Diabete. Fisiopatologia e recenti frontiere farmacologiche

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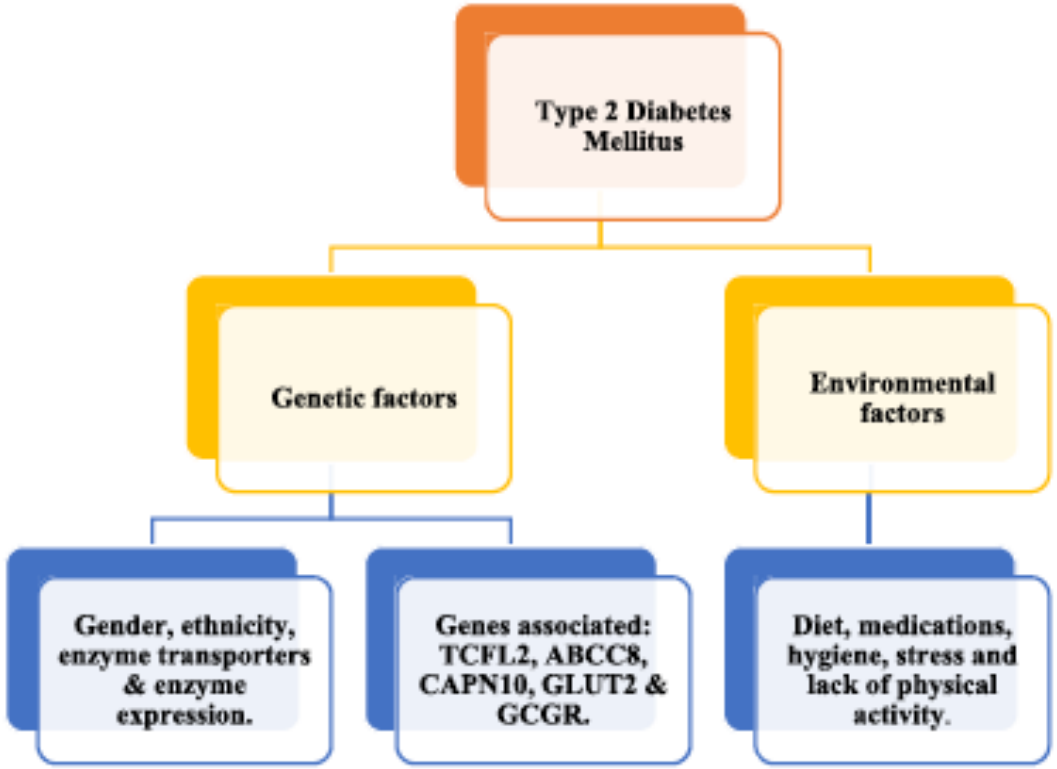
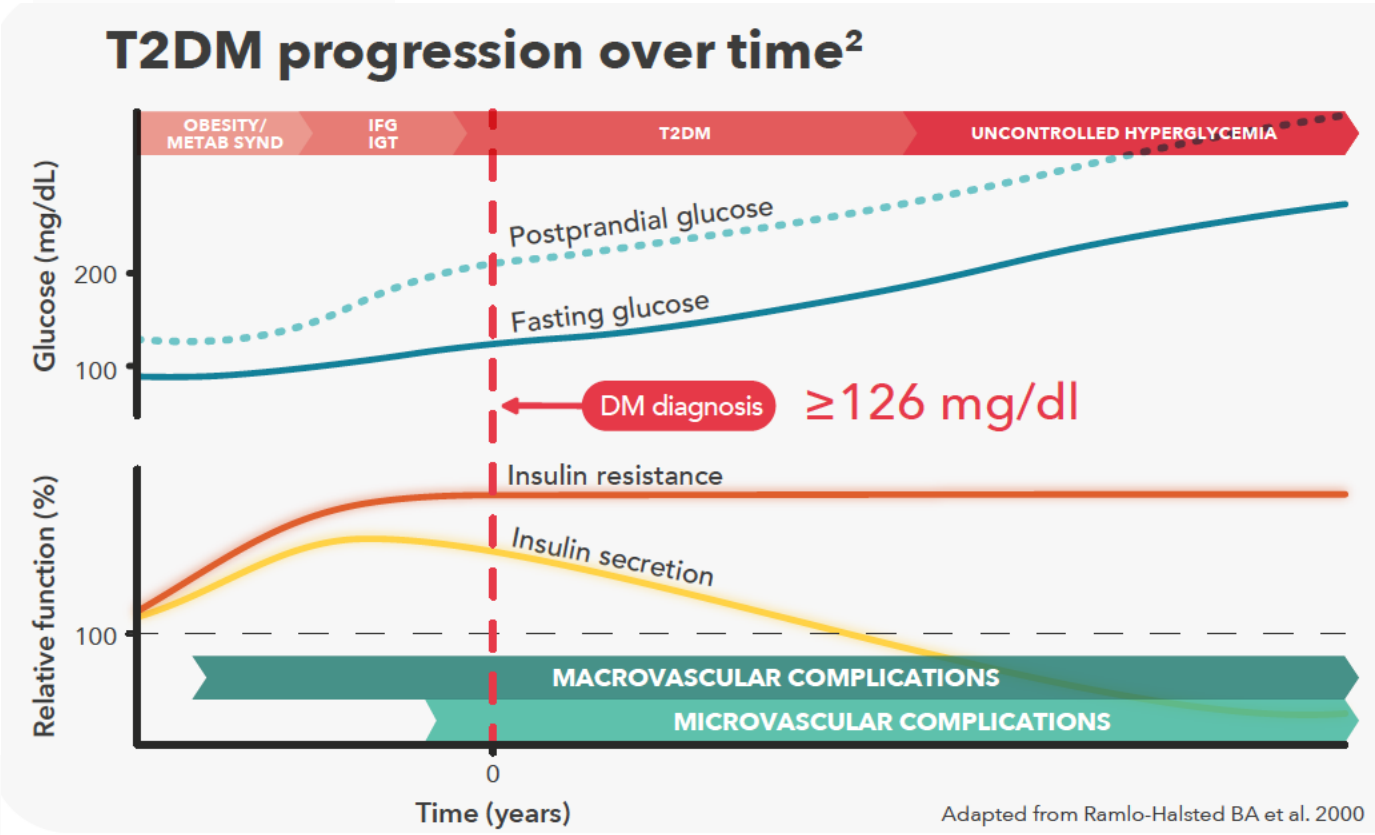
Disclosure information

No conflict of interest

Factors affecting type 2 diabetes mellitus

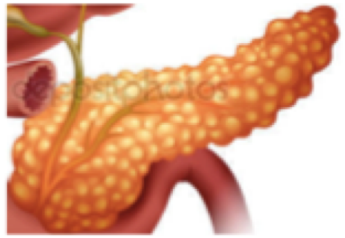


Medicine in Novel Technology and Devices 19 (2023) 100247



The Initially Described "Terrible Triumvirate" of Diabetes Pathophysiology

From the Triumvirate to……



Impaired Insulin secretion

Hyperglycemia

↑ Hepatic glucose Production

↓ Peripheral glucose uptake

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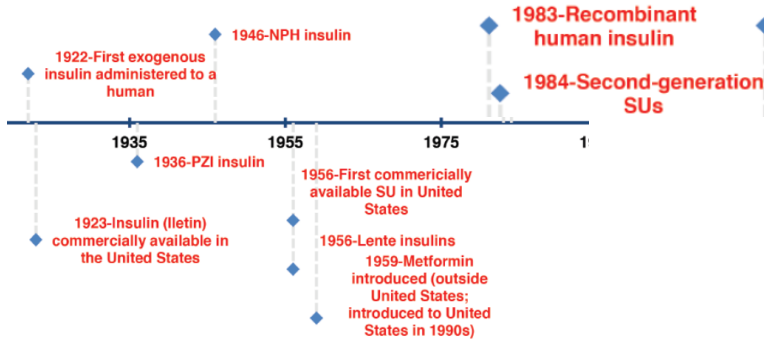
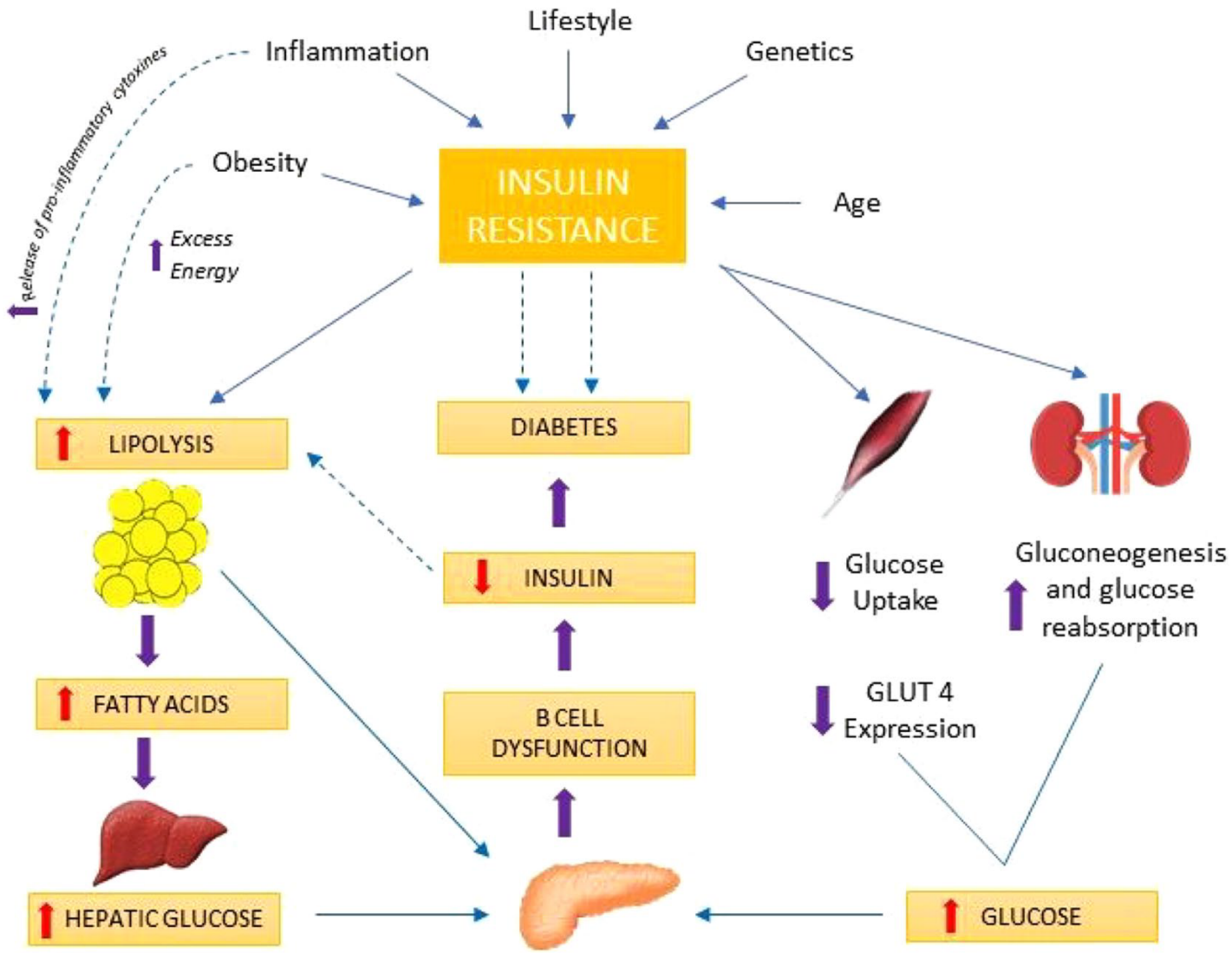


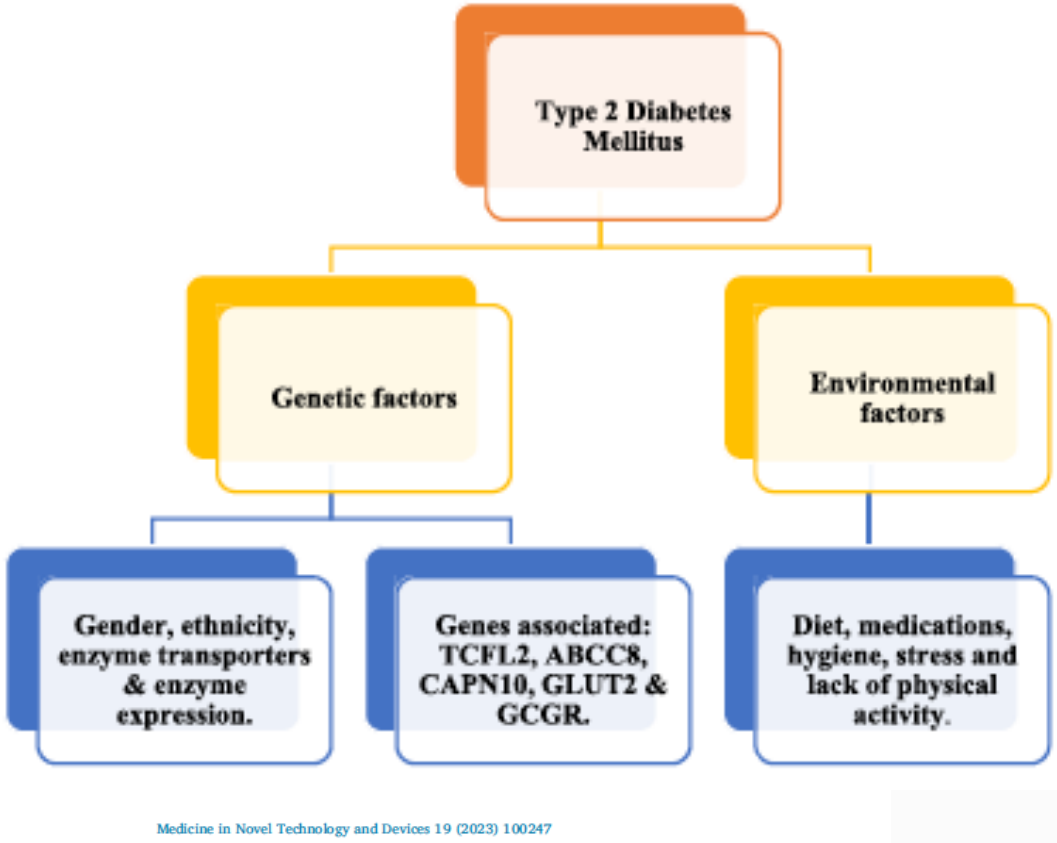
Ralph A DeFronzo, **Diabetes** 1988,

Molecular mechanisms responsible for insulin resistance in T2DM followed by a discussion on organ-specific contributions

