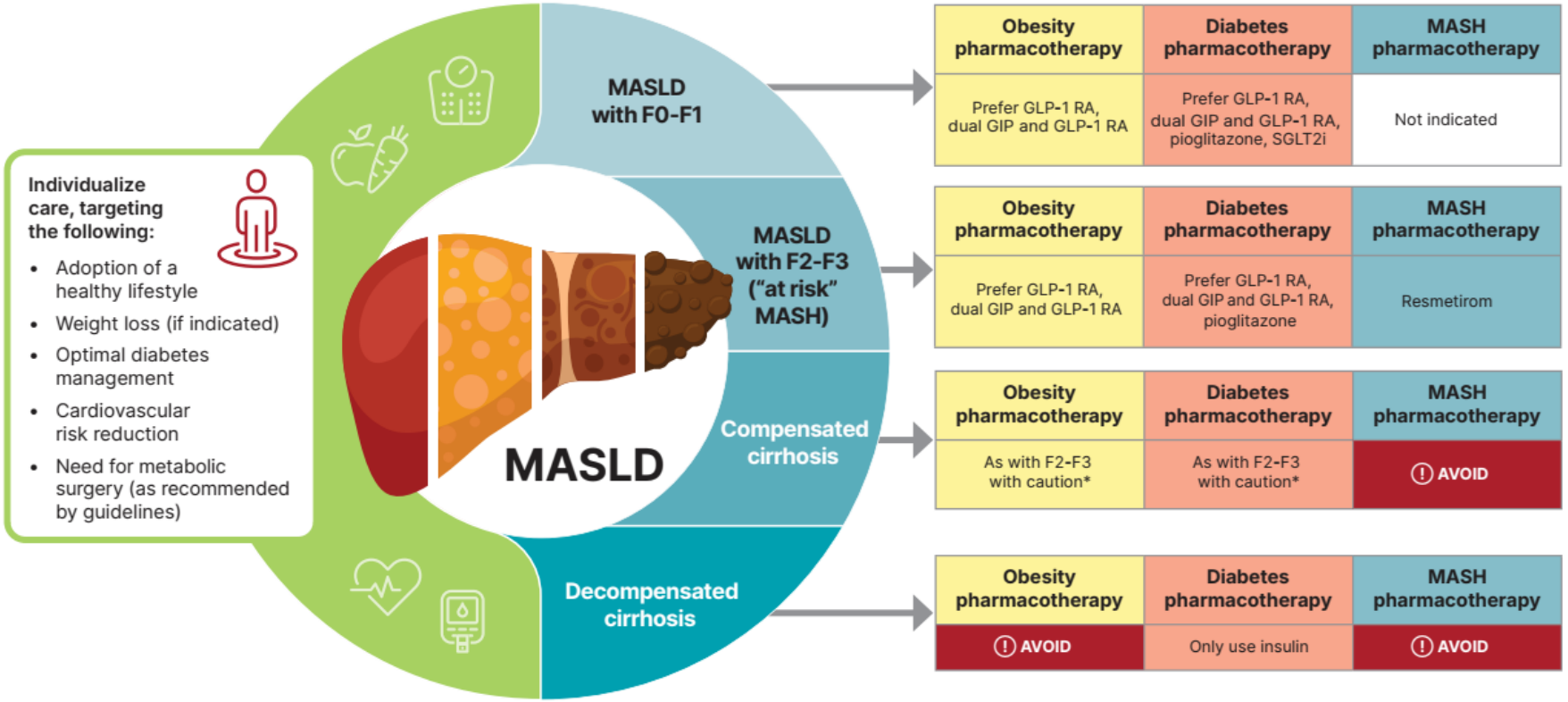


Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

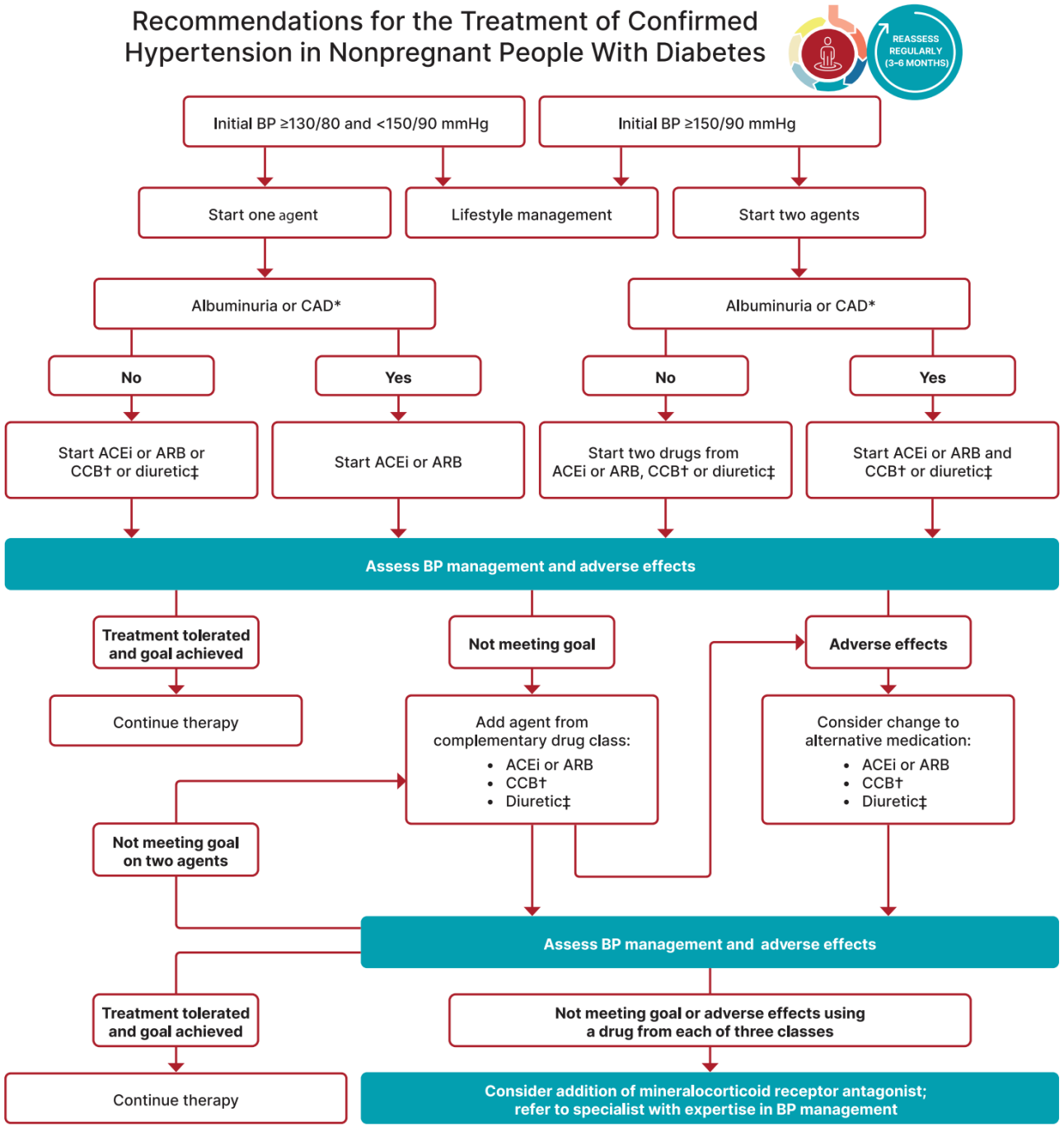
Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) Treatment Algorithm



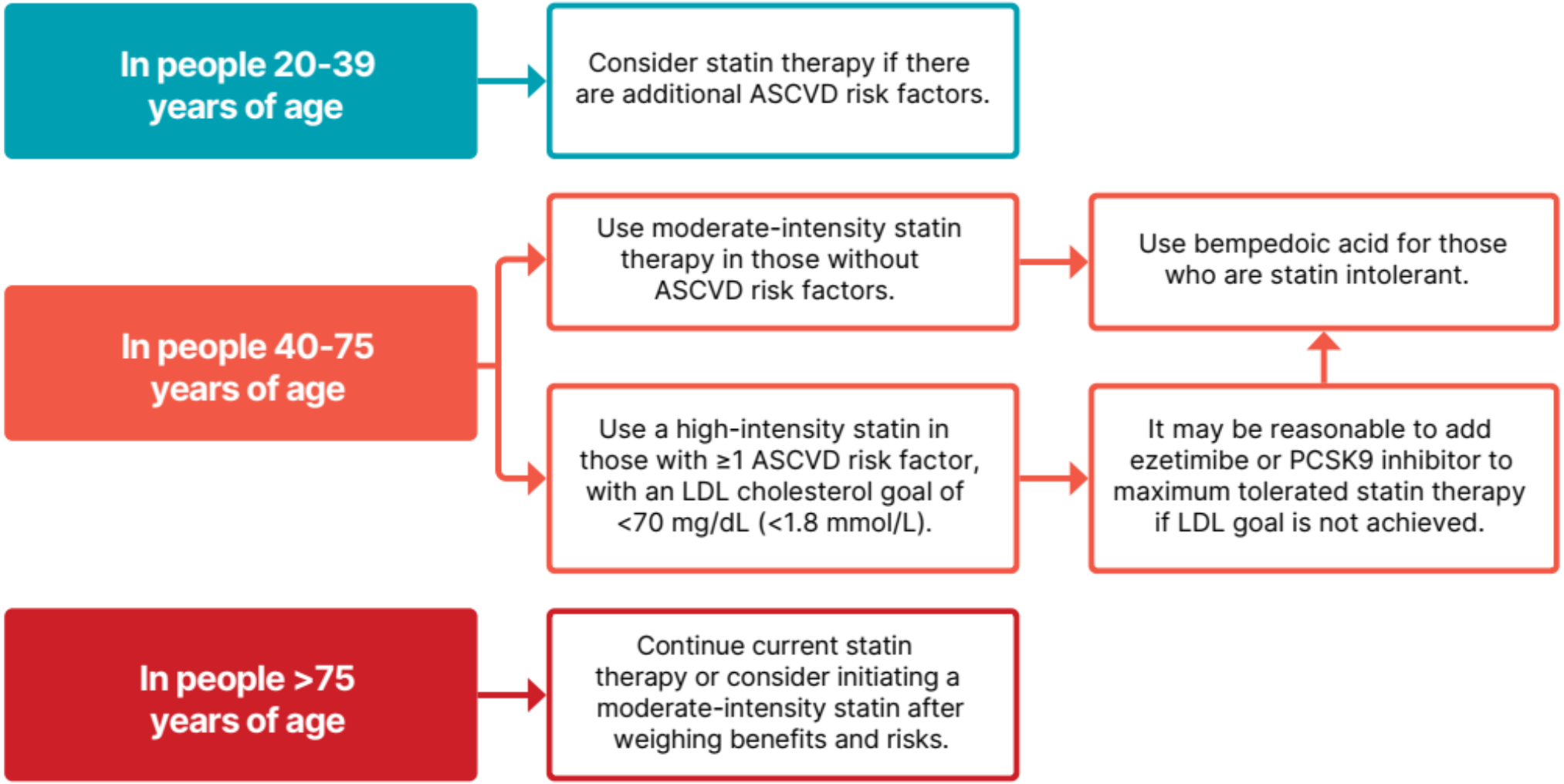
*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

- Recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes.
- *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested for the treatment of hypertension in people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and is strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine.
- †Dihydropyridine calcium channel blocker (CCB).
- ‡Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.