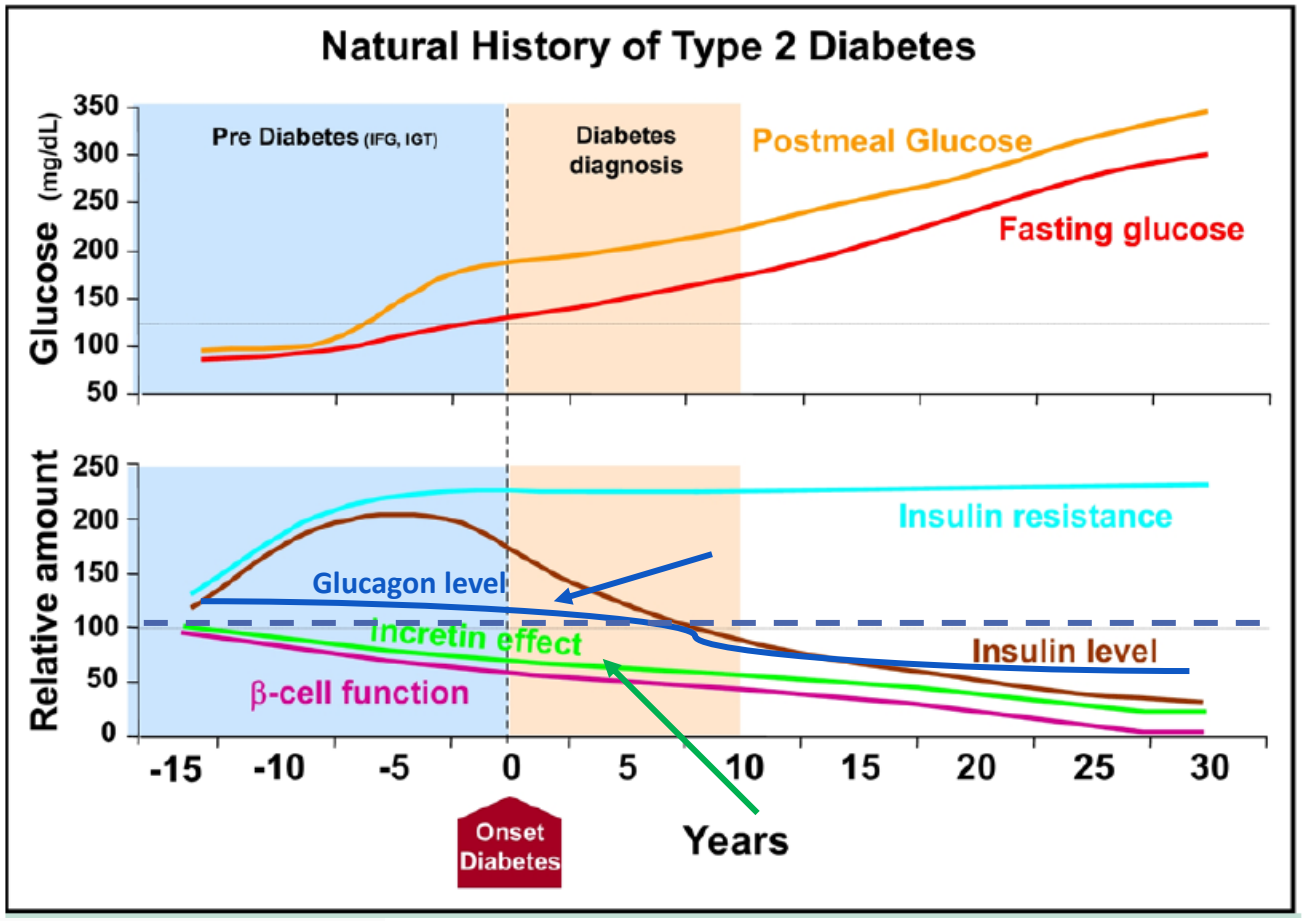


Insulin resistance in the muscles; defective insulin signalling, glucose transport, glucose phosphorylation, glycogen synthesis, pyruvate dehydrogenase complex activity, and mitochondrial oxidative activity.16,18,19 Events in the liver; insulin resistance/deficiency, hyperglucagonaemia, enhanced glucagon sensitivity, and increased substrate (fatty acids, lactate, glycerol, and amino acids) delivery, leads to increased gluconeogenesis, which is responsible for the increased basal rate of glucose production and fasting hyperglycaemia.20–22 Renal contribution; renal insulin resistance and augmented renal gluconeogenesis contribute to fasting hyperglycaemia.23 Vascular endothelium; impaired vasodilation due to insulin resistance resulting in reduced insulin and glucose delivery.24 Finally, post-prandial hyperglycaemia ensues due to increased hepatic glucose output, muscle insulin resistance, reduced noninsulin-mediated glucose uptake, and excessive renal glucose re-absorption

Factors affecting type 2 diabetes mellitus



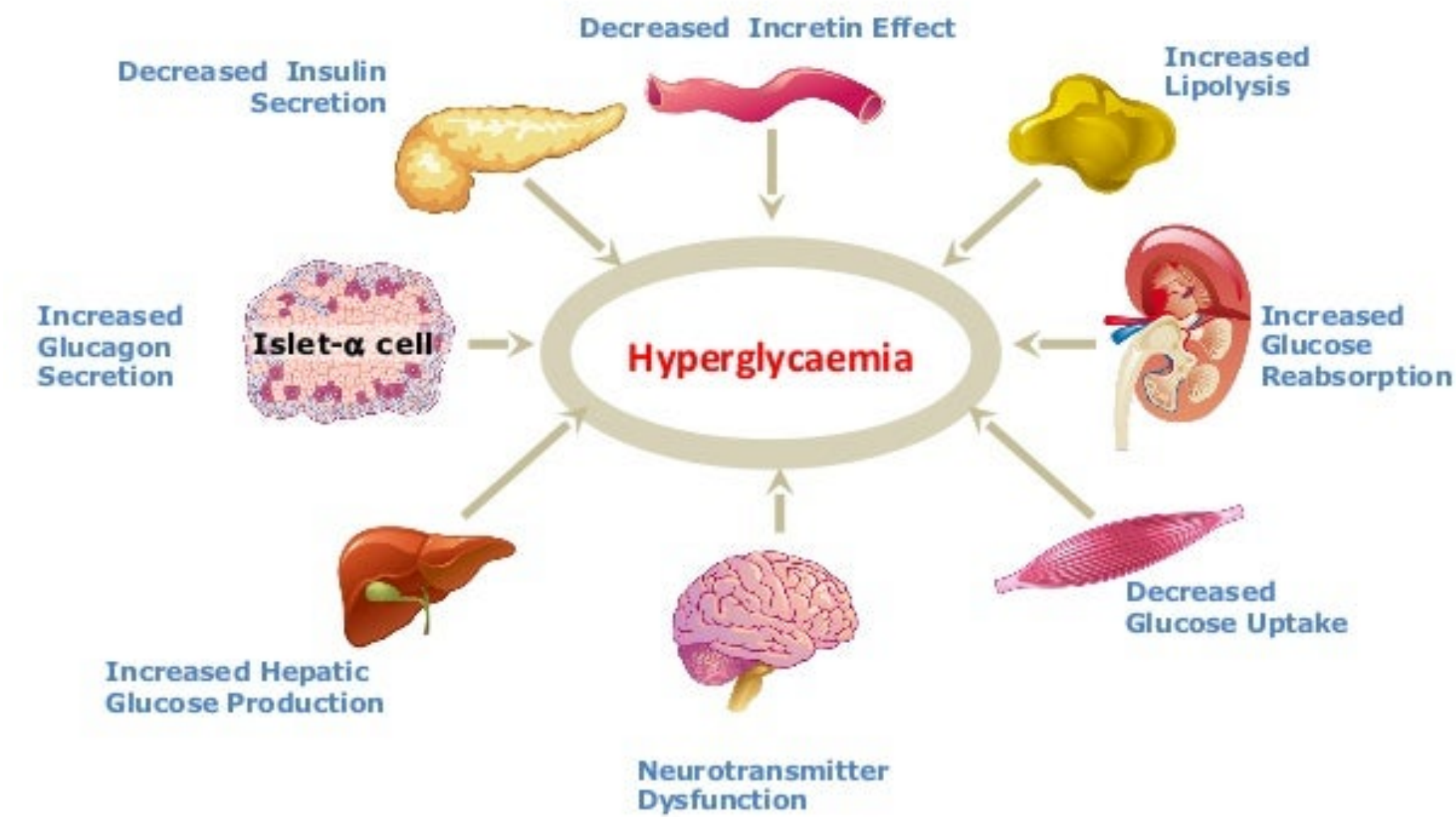
Medicine in Novel Technology and Devices 19 (2023) 100247



Kendall DM, 2009

Pathogenesis of type 2 diabetes - The Ominous Octet

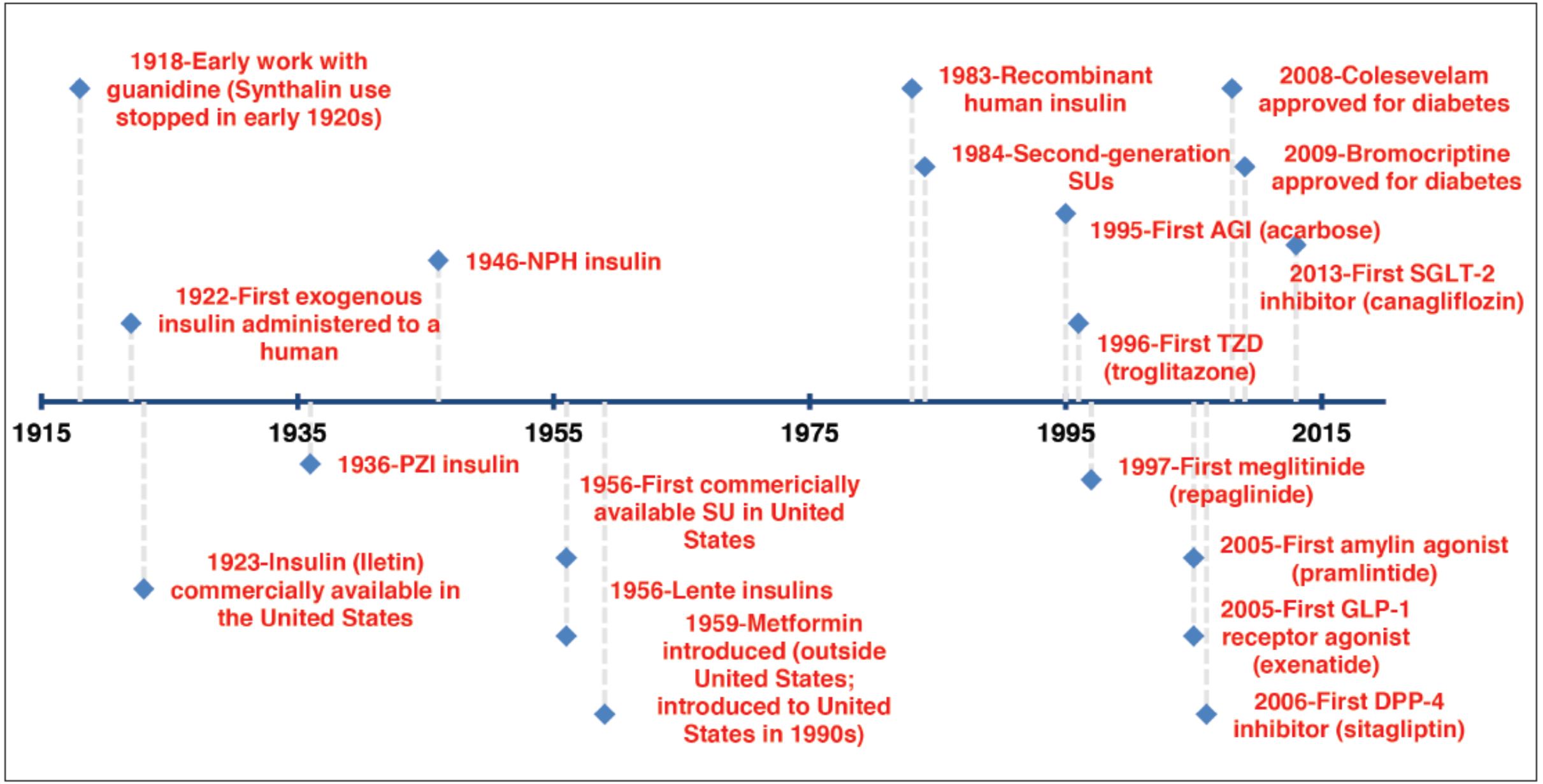
……to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus



tanti farmaci

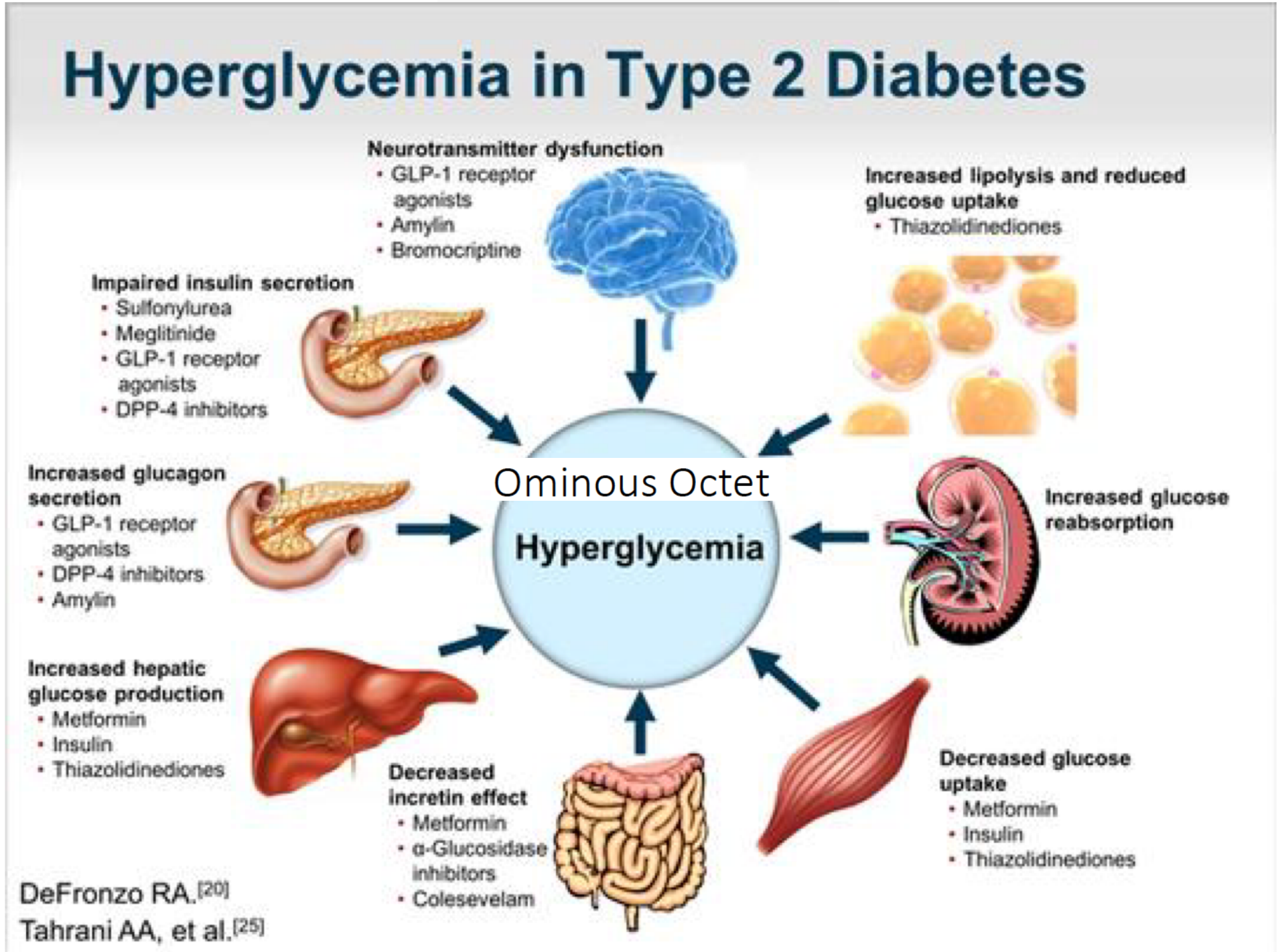
Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.

History of diabetes medications



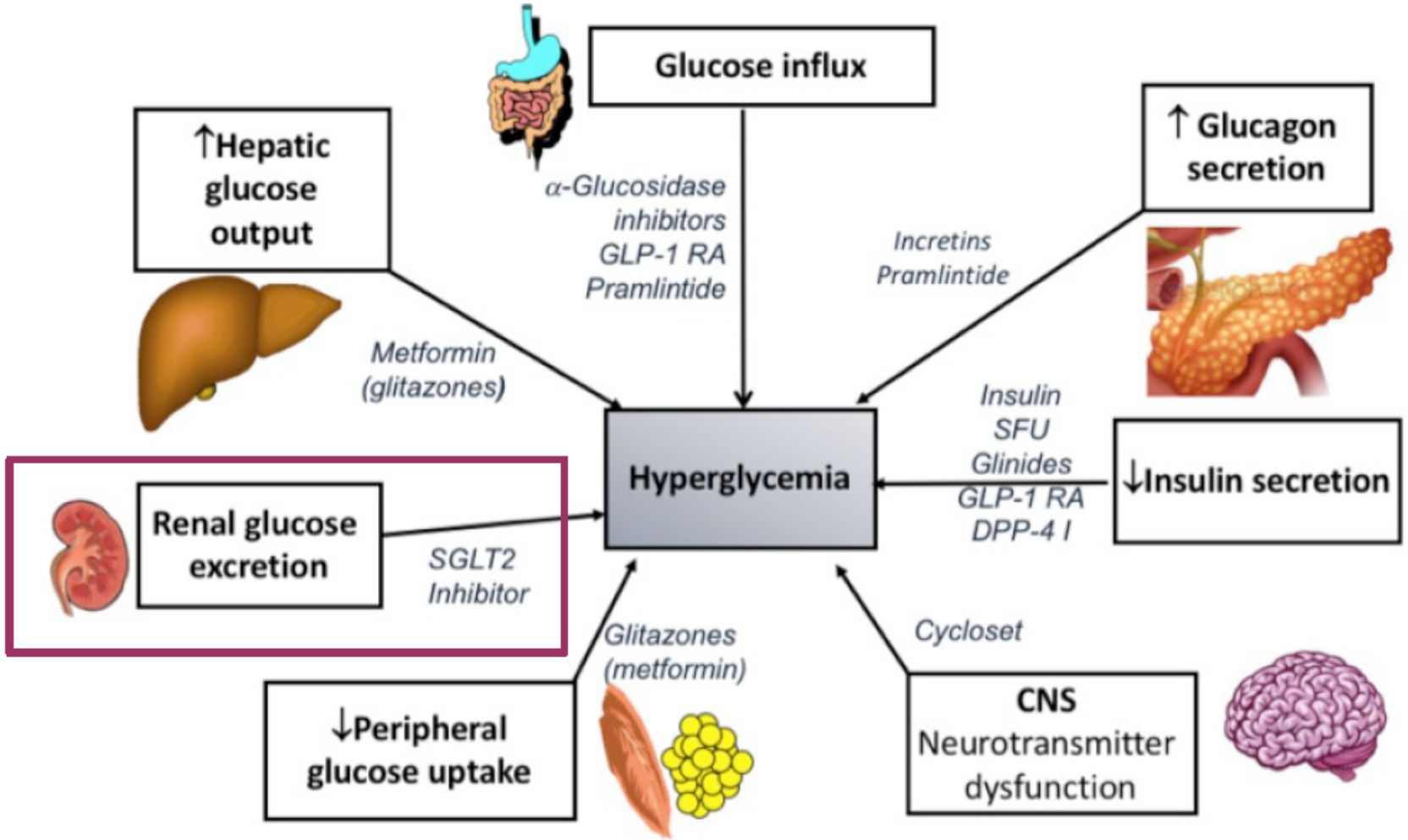
Diabetes Spectrum Volume 27, Number 2, 2014

Hyperglycemia in Type 2 Diabetes



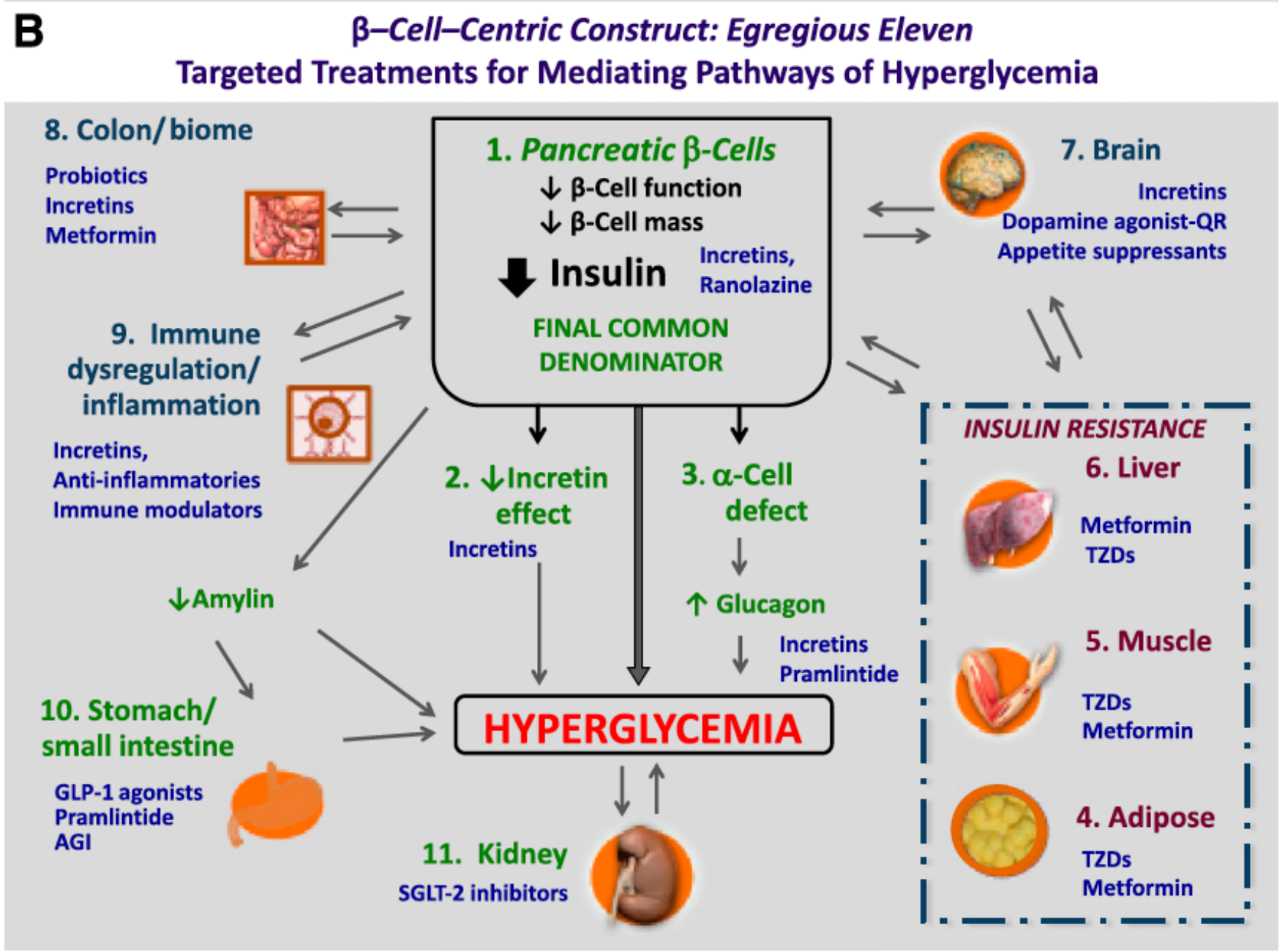
DeFronzo RA.[20]
Tahrani AA, et al.[25]

The Ominous Octet Pathways
(and Agents That Target Them)



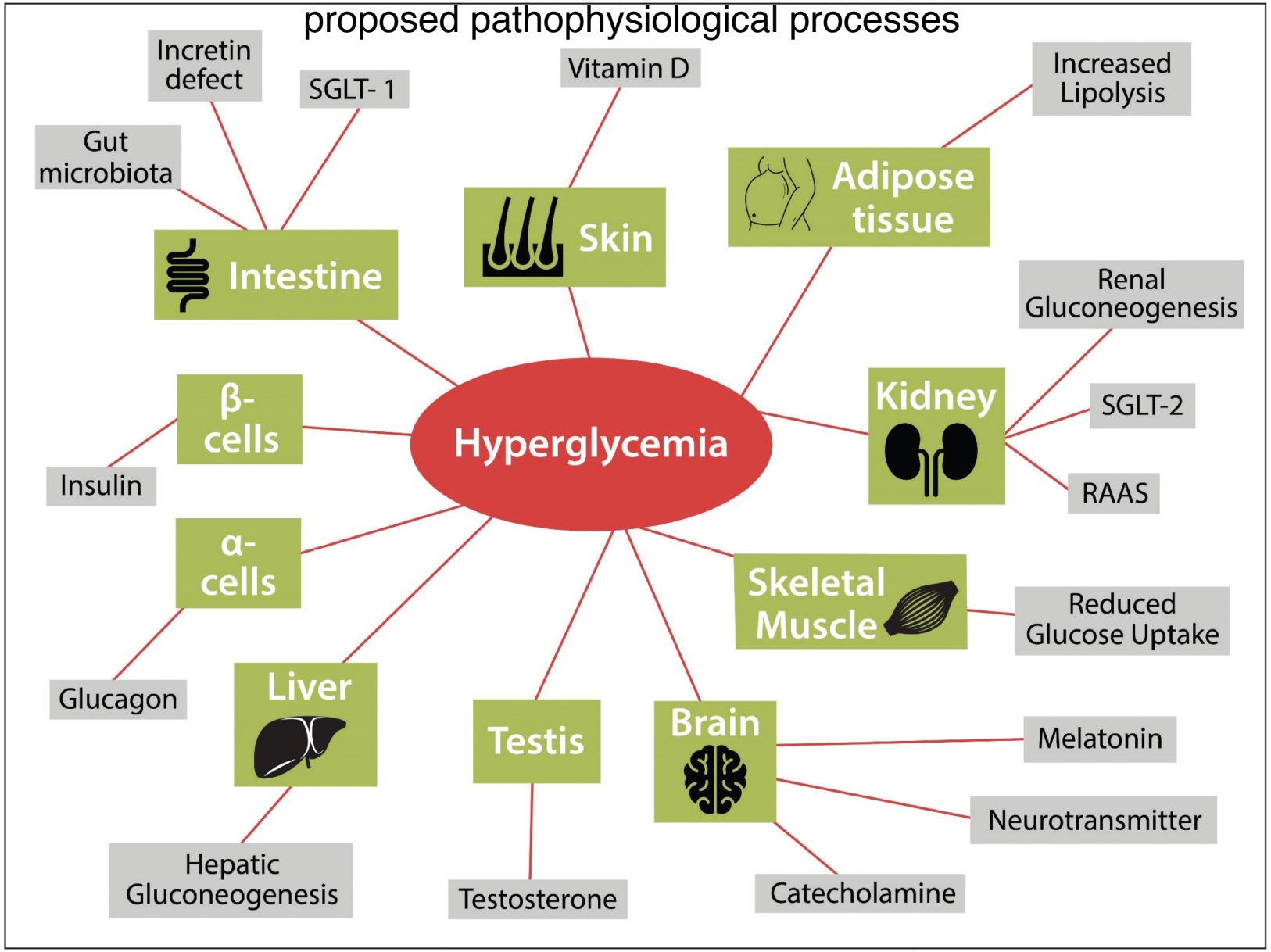
Mod. from DeFronzo RA.
Diabetes. 2009;58:773-795;
Tahrani AA et al. *Lancet* 2011;378:182–197.

Egregious 11



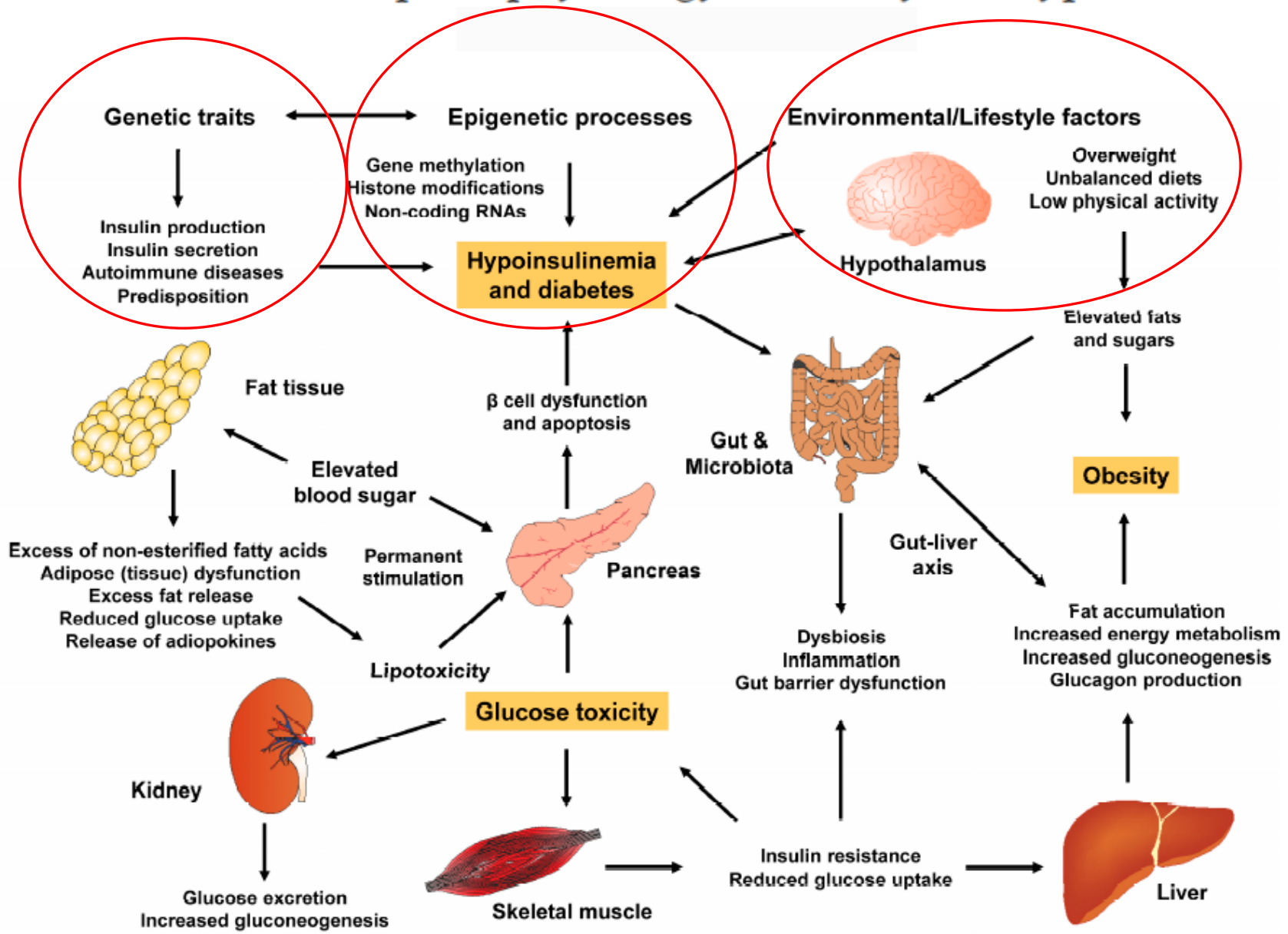
Diabetes Care 2016;39:179–186

...to Sweetening Sixteen: Beyond the Ominous Octet



Phatak SR, J Diabetol 2021;12:1-9.

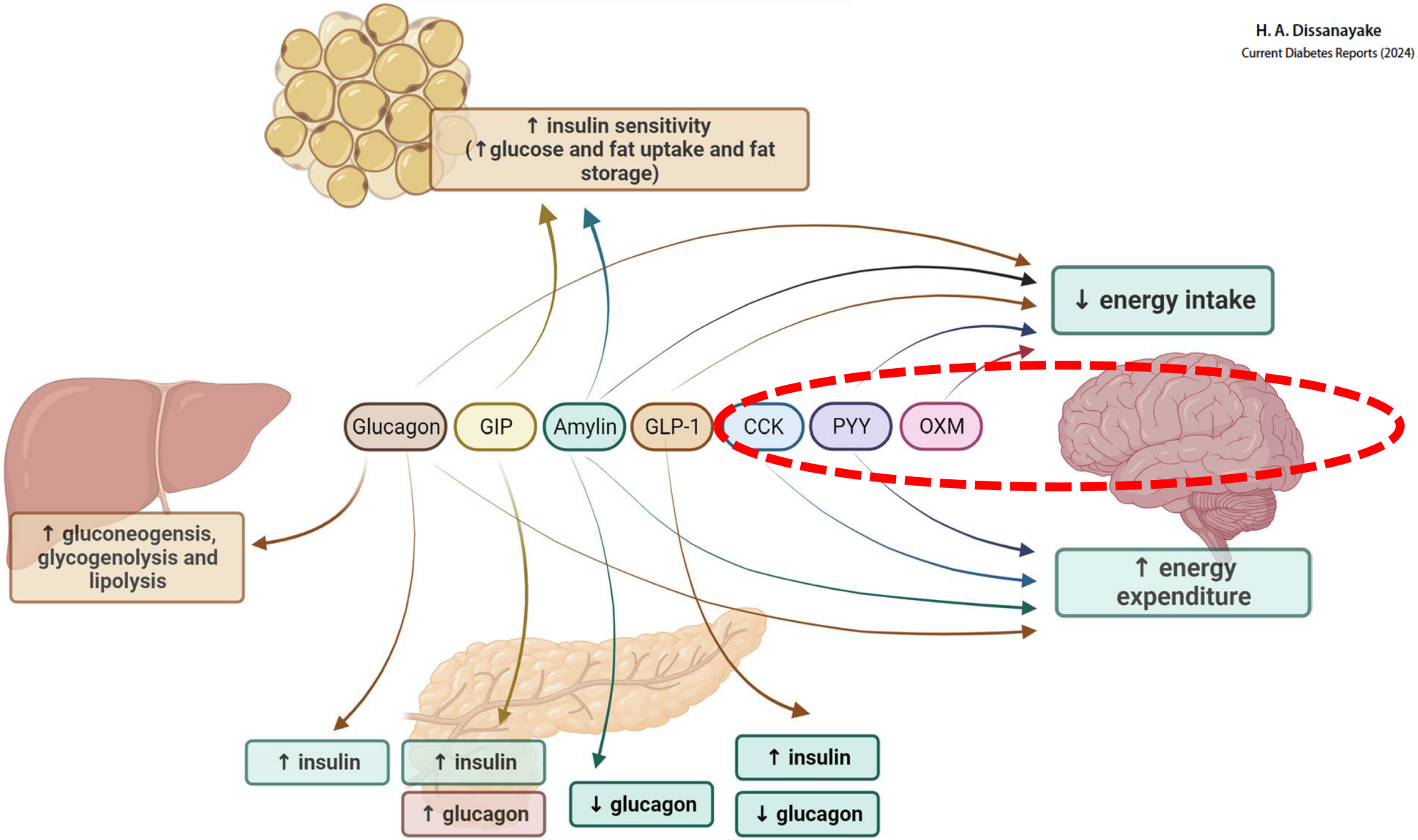
Multifactorial pathophysiology of obesity and type 2 diabetes.