Lipid Management for Primary Prevention of Atherosclerotic Cardiovascular Disease Events in People With Diabetes in Addition to Healthy Behavior Modification



Recommendations for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with diabetes using cholesterol-lowering therapy.

Lipid Management for Secondary Prevention of Atherosclerotic Cardiovascular Disease Events in People With Diabetes

Use lifestyle and high-intensity statin therapy to reduce LDL cholesterol by ≥50% from baseline to a goal of <55 mg/dL (<1.4 mmol/L).

→

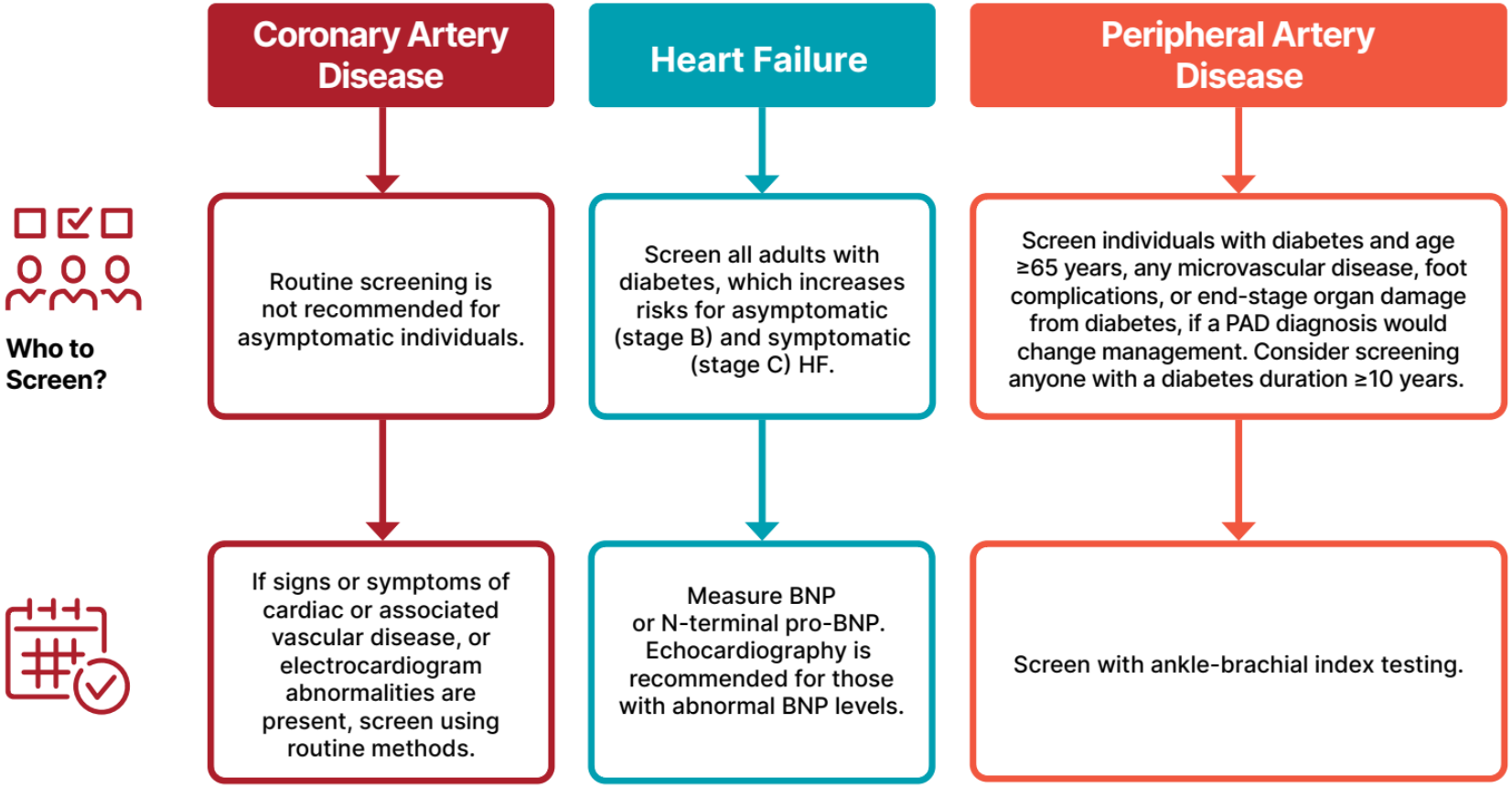
Add ezetimibe or a PCSK9-directed therapy with demonstrated benefit if LDL cholesterol goals are not met on maximum tolerated statin therapy.

→

Use an alternative lipid-lowering treatment for those who are statin intolerant:

- PCSK9 inhibitor with monoclonal antibody treatment
- Bempedoic acid
- PCSK9 inhibitor with siRNA inclisiran

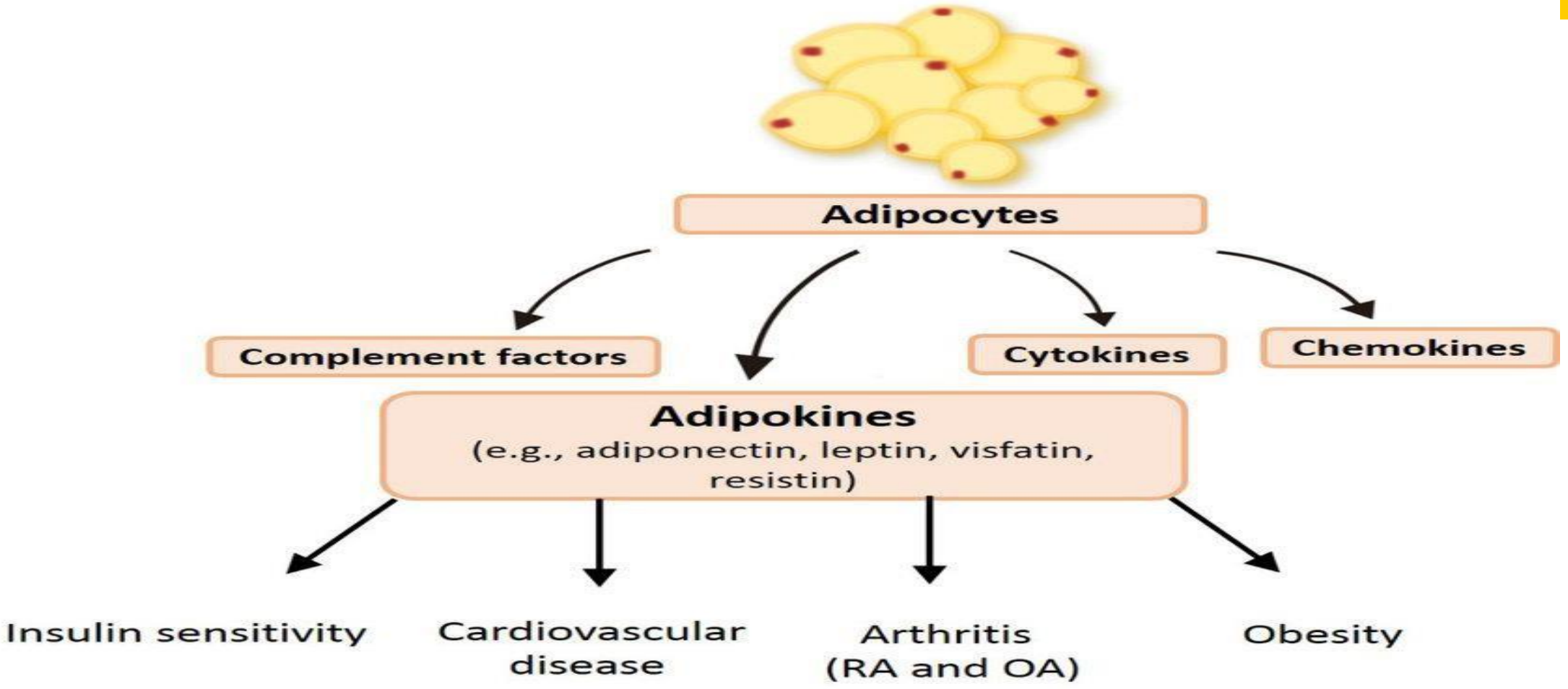
Recommendations for screening of asymptomatic and undiagnosed cardiovascular disease.