Preethi Chandrasekaran

Int. J. Mol. Sci. **2024**, *25*, 1882

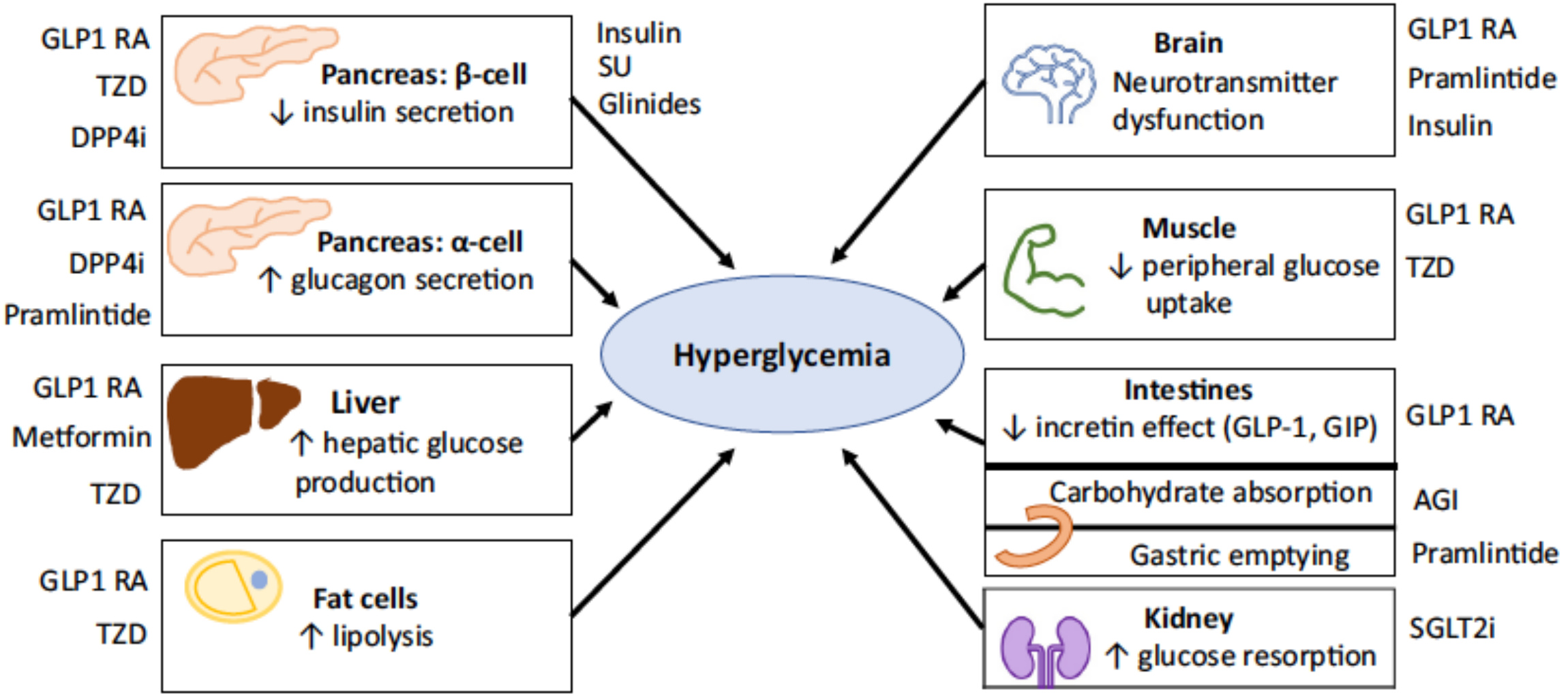
Role of key hormones in glucose and energy homeostasis



Role of key hormones in glucose and energy homeostasis. Glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and oxyntomodulin (OXM) are preproglucagon derivatives with varying effects on the pancreas, liver, adipose tissue, and brain to regulate glucose and energy homeostasis. Cholecystokinin (CCK) and peptide-tyrosine-tyrosine (PYY) are pancreatic peptides predominantly act through central mechanisms to regular energy intake and expenditure (image created using BioRender. com)

Glucagon, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), oxyntomodulin (OXM), Cholecystokinin (CCK) and peptide-tyrosine-tyrosine (PYY)

Targets of action of medications for T2D versus abnormalities contributing to hyperglycemia.



GLP1 RA, glucagon like peptide 1 receptor agonist; TZD, thiazolidinediones; SU, sulfonylurea; DPP4i, dipeptidyl peptidase 4 inhibitor; AGI, alpha glucosidase inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; GIP, gastric inhibitor polypeptide.

A. DeMarsilis et al.
Metabolism 137 (2022) 155332

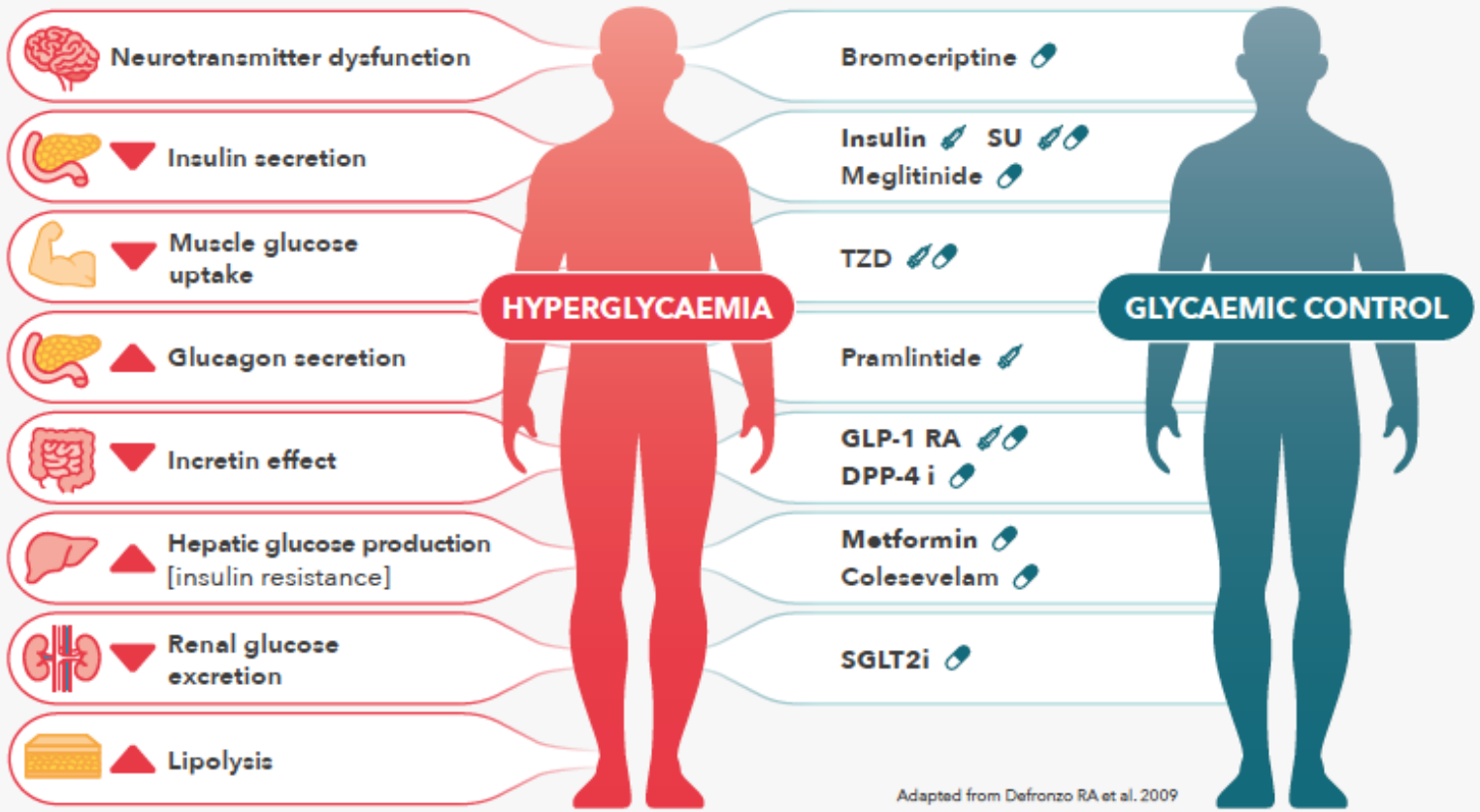
Diabetes Pathophysiology

Radcliffe Medical Education

Supported by an educational grant from Novo Nordisk A/S

8 pathophysiologic abnormalities, collectively referred to as the "**Ominous Octet**" lead to T2DM[1]

Several **pathophysiologically-based therapies** have been developed that lead to improved glucose control in T2DM



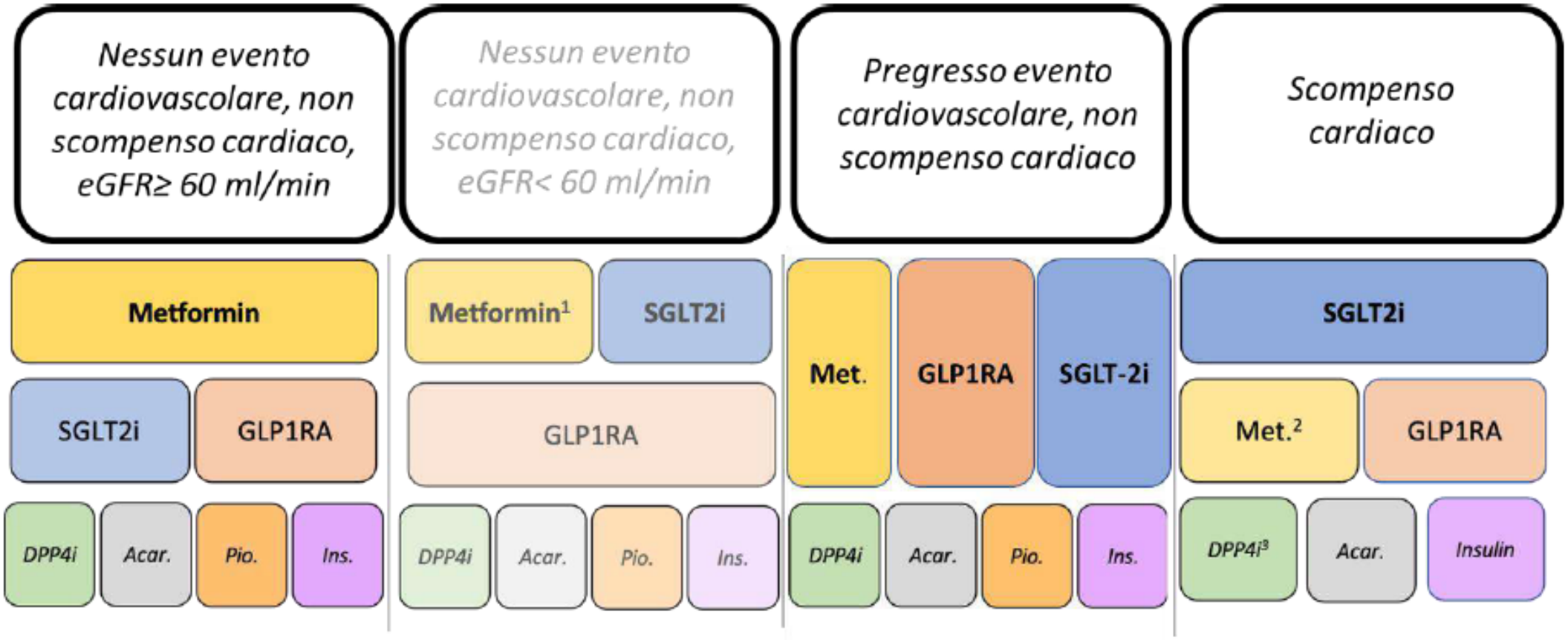
The **incretin effect** is due to gut hormones, **GLP-1** and **GIP** which are secreted in response to meal ingestion and are served to increase insulin secretion and supress glucagon secretion.

Reduced incretin effect result in hyperglycaemia and eventually in T2DM

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

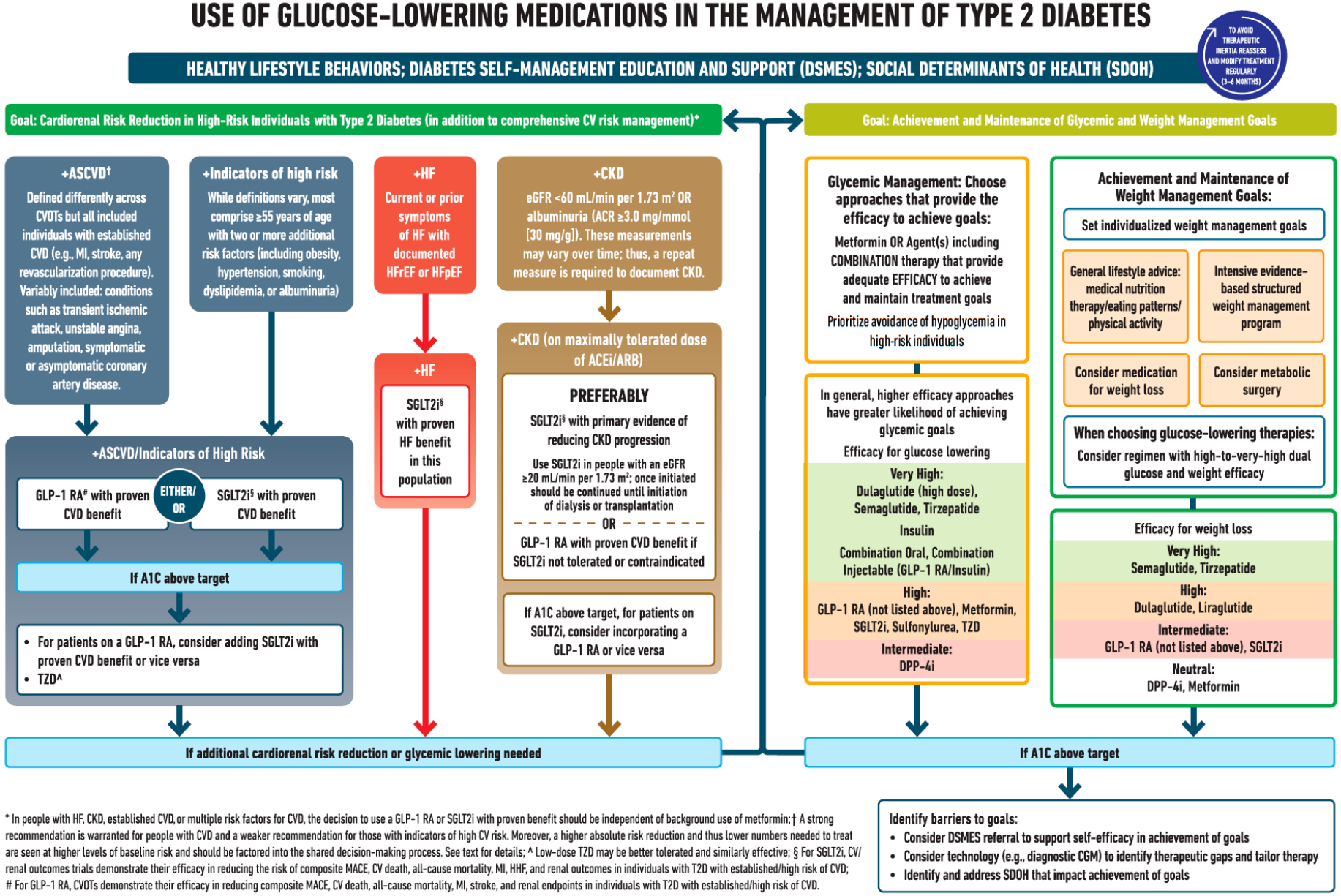
La terapia del diabete mellito di tipo 2

Versione aggiornata a dicembre 2022



[1]*Se la metformina non è controindicata per ridotto eGFR.*
[2]*Se la metformina non è controindicata per ridotta funzione cardiaca.*
[3]*Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.*
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

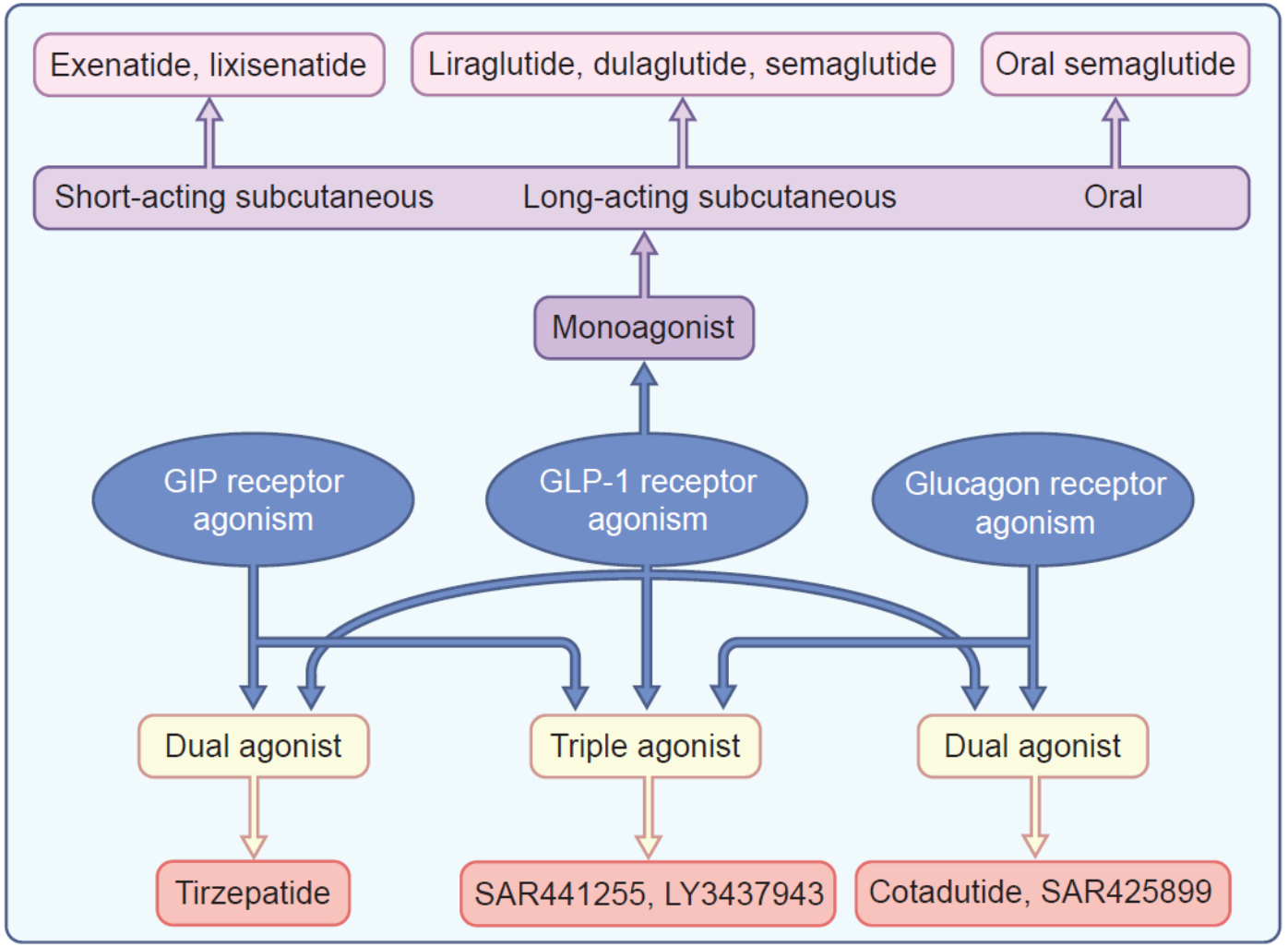
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

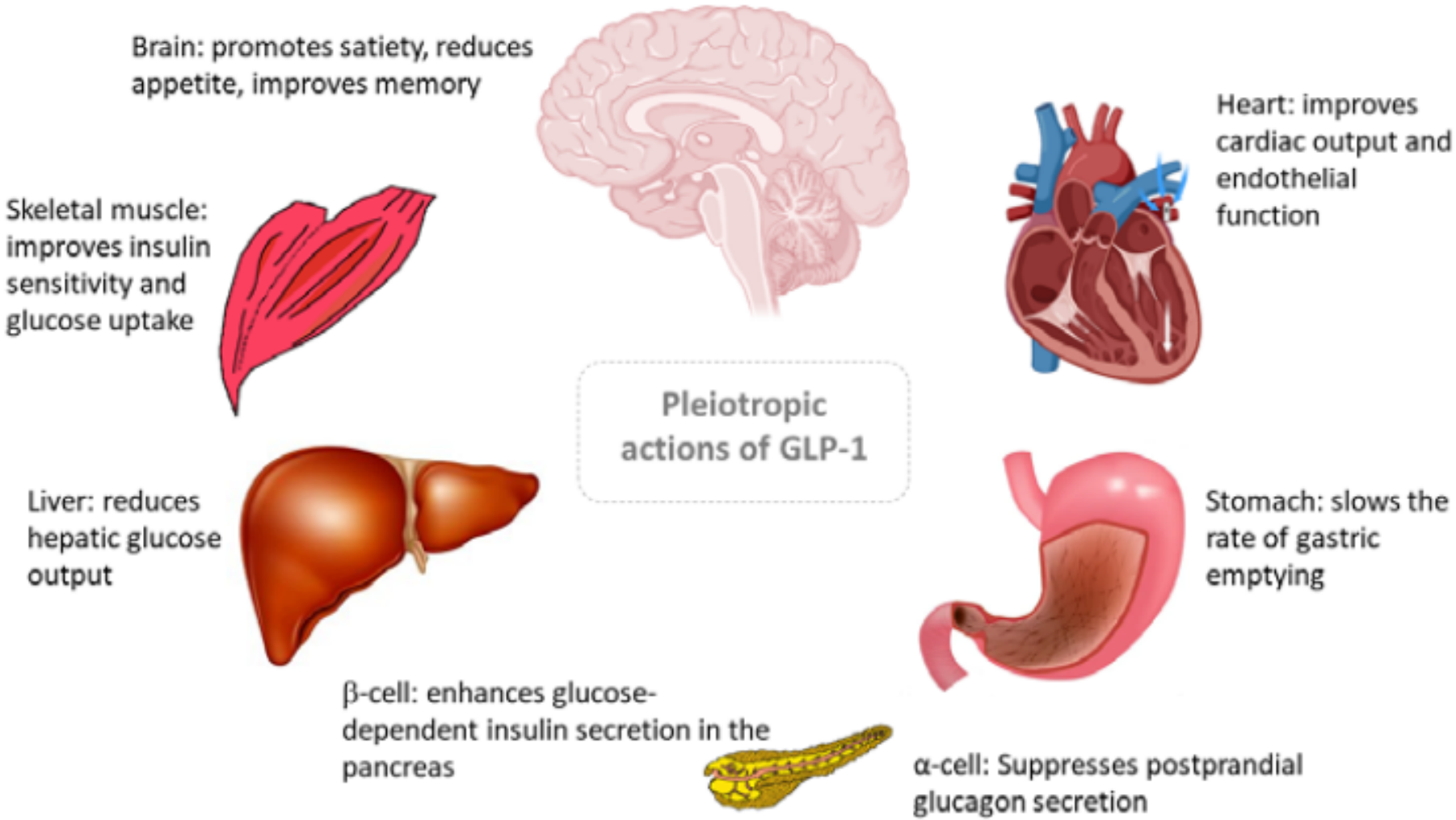
Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (84).

Schematic illustration of monoagonists, dual agonists and triple agonists based on GLP-1, GIP and glucagon receptor activation



Tschöp et al (2023) Diabetologia DOI 10.1007/s00125-023-05929-0

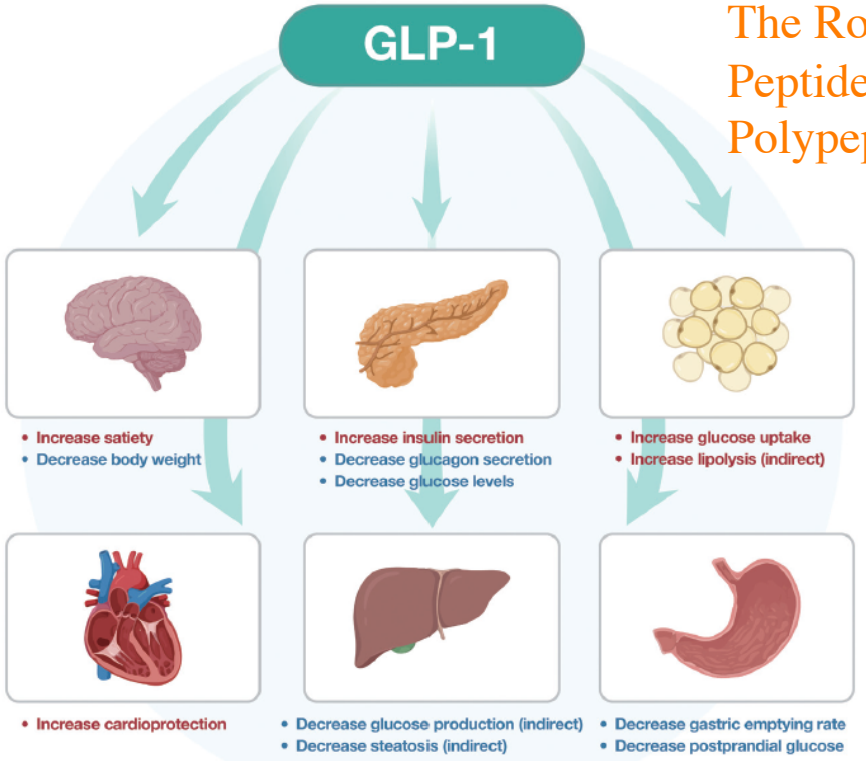
Pleiotropic actions of glucagon-like peptide 1.

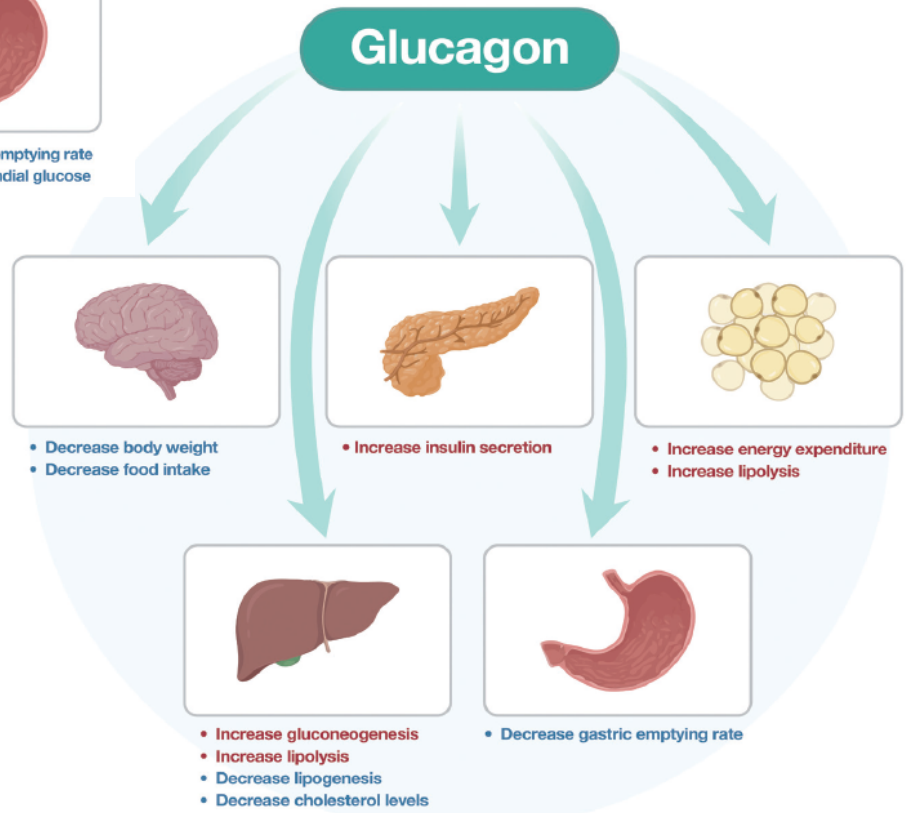


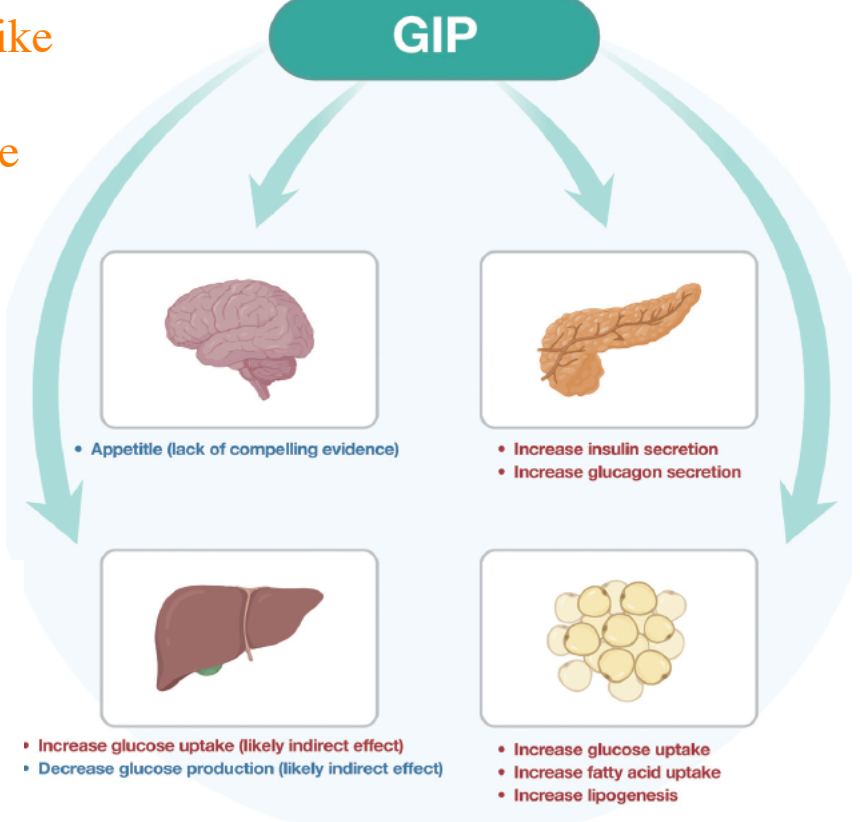
EMJ Innov. 2022.

The Road towards Triple Agonists: Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide and Glucagon Receptor - An Update