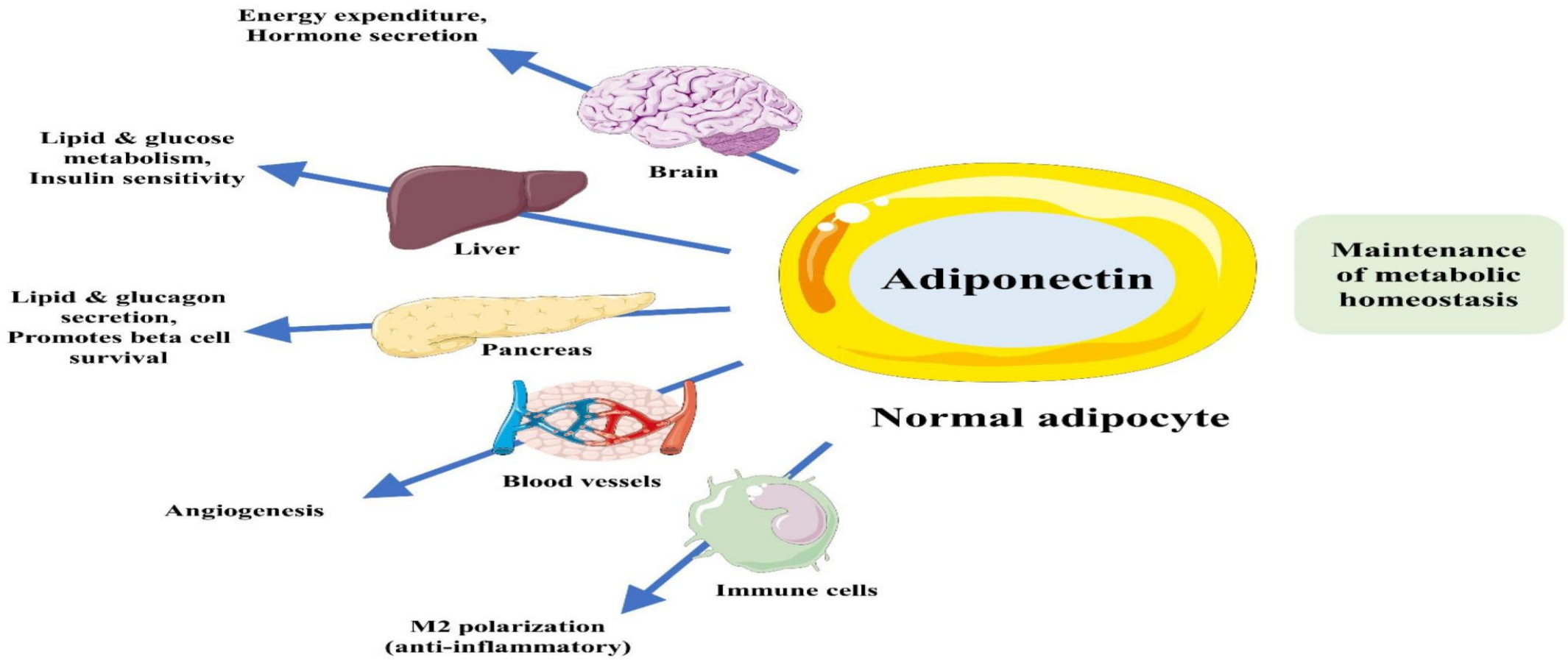
Overview of Adiponectin

- **What is Adiponectin?**
  - A hormone produced by adipose tissue
  - Role in metabolism and insulin sensitivity
- **Functions:**
  - Increases insulin sensitivity
  - Anti-inflammatory effects
  - Influences lipid metabolism

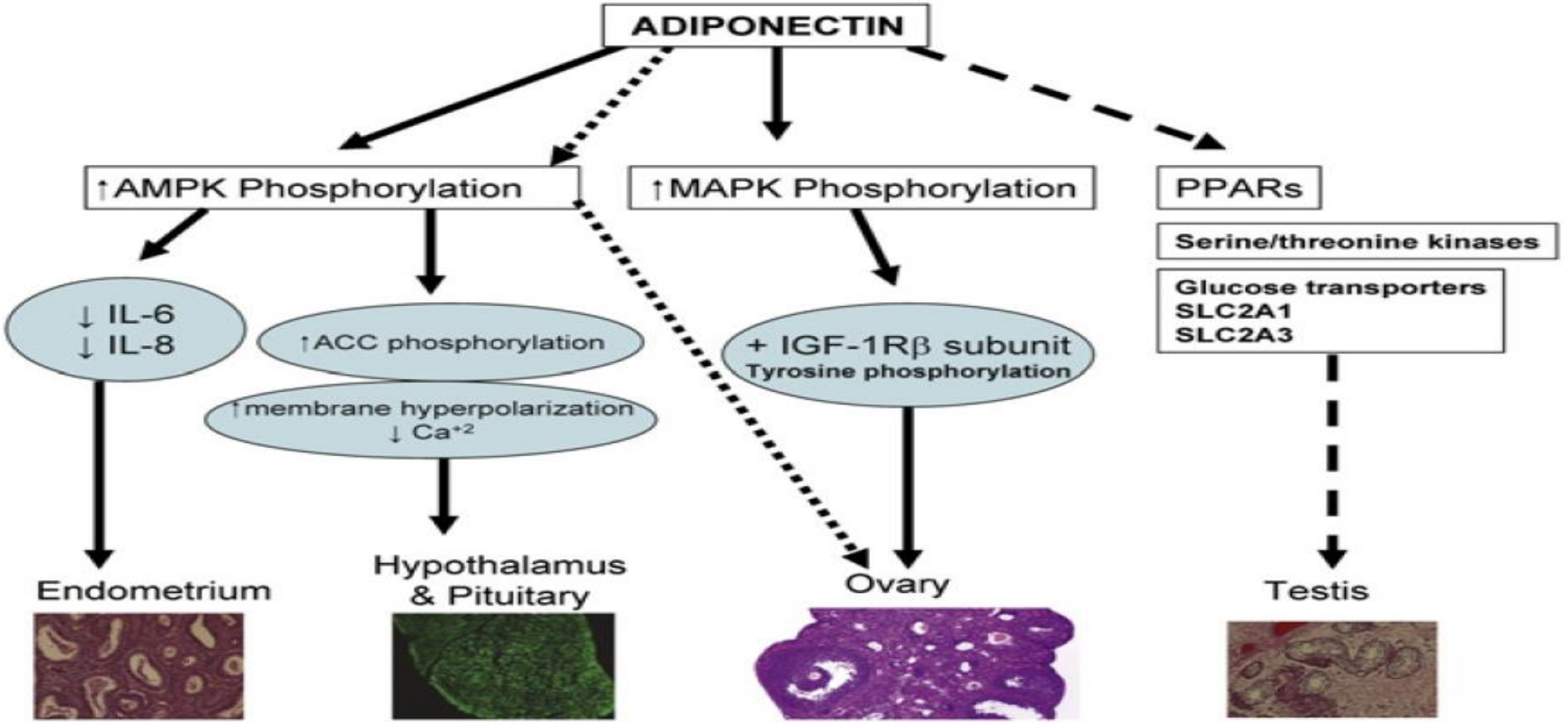
Overview of Adiponectin



What is Adiponectin



What is Adiponectin



VRA RAHESH

Elite innovation

proGsterol

Healthy Glucose Level with Deglusterol™*

VIRA RAHESH

Healthy Glucose Level with proGsterol

- ProGsterol is a nutritional supplement designed to help prediabetic and type 2 diabetic patients lower their blood sugar levels. It is composed of edible peptides called deglusterol, including Adiporin and Deobetide, which are synthetically produced by modeling herbal protein content.
- ProGsterol improves insulin resistance by affecting inflammatory cytokines and increasing the activation of certain proteins.:
- It improves insulin resistance by phosphorylation and inactivation of inflammatory cytokines such as TNF-α, JNK, IRS 302, and NF-kB.
- It increases phosphorylation and activation of IRS Tyr632, PI3k/AKT and AMPK and expression of adiponectin, leptin, IRS-1, and GLUT-4.