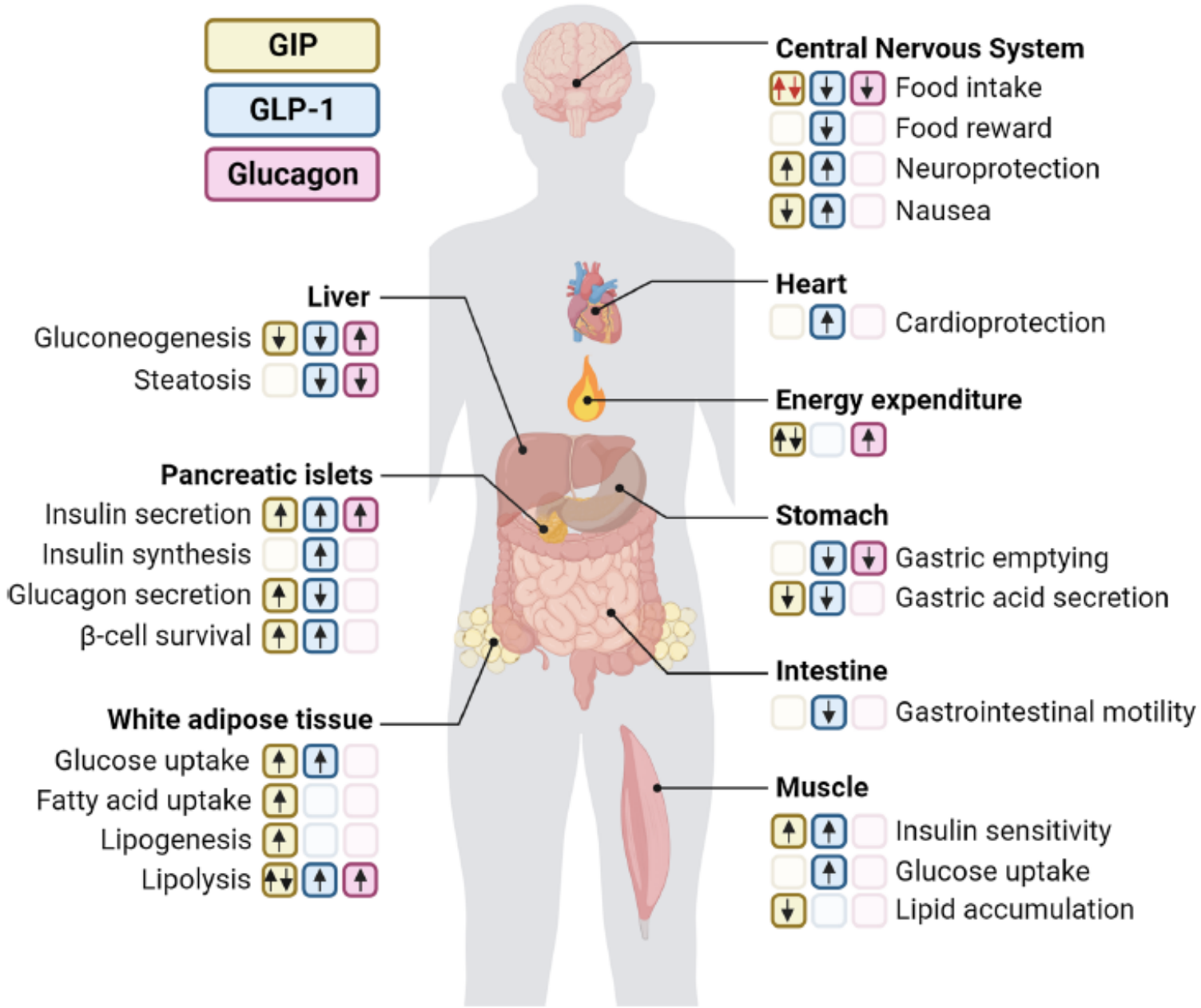
Endocrinol Metab 2024;39:12-22







Poly-Agonist Pharmacotherapies for Metabolic Diseases



Camille Allard

Drugs
https://doi.org/10.1007/s40265-023-01982-6

Pharmacological treatment of hyperglycemia in type 2 diabetes

Simeon I. Taylor, Zhinous Shahidzadeh Yazdi, and Amber L. Beitelshees

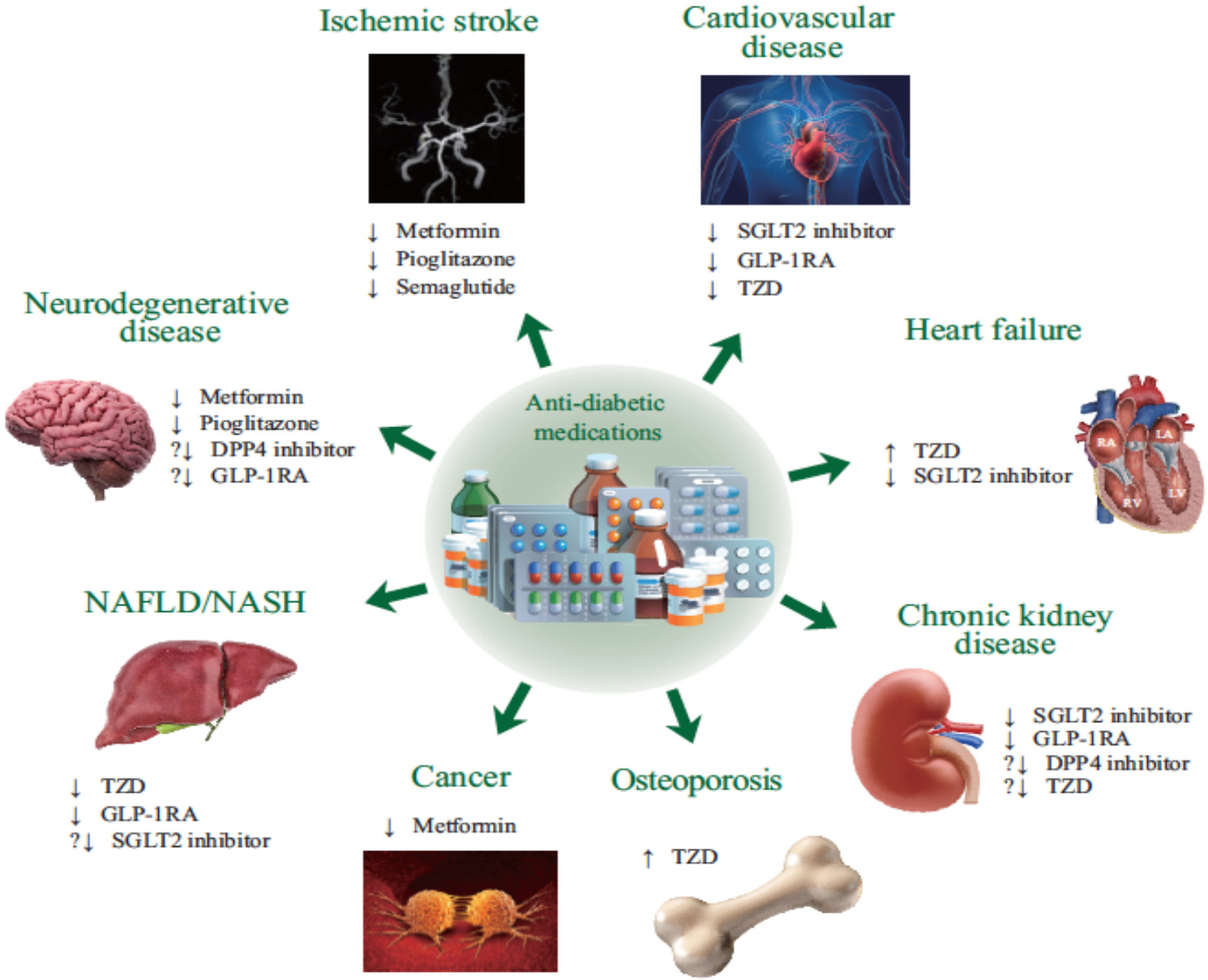
J Clin Invest. 2021;131(2):e142243.

Table 1. Twelve classes of drugs approved in the United States to decrease HbA1c in patients with T2D

Drug class	Approved drugs (US)	Baseline HbA1c	Δ HbA1c (%)	Selected safety issues	Comments
Biguanides	Metformin HCl Metformin extended release	8.4% 8.4%	Met-HCl: −1.8% (titrated dose) Met-XR: −1.0% (2000 mg/d)	Lactic acidosis; vitamin B_{12} deficiency; abdominal pain, diarrhea, nausea	Placebo-subtracted monotherapy. Sources: metformin HCl (92); metformin XR (93).
Sulfonylureas	Glimepiride Glipizide Glibenclamide (glyburide)	7.7% 7.6%	Glimepiride (mean, 3 mg/d): −0.6% Glipizide (5–20 mg/d): −0.6%	Hypoglycemia; weight gain; potential increased risk of CV mortality	HbA1c-lowering from baseline in patients inadequately controlled on metformin. Glimepiride data from PI for linagliptin. Glipizide data from PI for sitagliptin.
Thiazolidinediones	Pioglitazone Rosiglitazone	9.9% 8.9% 8.9%	Pioglitazone (30 mg/d): −0.8% Rosiglitazone (4 mg/d): −1.0% Rosiglitazone (8 mg/d): −1.2%	Peripheral edema; congestive heart failure; weight gain; bone fractures (esp. in females)	Source: PIs for 2 drugs. ΔHbA1c: placebo-subtracted data. PROactive suggested decreased risk of MACE-3 for pioglitazone.
Dipeptidylpeptidase-4 (DPP4) inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	8.6% 7.7% 8.1% 8.0%	Alogliptin (25 mg/d): −0.9% Linagliptin (5 mg/d): −0.4% Saxagliptin (5 mg/d): −0.8% Sitagliptin (100 mg/d): −0.7%	Angioedema (esp. with ACE inhibitor); joint pain; pancreatitis listed in some PIs	ΔHbA1c: placebo-subtracted data for saxagliptin; change from baseline for other drugs. Studies conducted in patients inadequately controlled on metformin. Source: PI for each drug.
Sodium-glucose cotransporter-2 (SGLT2) inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	7.95% 7.9% 7.9% 8.1%	Canagliflozin (300 mg/d): −0.77% Dapagliflozin (10 mg/d): −0.7% Empagliflozin (25 mg): −0.6% Ertugliflozin (15 mg): −0.7%	Genitourinary infections; increased risk of DKA; increased risk of amputations (canagliflozin, ertugliflozin)	Placebo-subtracted HbA1c-lowering in patients inadequately controlled on metformin. Source: PI for each drug. Decreased risk of MACE-3 for canagliflozin and empagliflozin.
Glucagon-like peptide 1 (GLP1) receptor agonists	Albiglutide Dulaglutide Exenatide ER Liraglutide Lixisenatide Semaglutide (s.c. injection) Semaglutide (oral)	8.1% 8.1% 8.6% 8.4% 7.95% 8.4% 8.1%	Albiglutide (30 mg/d): −0.9% Dulaglutide (1.5 mg/wk): −1.1% Exenatide ER (2 mg/wk): −1.5% Liraglutide (1.8 mg/d): −1.5% Lixisenatide (10 μg/d): −0.73% Semaglutide (1 mg/wk, s.c.): −1.4% Semaglutide (14 mg/d, p.o.): −1.3%	Nausea and vomiting; PI for some drugs lists pancreatitis; contraindicated in case of personal or familial history of MTC or MEN2	HbA1c-lowering from baseline in patients inadequately controlled on metformin. Source: PI for each drug. Clinical trials: decreased risk of MACE-3 for liraglutide, dulaglutide, semaglutide, and albiglutide.
Insulins	Rapid-acting insulins Basal insulins	Various	Dose-dependent	Hypoglycemia; weight gain	HbA1c-lowering depends on insulin dose.
α-Glucosidase inhibitors	Acarbose	8.46%	Acarbose (50–100 mg, tid): −0.65%	Diarrhea, flatulence, abdominal discomfort	Placebo-subtracted HbA1c-lowering on top of metformin. Source: PI.
Dopaminergic agonists	Bromocriptine	8.3%	Bromocriptine (0.8–1.6 mg/d): −0.4%	Retroperitoneal fibrosis; orthostatic hypotension	Change from baseline in patients inadequately controlled on 1–2 oral drugs. Source: PI.
Bile acid sequestrants	Colesevelam	8.2%	Colesevelam (3.8 g/d): −0.4%	Increased susceptibility to vitamin K deficiency	Change from baseline HbA1c in patients receiving background therapy with metformin. Source: PI.
Meglitinides	Repaglinide	8.3%	Repaglinide (0.5–4 mg, tid): −1.08%	Hypoglycemia	HbA1c-lowering corrected for effect of metformin monotherapy. Source: PI.
	Nateglinide	8.7%	Nateglinide (120 mg, tid): −0.6%		
Amylinomimetic	Pramlintide	9.0%	Pramlintide (120 μg, tid): −0.3%	Hypoglycemia; contraindicated in gastroparesis or hypoglycemia unawareness	HbA1c-lowering assessed relative to the effects of background insulin therapy. Source: PI.

Most data were obtained from FDA-approved prescribing information (PI). When sulfonylureas were approved, the PI did not report HbA1c-lowering; so efficacy data for glimepiride and glipizide were obtained from PI for linagliptin and sitagliptin, respectively. The table lists HbA1c-lowering for monotherapy with metformin (92, 93). For other drugs, the table lists efficacy data for second-line therapy — most often in patients who were inadequately controlled on metformin. ACE, angiotensin-converting enzyme; CV, cardiovascular; DKA, diabetic ketoacidosis; ER, extended release; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer.

Extra-glycemic effects of anti-diabetic medications



Endocrinol Metab 2022;37:415-429

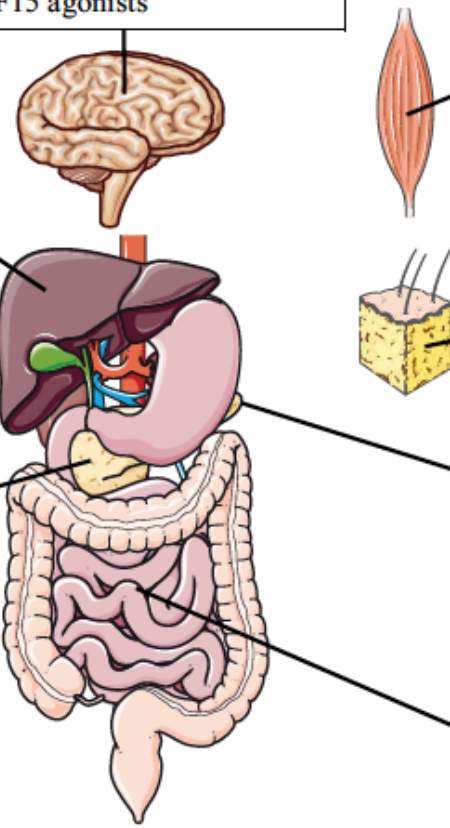
What is on the horizon for type 2 diabetes pharmacotherapy? – An overview of the antidiabetic drug development pipeline

Liver
- FGF21 analogues
- Fructose-1,6-biphosphatase inhibitors
- Glucokinase activators
- Glimins
- GLP-1/glucagon/GIP receptor agonists
- Glucagon receptor antagonists
- Lyn kinase activators

Pancreas
- Amylin receptor agonists
- Glucokinase activators
- Glimins
- GLP-1/glucagon/GIP receptor agonists

Multiple tissues
- Direct AMPK activators
- PTB-1B inhibitors

Central nervous system
- GDF15 agonists



Muscle tissue
- Activin type II receptor modulators
- Glimins
- Glucagon receptor antagonists
- PTB-1B inhibitors

Adipose tissue
- FGF21 analogues
- Lyn kinase activators

Kidneys
- SGLT inhibitors

Intestines
- Amylin receptor agonists
- Glucokinase activators
- GLP-1 receptor agonists
- GPR119 agonists
- SGLT inhibitors

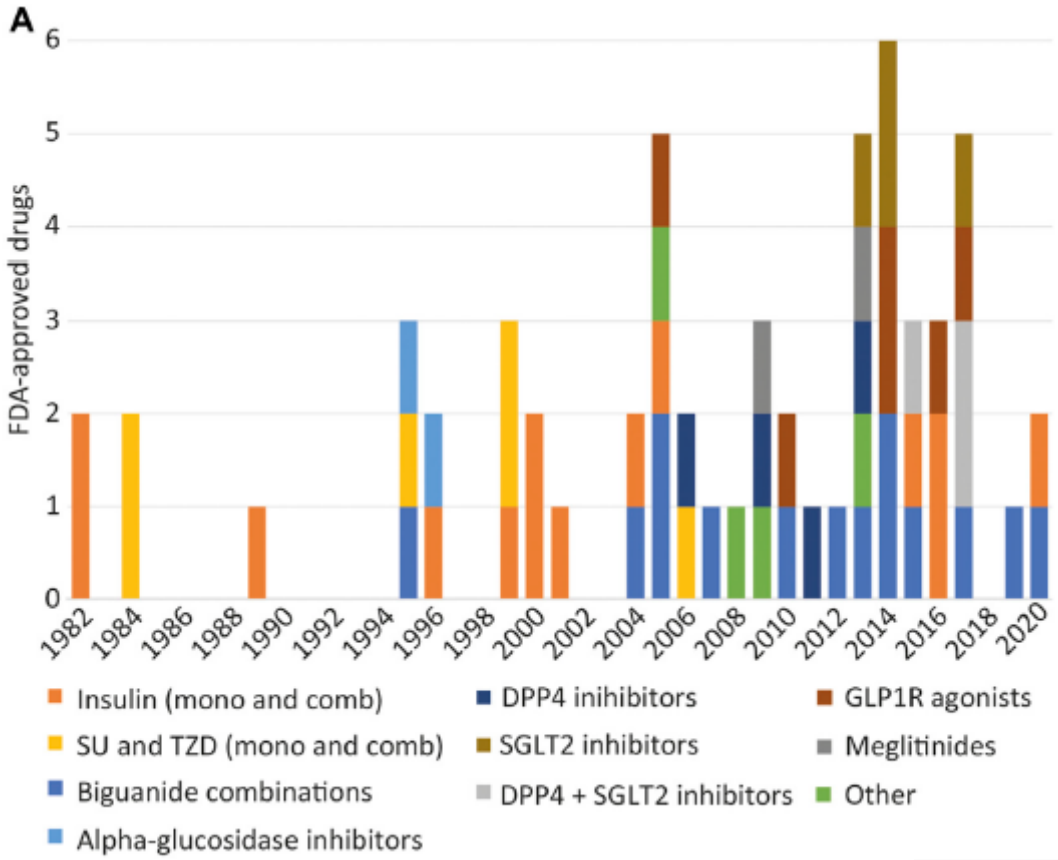
Karl Sebastian Johansson
Expert Opinion on Drug Discovery
10.1080/17460441.2020.1791078

Polyagonists in Type 2 Diabetes Management

Table 1 Polyagonists in clinical trials

Agent	Mechanism of action	Route and frequency of administration	Active trials	Phase
Tirzepatide (LY3298176)	GLP-1/GIP dual agonists	Subcutaneous once a week	Multiple (see text)	3
CT-868	GLP-1/GIP dual agonists	Subcutaneous once a day	NCT05110846	2
VK2735/VK2735-oral	GLP-1/GIP dual agonists	Subcutaneous once a week/oral once daily	NCT05203237	1
LY-3537031	GLP-1/GIP dual agonists	Subcutaneous	NCT04648865	1
CT-388	GLP-1/GIP dual agonists	Subcutaneous once a week	NCT04838405	1
DR10627, DR10628	GLP-1/GIP dual agonists	Subcutaneous	CTR20232870	1
BI456906	GLP-1/GCGR dual agonist	Subcutaneous once or twice a week	NCT06066528	3
HEC88473	GLP-1/FGF21 dual agonist	Subcutaneous once a week	NCT05943886	1
Maridebart cafraglutide (AMG133)	GLP-1R agonist/GIPR antagonist	Subcutaneous injection once in 4 weeks	NCT05669599	2
Retatrutide (LY3437943)	GLP-1, GIP, GCGR triagonist	Subcutaneous once a week	NCT05929079	3
DR10624	GLP-1, GCGR, FGFR21 triagonist	Subcutaneous injection	NCT05378893	1

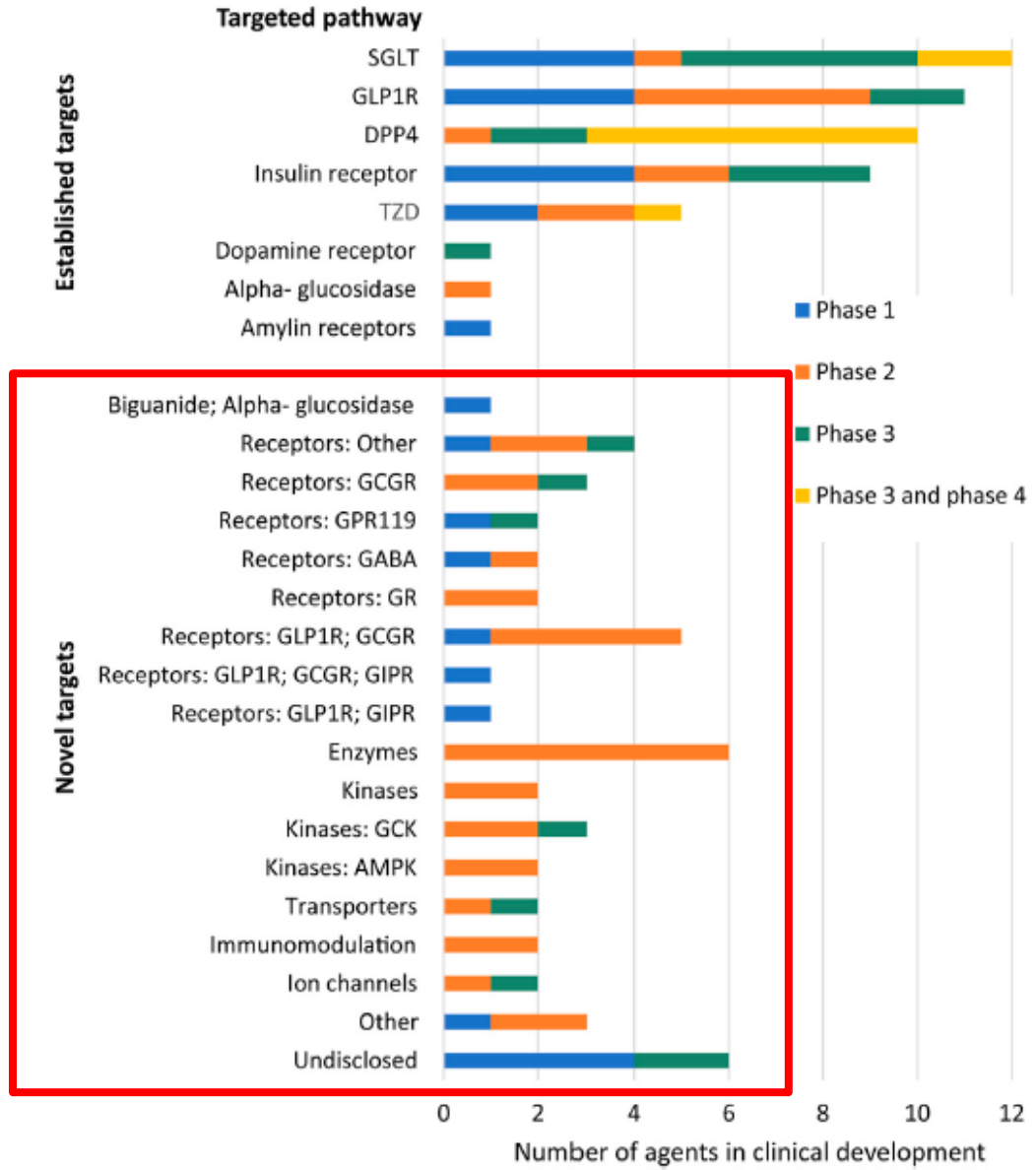
Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales



Dahlén AD,

Front. Pharmacol. 12:807548.
doi: 10.3389/fphar.2021.807548

The molecular targets of the 99 anti-diabetic agents in clinical trials



DPP4, Dipeptidyl peptidase 4; GLP-1R, Glucagon-like peptide-1 (GLP-1) receptor; SGLT2, Sodium-glucose co-transporter-2; TZD, Thiazolinediones; GCGR, Glucagon receptor; GPR119, Glucose-dependent insulinotropic receptor (G-Protein coupled receptor 119); GR, Glucocorticoid receptor; GIPR, Gastric Inhibitory Polypeptide Receptor; GCK, glucokinase; AMPK, 5′-AMP-activated protein kinase.

L'evoluzione della terapia del diabete tipo 2
- Take home message -

Terapia basata sul raggiungimento del target glicemico

Terapia basata sul target "globale" del diabete

Terapia sempre più personalizzata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15 CREDITI FORMATIVI

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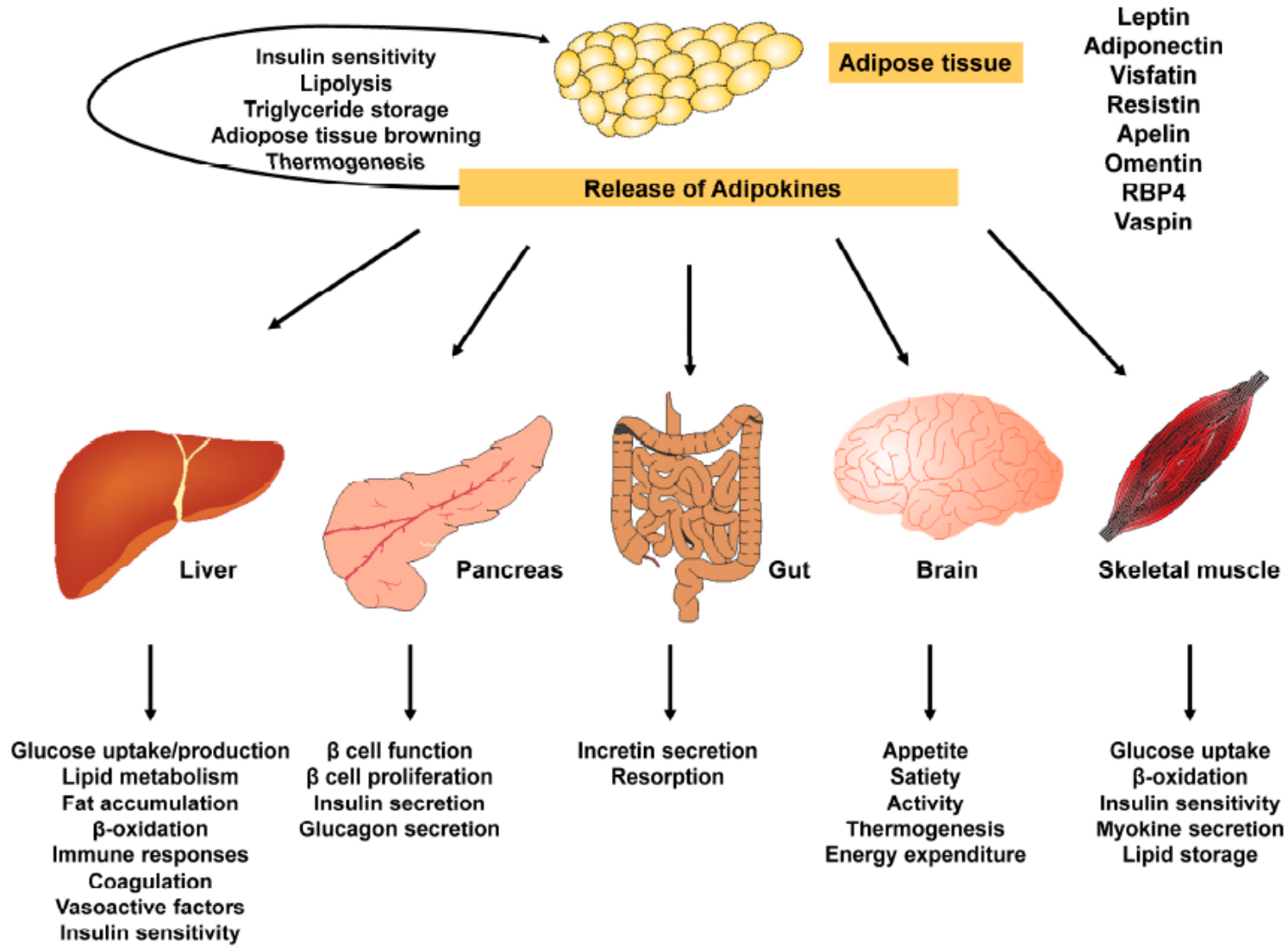
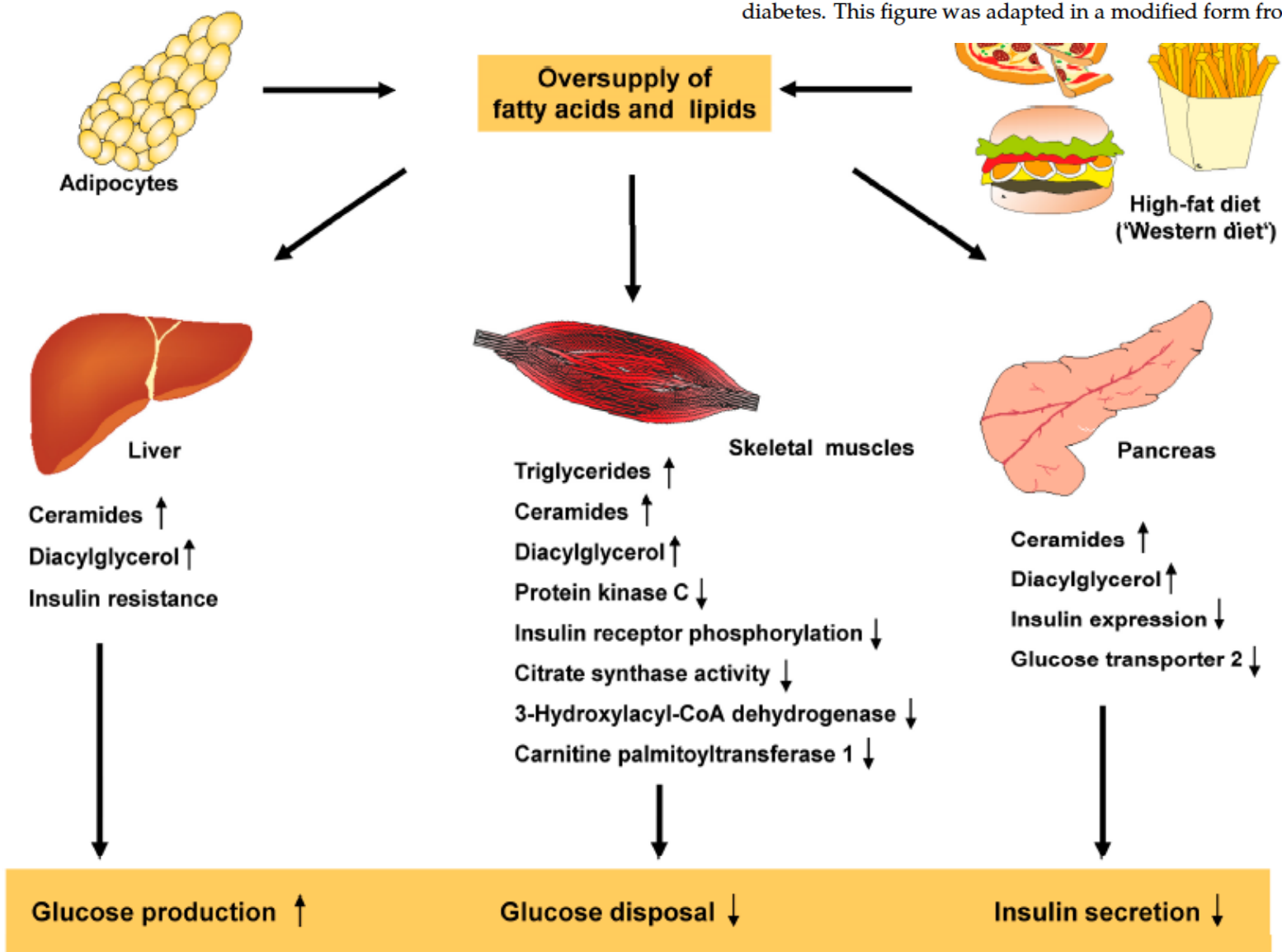
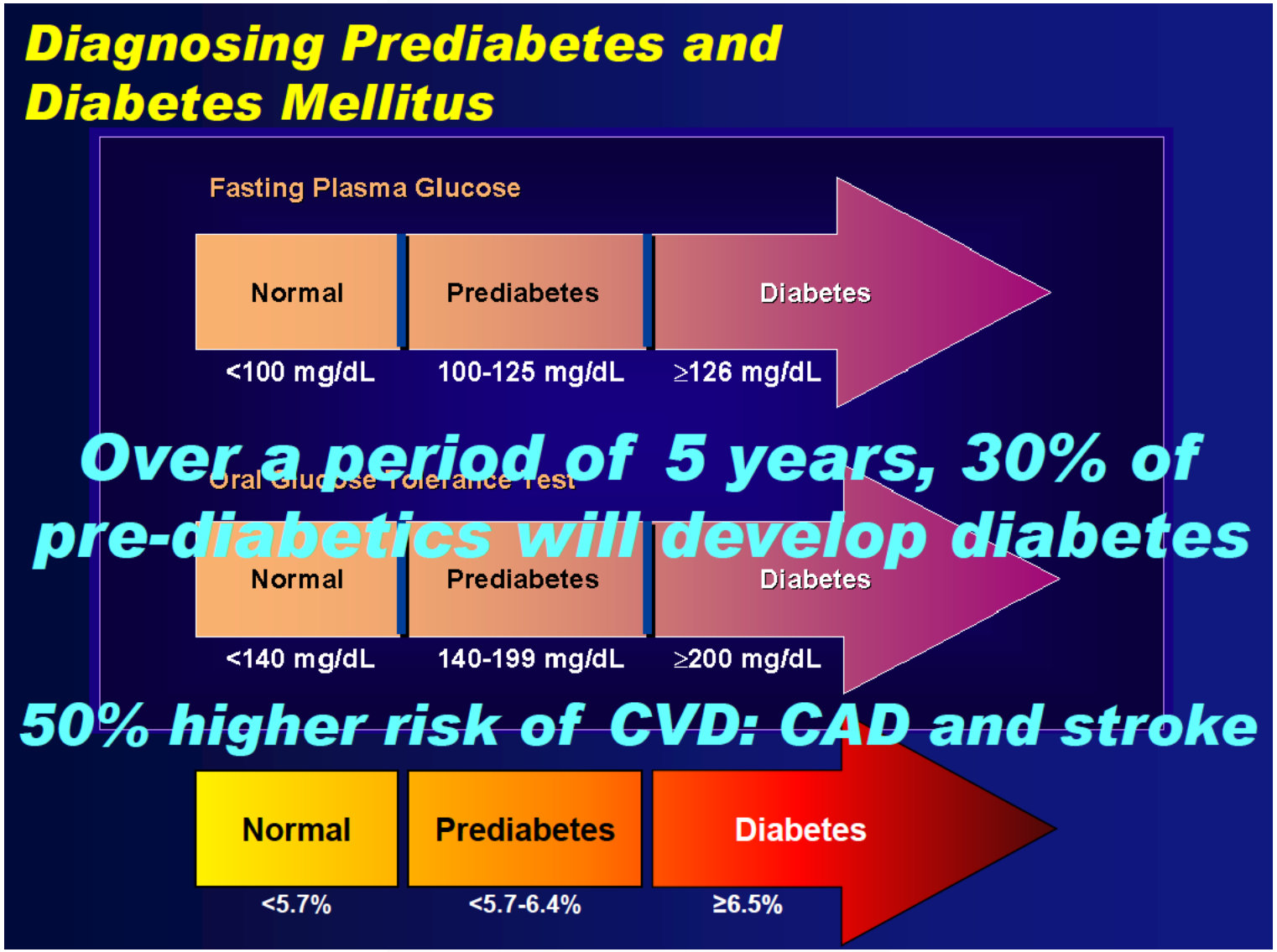


Figure 4. Adipokines released by adipose tissue are central in the control of endocrine and secretory functions of many organs. The adipose tissue secretes various molecules known as adipokines which act as powerful signal molecules. The activity of these adipokines impacts biological processes in liver, pancreas, gut, brain, skeletal muscles and many other organs.