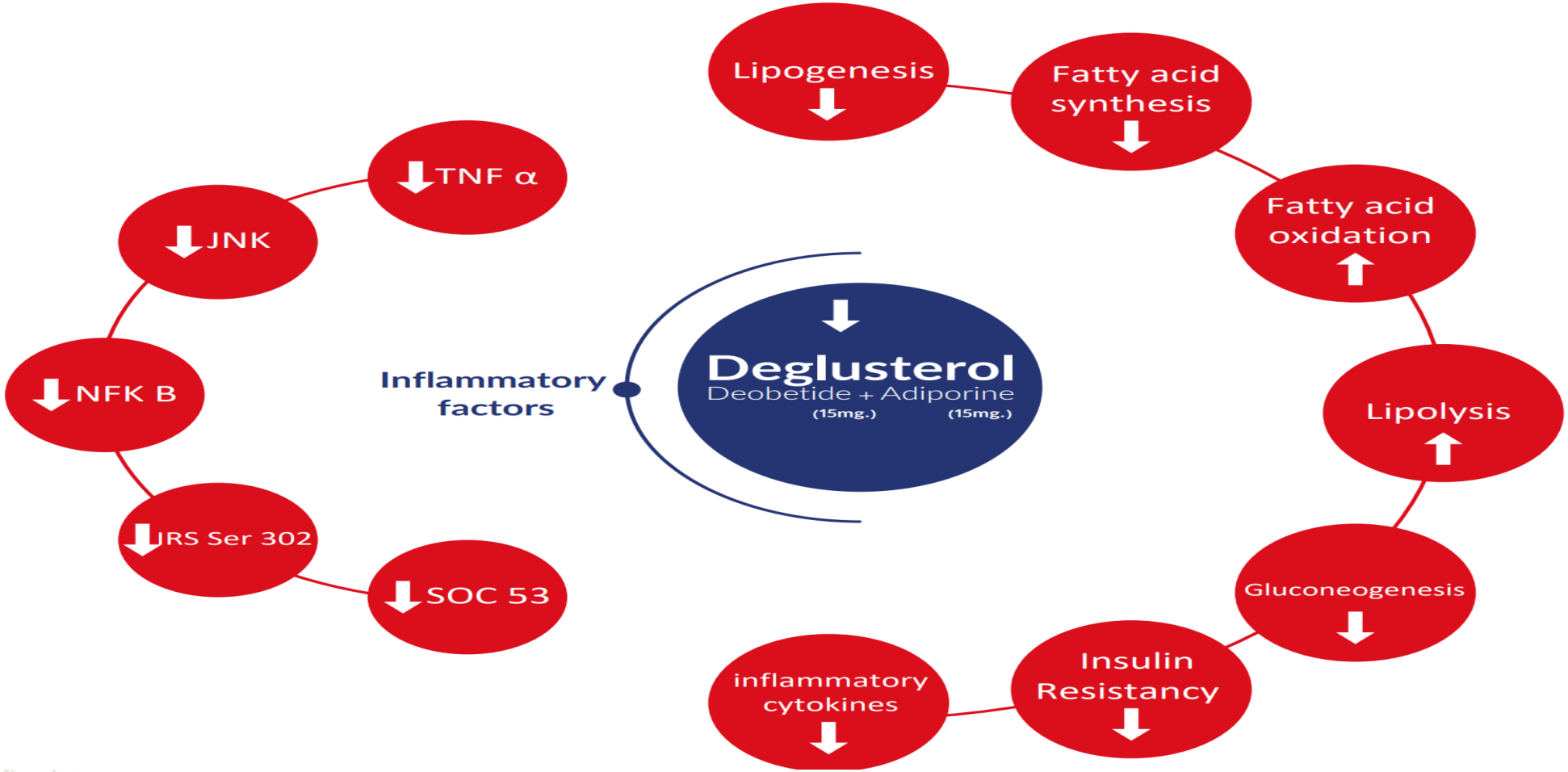
proGsterol

Dietary supplement approved by FDA as NDI for type II Diabetes and prediabetes

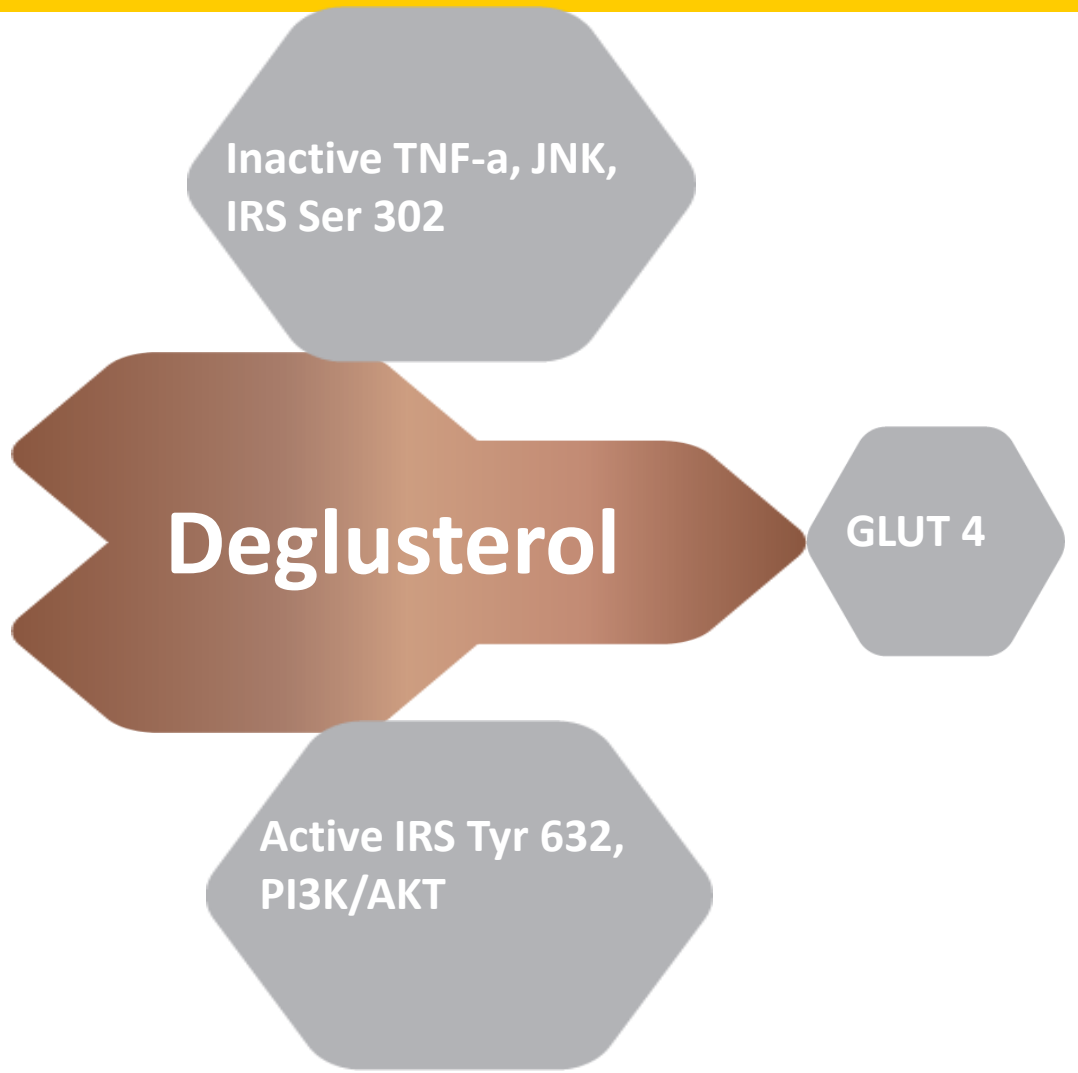
Reduced Insulin resistance in Insulin receptor
Treatment of NAFLD
PCOS
Weight loss

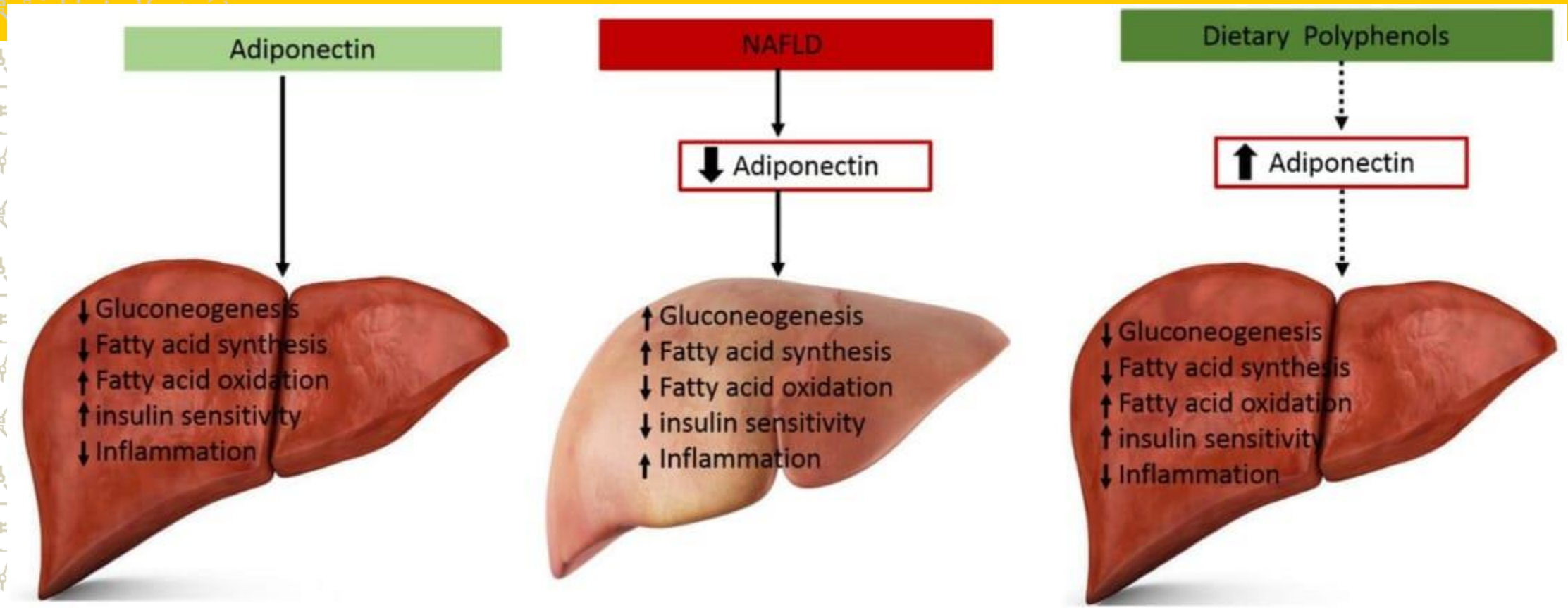
Safe without any side effect

ProGsterol as Adiponectin Agonist

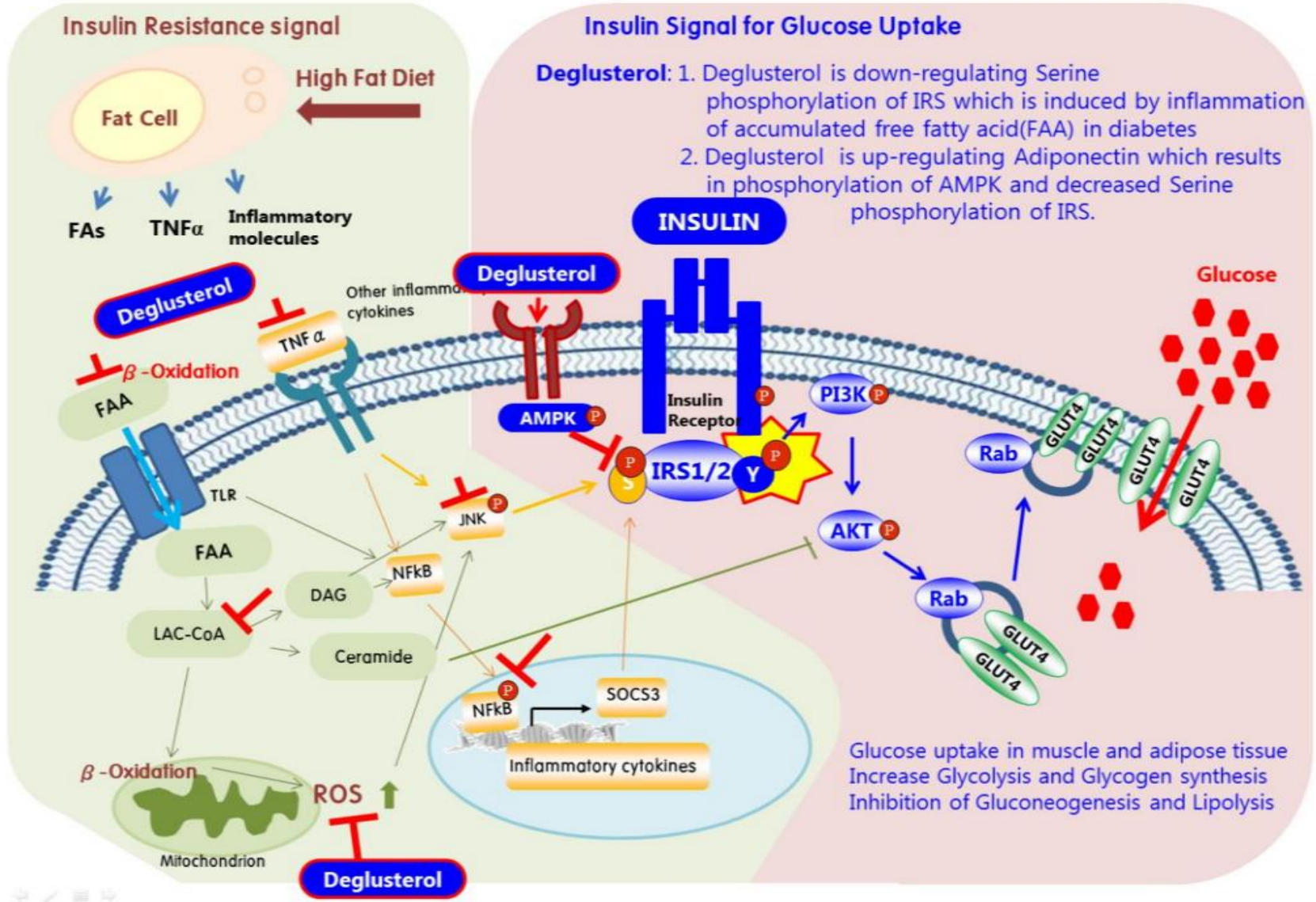


Effect on Insulin receptor




Adiponectin
↓ Gluconeogenesis
↓ Fatty acid synthesis
↑ Fatty acid oxidation
↑ insulin sensitivity
↓ Inflammation
NAFLD
↓ Adiponectin
↑ Gluconeogenesis
↑ Fatty acid synthesis
↓ Fatty acid oxidation
↓ insulin sensitivity
↑ Inflammation
Dietary Polyphenols
↑ Adiponectin
↓ Gluconeogenesis
↓ Fatty acid synthesis
↑ Fatty acid oxidation
↑ insulin sensitivity
↓ Inflammation

Mechanism of Action



Deglusterol

VRA RAHESH

Elite innovation

How to use:

Take 1 sachet with water (100 cc water) once a day (before breakfast)

Product development

Scientific approach

- Invitro (cell evaluation)
- **Invivo (Animal study)**
- Clinical (Human study)
- Post marketing surveillance

Glucose uptake assessment

Cell lines

- 3T3-L1 (Pre-adipocyte)
- **C2C12 (Myoblast)**
- INS-1 (Rat pancreatic beta cell)
- Hep G2 (Hepatocellular cell)

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Research Article | NO ACCESS | Published Online: 11 February 2022

Lowering of Blood Glucose Levels with the Peptide Mixture Deglusterol in *In Vitro* and *In Vivo* Models

Authors: Eun Mi Kim, Seon Soo Kim, and Yong Ji Chung | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Medicinal Food • https://doi.org/10.1089/jmf.2021.K.0159

Abstract

This study aimed to investigate the blood glucose-lowering effect of the peptide complex Deglusterol, which was isolated from corn extract, in insulin-resistance models. It was found to inhibit insulin receptor substrate (IRS) Ser302 phosphorylation, known as the insulin resistance mechanism, through the inhibition of tumor necrosis factor-α (TNF-α) signaling and the induction of AMP-activated protein kinase phosphorylation. Furthermore, the phosphorylation of IRS Tyr632, phosphoinositide 3-kinase (PI3K), and AKT that is involved in the insulin action mechanism was decreased by TNF-α, whereas Deglusterol increased their phosphorylations, leading to an increase of glucose uptake rate by 190% through glucose transporter type 4 (GLUT4) compared with TNF-α-treated group in C2C12 cells. In addition to insulin signaling activation, Deglusterol treatment resulted in significantly greater mRNA expressions of IRS (190%) and GLUT4 (140%) as well as that of leptin (260%) and adiponectin (140%), which are indicators of insulin sensitivity. In animal models with type 2 diabetes, the blood glucose concentrations in the Deglusterol-administered group were significantly reduced by 50% compared with the control group. Deglusterol suppressed insulin resistance and restored insulin sensitivity, which contributed to lowering blood glucose concentrations in the insulin-resistant models, suggesting its potential as a blood glucose-lowering agent for people at high risk of type 2 diabetes or prediabetes.

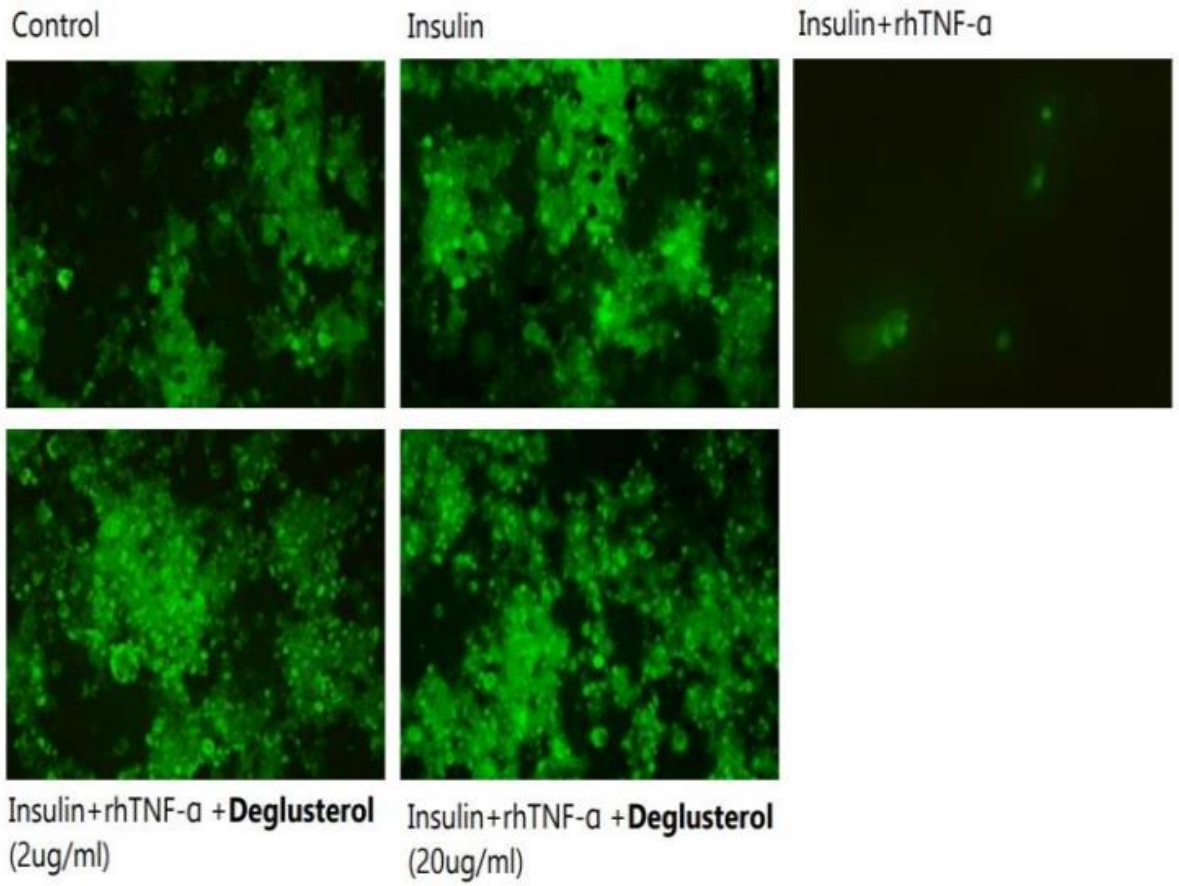
Abstract

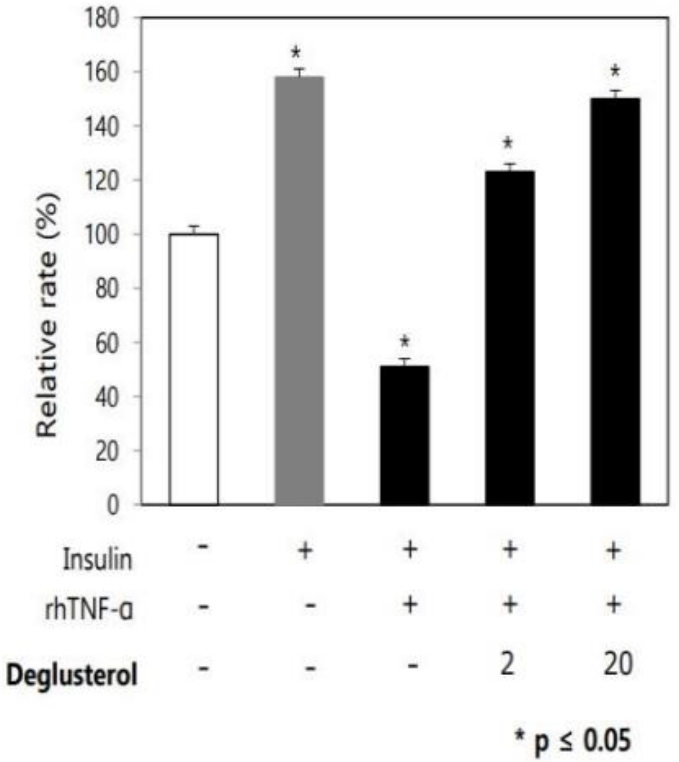
- This study aimed to investigate the blood glucose-lowering effect of the peptide complex Deglusterol, which was isolated from corn extract, in insulin-resistance models.
- It was found to inhibit insulin receptor substrate (IRS) Ser302 phosphorylation, known as the insulin resistance mechanism, through the inhibition of tumor necrosis factor-α (TNF-α) signaling and the induction of AMP-activated protein kinase phosphorylation.
- Furthermore, the phosphorylation of IRS Tyr632, phosphoinositide 3-kinase (PI3K), and AKT that is involved in the insulin action mechanism was decreased by TNF-α, whereas Deglusterol increased their phosphorylations, leading to an increase of glucose uptake rate by 190% through glucose transporter type 4 (GLUT4) compared with TNF-α-treated group in C2C12 cells.
- In addition to insulin signaling activation, Deglusterol treatment resulted in significantly greater mRNA expressions of IRS (190%) and GLUT4 (140%) as well as that of leptin (260%) and adiponectin (140%), which are indicators of insulin sensitivity.
- In animal models with type 2 diabetes, the blood glucose concentrations in the Deglusterol-administered group were significantly reduced by 50% compared with the control group.
- Deglusterol suppressed insulin resistance and restored insulin sensitivity, which contributed to lowering blood glucose concentrations in the insulin-resistant models, suggesting its potential as a blood glucose-lowering agent for people at high risk of type 2 diabetes or prediabetes.