Figure 6. Fats and lipids in the pathogenesis of type 2 diabetes. An overabundance of fatty acids and ıed in fat (which cannot be stored in adipocytes), lead to ılate in peripheral tissues such as the liver, muscles and pancreas. This accumulation triggers numerous molecular changes that result in increased glucose production, lowered glucose disposal and impaired insulin secretion. These factors are hallmarks of diabetes. This figure was adapted in a modified form from [65].



Diagnosing Prediabetes and Diabetes Mellitus



Over a period of 5 years, 30% of pre-diabetics will develop diabetes

50% higher risk of CVD: CAD and stroke

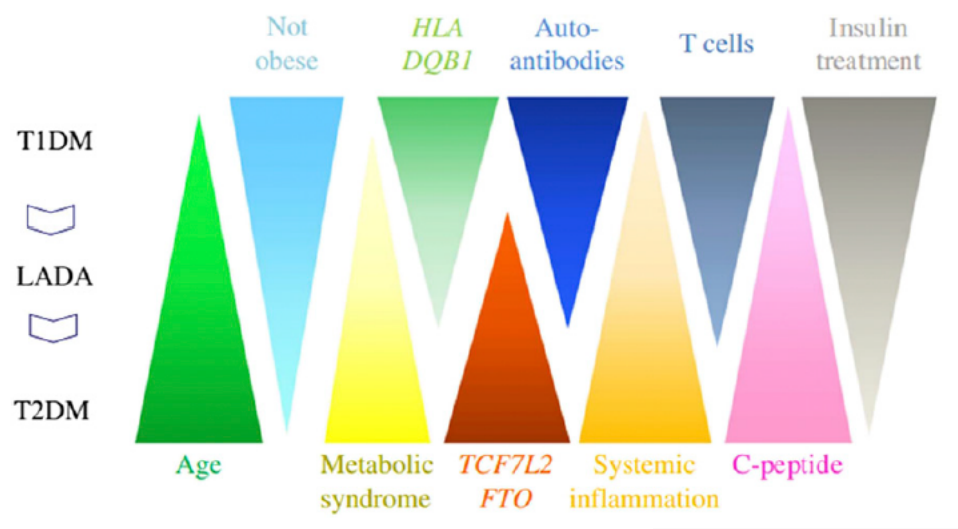
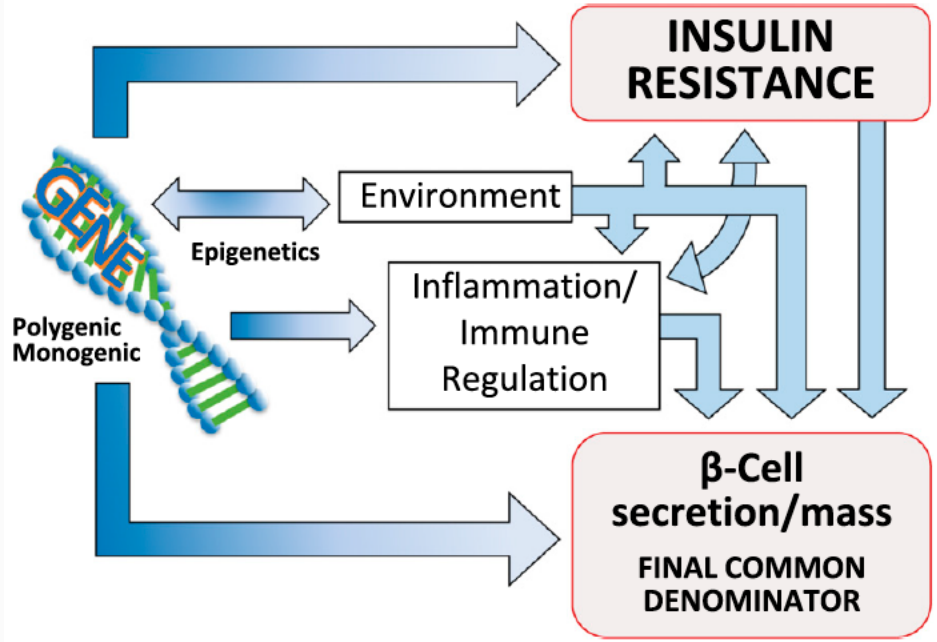
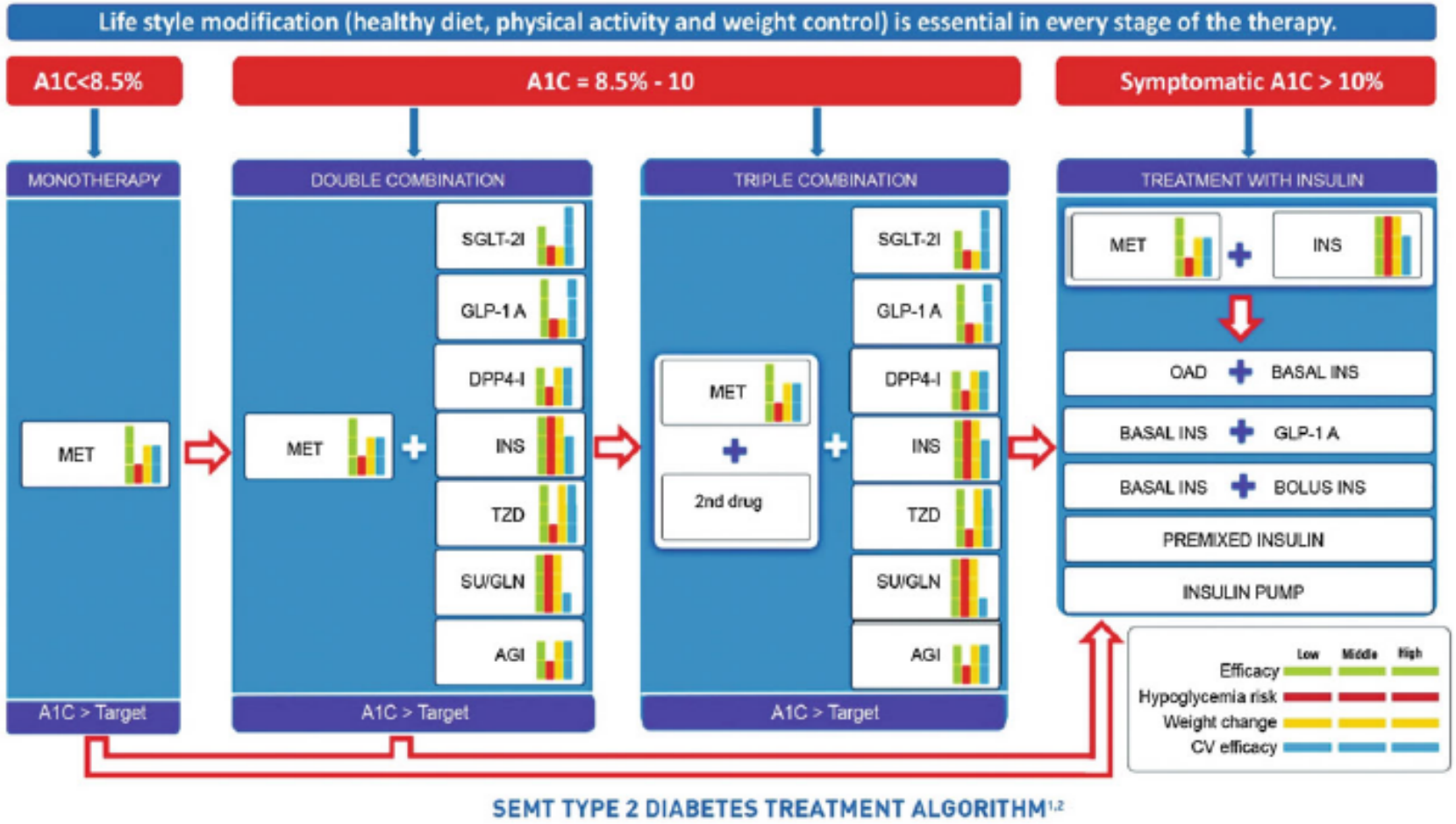


Figure 2—Genetic determinants influence IR (whether centrally or peripherally induced), loss of β-cell function and mass, environmental triggers (such as viruses, endocrine disruptors, food advanced glycosylation end products, gut biome), and immune modulation and inflammation. Singly or, more commonly, in various combinations, these factors converge on the genetically susceptible β-cell, impinge on β-cell function and biology, and orchestrate the shift from normoglycemia to hyperglycemia. As this process takes place regardless of subtype of DM, the dysfunctional β-cell is the final common denominator in all DM.



Glucose Lowering Treatment Modalities of Type 2 Diabetes Mellitus



SEMT TYPE 2 DIABETES TREATMENT ALGORITHM[1,2]

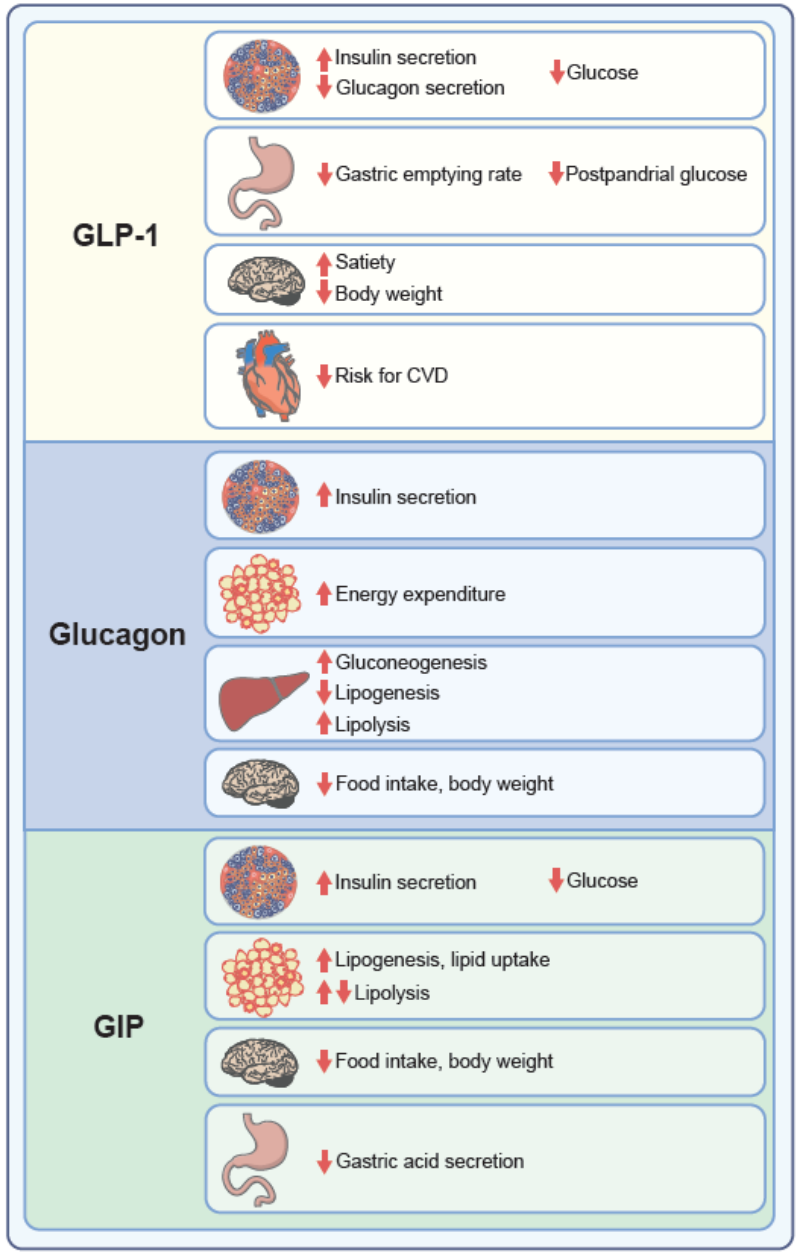
[1]If A1C is >7% or above the individual target, then the treatment should be changed. [2]MET is the preferred monotherapy drug. If MET is contraindicated or there is intolerance for MET, treatment with another drug can be initiated.

A1C, glycated HbA1c; MET, metformin; SGLT2-I, sodium glucose co-transporter 2 inhibitor; GLP-1A, glucagon-like peptide-1 receptor agonist; DPP4-I, Dipeptidyl peptidase-4 inhibitor; INS, insulin; TZD, thiazolidinedione; SU, sulphonylurea; GLN, glinide; AGI, alpha-glucosidase inhibitor; CV, cardiovascular.

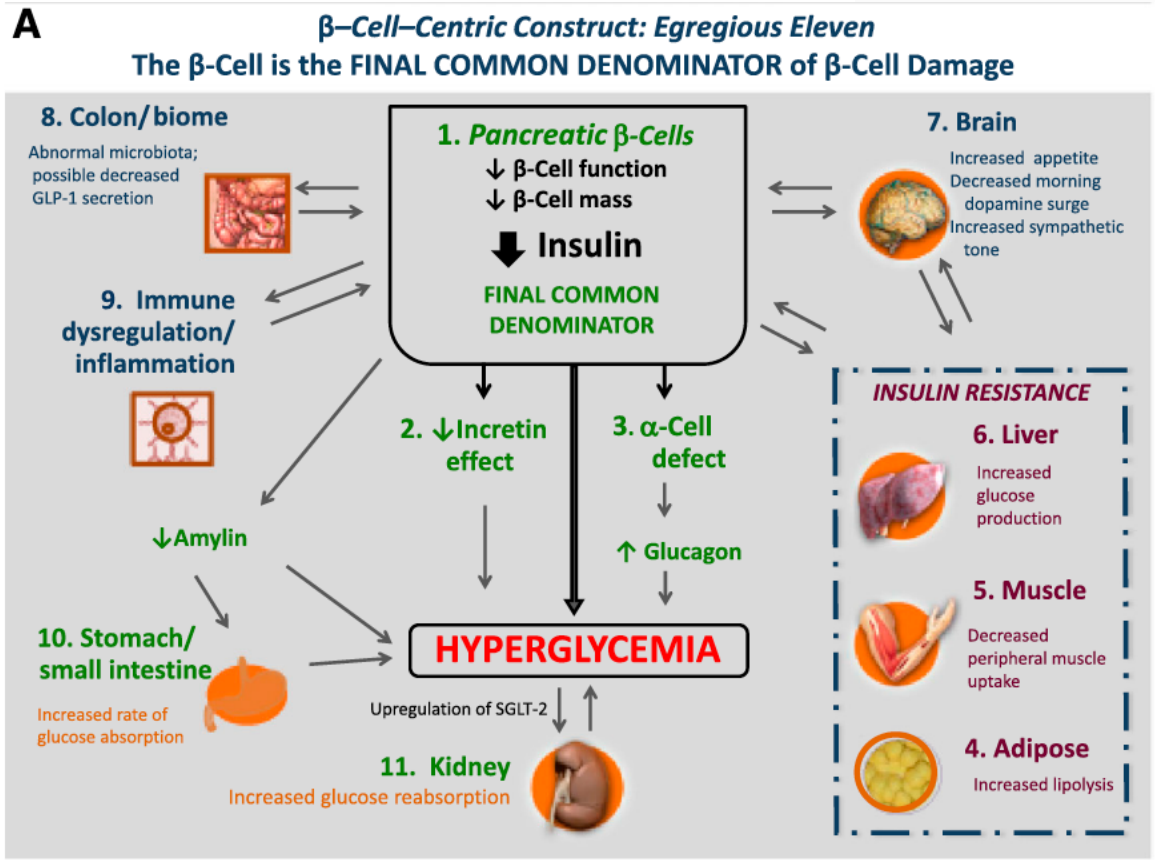
Fig. 2 Antiglycemic agent selection due to efficacy, Hba1c targets, and co-morbidities according to The Society of Endocrinology and Metabolism of Turkey

Adv Exp Med Biol - Advances in Internal Medicine
https://doi.org/10.1007/5584_2020_516

The clinically most relevant mechanisms of action of GLP-1, glucagon and GIP



Tschöp et al (2023) Diabetologia DOI 10.1007/s00125-023-05929-0


A
β–Cell–Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage
8. Colon/biome
Abnormal microbiota; possible decreased GLP-1 secretion
1. Pancreatic β-Cells
↓ β-Cell function
↓ β-Cell mass
Insulin
FINAL COMMON DENOMINATOR
7. Brain
Increased appetite
Decreased morning dopamine surge
Increased sympathetic tone
9. Immune dysregulation/ inflammation
2. ↓Incretin effect
3. α-Cell defect
INSULIN RESISTANCE
6. Liver
Increased glucose production
↓Amylin
↑ Glucagon
5. Muscle
Decreased peripheral muscle uptake
10. Stomach/ small intestine
Increased rate of glucose absorption
HYPERGLYCEMIA
Upregulation of SGLT-2
4. Adipose
Increased lipolysis
11. Kidney
Increased glucose reabsorption