1. Effect of Deglusterol on Glucose uptake

1) Glucose uptake in pre-adipocyte

Cell: 3T3-L1 (Preadipocyte)



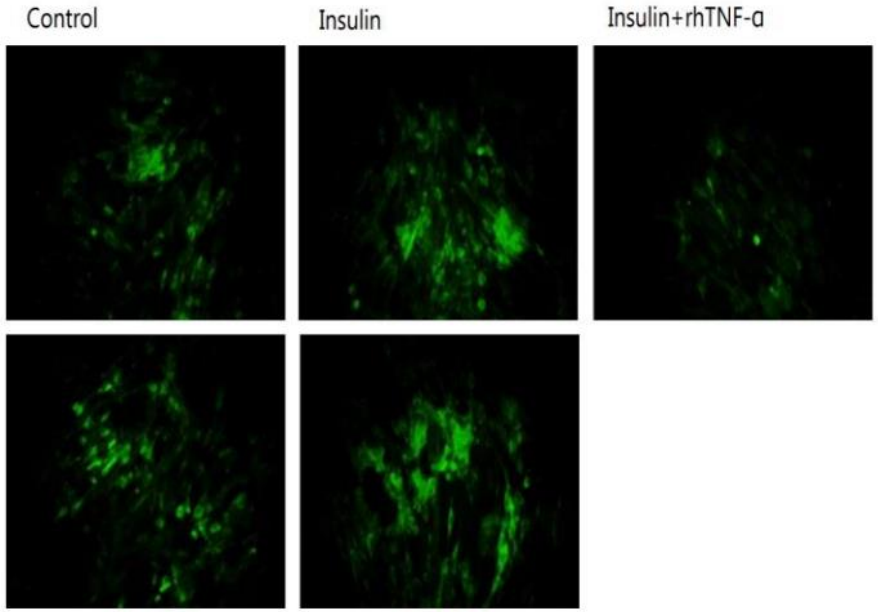


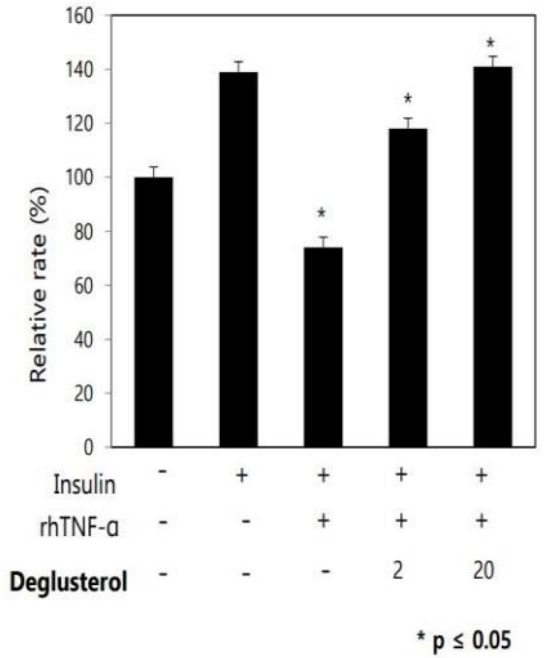
2-NBDG uptake was increased in differentiated adipocytes by Deglusterol treatment

1. Effect of Deglusterol on Glucose uptake

2) Glucose uptake in Myoblast

Cell: C2C12 (Myoblast)



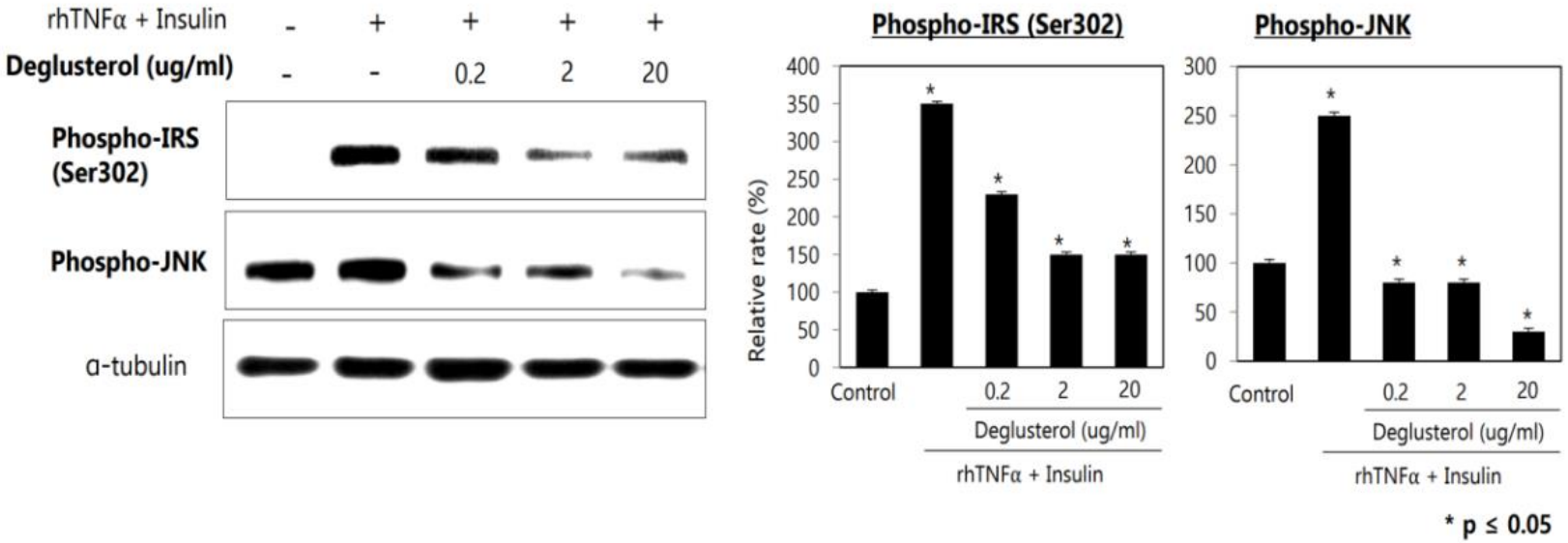


2-NBDG uptake was increased in differentiated myoblast by Deglusterol treatment

2. Effect of Deglusterol on Insulin Sensitivity and Resistant

1) Inhibition of Insulin Resistant signal

Cell: Differentiated 3T3-L1 (preadipocyte)

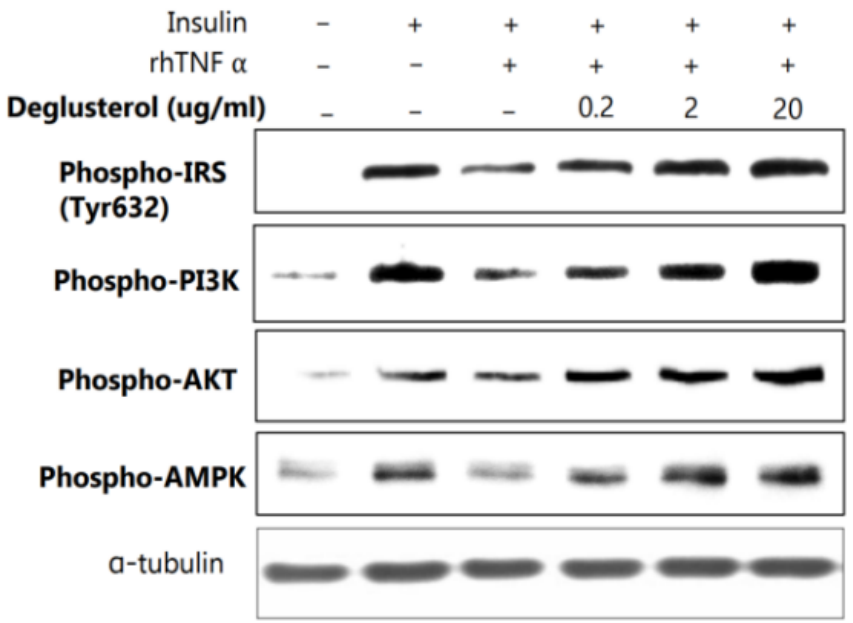


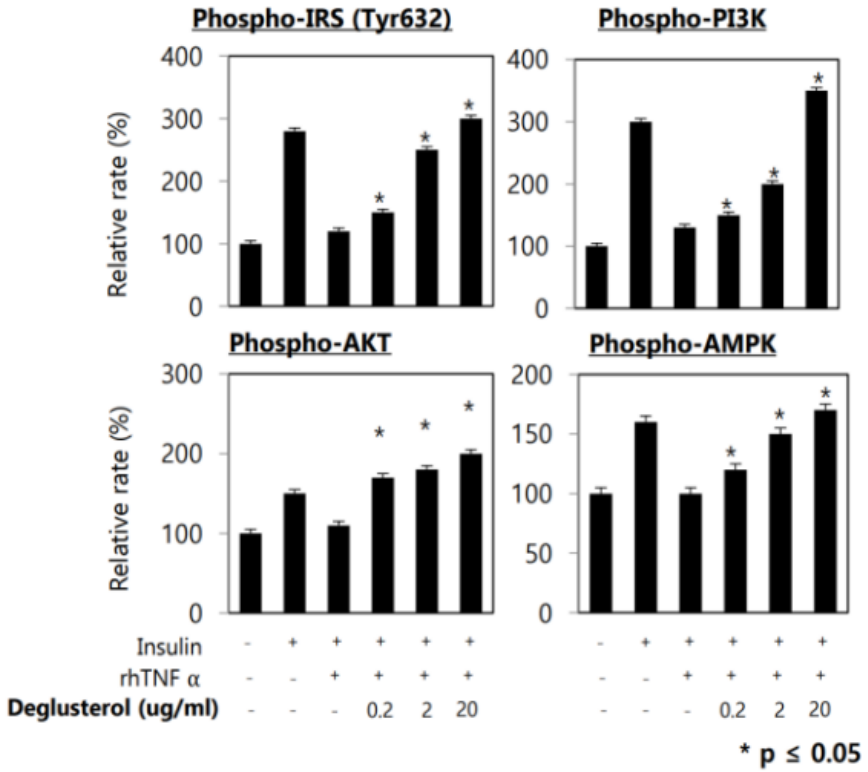
Phosphorylation levels of insulin resistance-related signaling molecules were induced by rhTNF-α and Insulin co-treatment and those were decreased by Deglusterol treatment.

2. Effect of Deglusterol on Insulin Sensitivity and Resistant

2) Increase Insulin Sensitivity signal

Cell: Differentiated 3T3-L1 (preadipocyte)



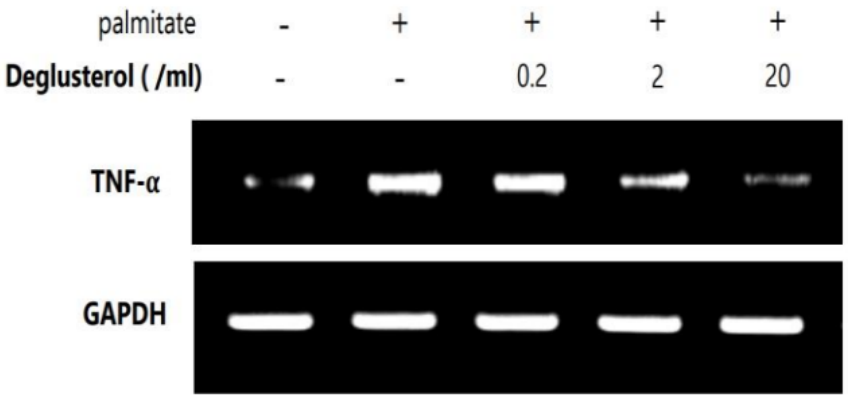


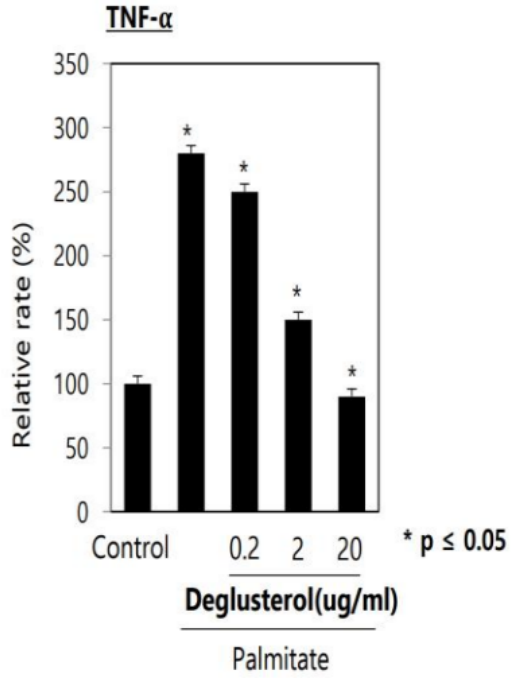
Phosphorylation levels of insulin sensitivity-related signaling molecules were reduced by rhTNF-α and those were increased by Deglusterol treatment

3. Effect of Deglusterol on FFA-induced inflammation

1) Inhibition of Palmitate–induced TNF-α expression

Cell: INS-1 (Rat pancreatic beta cell)



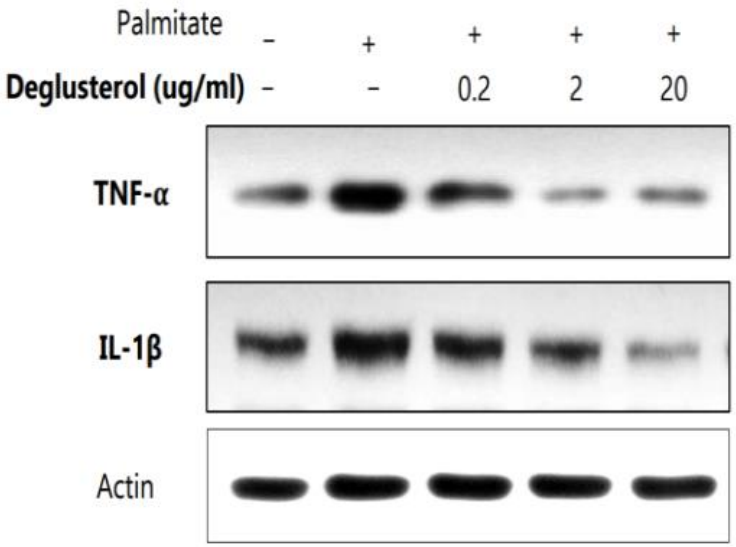


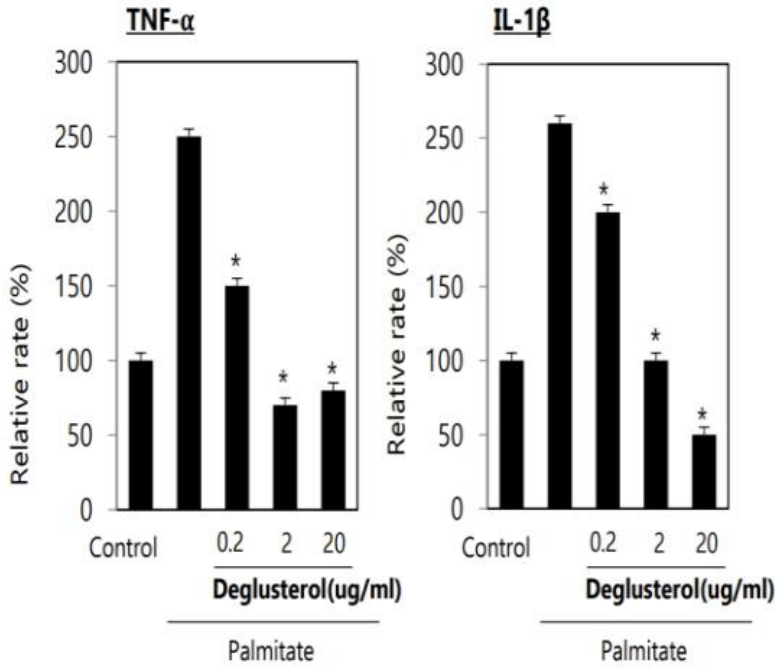
Palmitate-induced TNF-α mRNA level was decreased by Deglusterol treatment with dose-dependent manner.

3. Effect of Deglusterol on FFA-induced inflammation

2) Inhibition of Palmitate-induced inflammatory cytokine expression

Cell: INS-1 (Rat pancreatic beta cell)





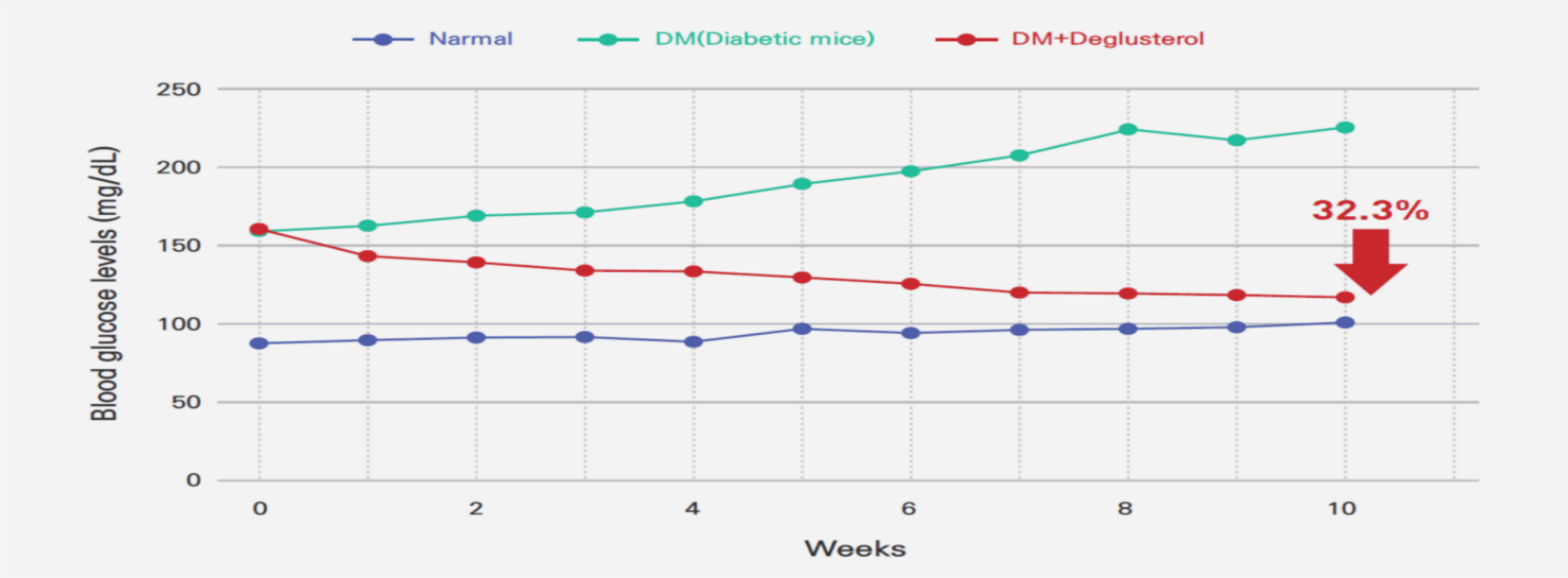
* p ≤ 0.05

Palmitate-induced TNF-α and IL-1β protein levels were decreased by Deglusterol treatment

Animal study

Effect of Deglusterol on blood glucose level of HFD-induced mouse diabetic model

Animal: Diabetic mouse: 15 weeks, Male, C57BL/6J mouse treated with high fat diet for 9 week
Normal mouse: 15 weeks, Male, C57/BL6J mouse treated with normal diet
Treatment: Daily treatment of 0.5 mg/kg Deglusterol for 10 weeks with or without high fat diet

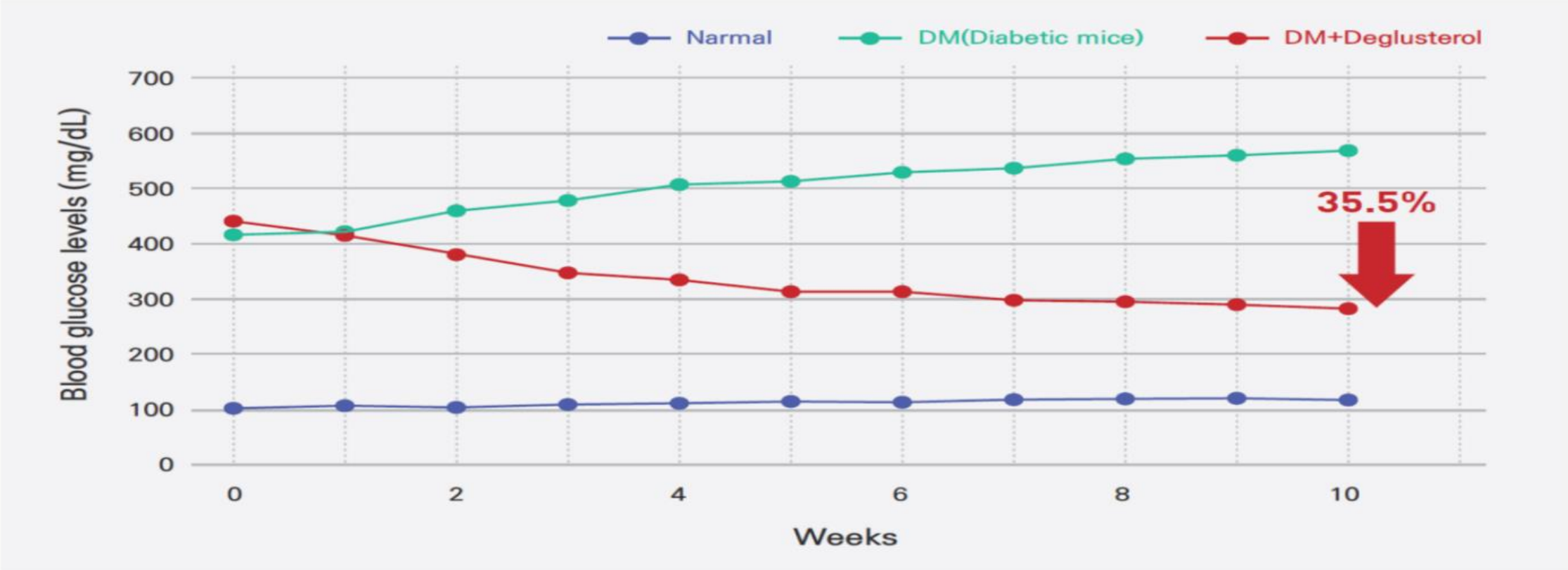


Fasting blood glucose level was significantly decreased by Deglusterol treatment in HFD-induced mouse diabetes model.

Animal study

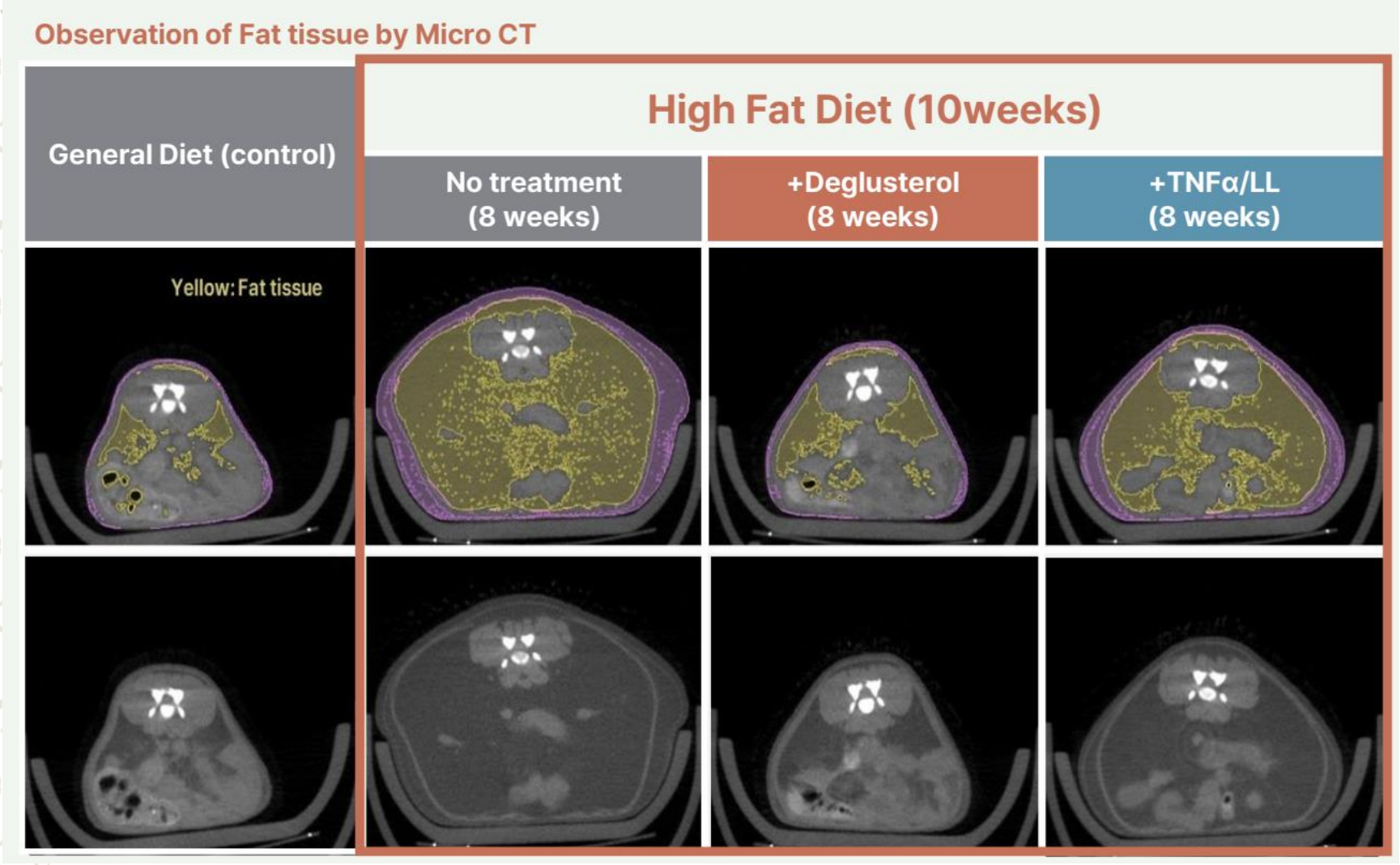
Effect of Deglusterol on blood glucose level of db/db mouse

Animal: Diabetic mouse: 12 weeks, Male, C57BLKS/J Iar-+Lepr^{db}/ +Lepr^{db} (db/db)
Normal mouse: 12 weeks, Male, C57BLKS/J Iar- m+/m+
Treatment: Daily treatment of 0.5 mg/kg Deglusterol for 10 weeks



Fasting blood glucose level was significantly decreased by Deglusterol treatment in db/db mouse

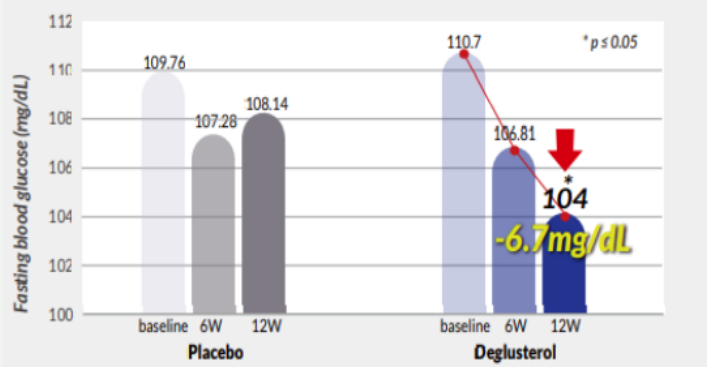
Animal studies



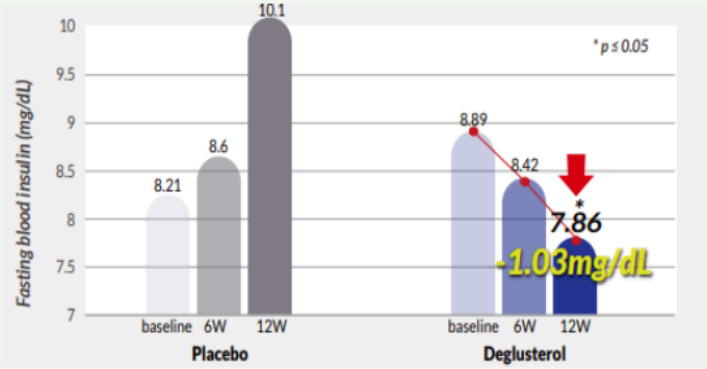
Human clinical studies

As a result of human clinical tests, Deglusterol significantly decreased Fasting blood glucose, fasting blood insulin, C-peptide, and HOMA-IR.

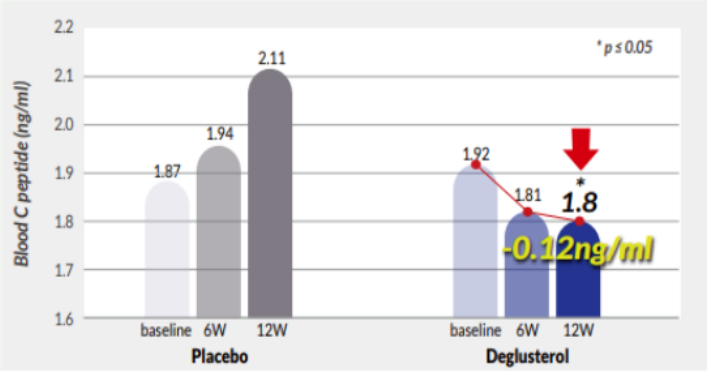
① Fasting blood glucose level at each visit compared to baseline



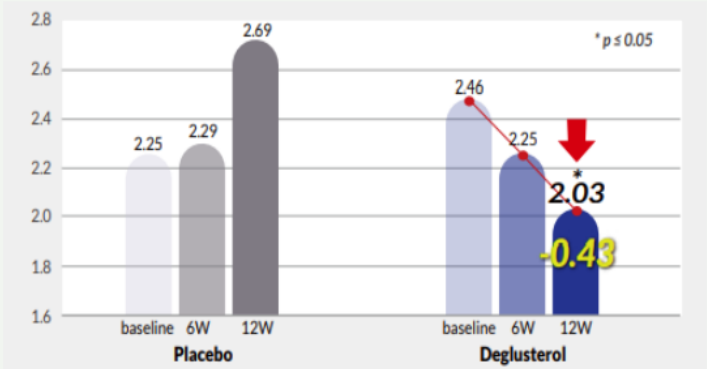
② Blood fasting insulin at each visit compared to baseline



③ Blood C-peptide at each visit compared to baseline



④ HOMA-IR at each visit compared to baseline



Thank you and hope for a good rain