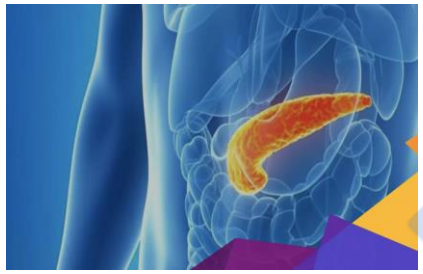
Greetings from Nepal



Novel Therapeutics in Diabetes

Ratna Mani Gajurel

Professor , TU Maharajgunj Medical campus

President, Society of Internal medicine of Nepal (SIMON)

Immediate Past President, Cardiac Society of Nepal

Outline of my presentations

- Introduction
- Burden of disease/ Epidemiology
- Screening and diagnosis
- Disease prevention
- Comprehensive medical evaluation and assessment of comorbidities
- Clinical manifestation
- Management
- Novel therapy in Diabetes

Disclosure

- No conflict of interest

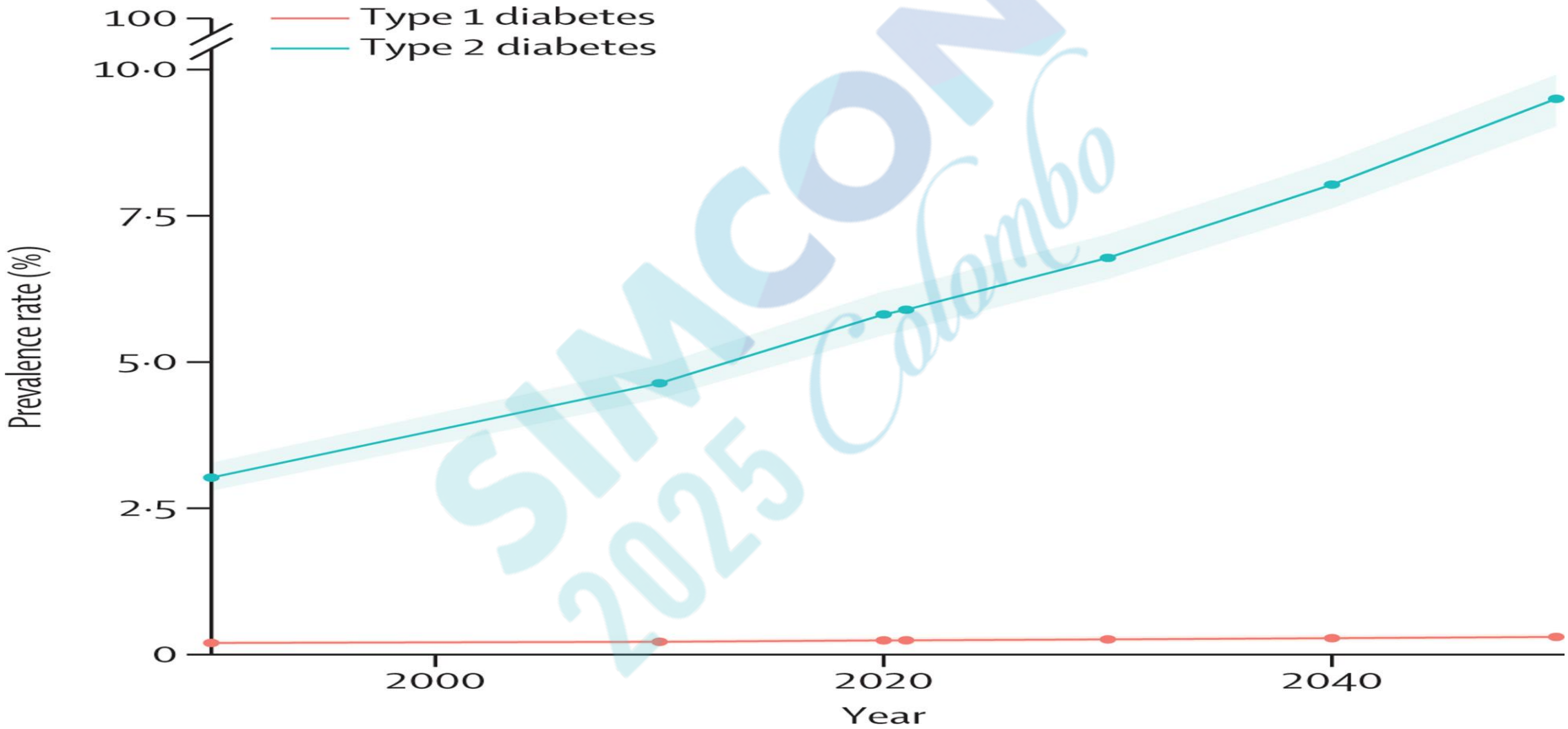
Novel Therapeutics in Diabetes

537 million
adults are living with diabetes

3 in 4 adults with diabetes
live in low-and middle income countries

6.7 million
deaths due to diabetes in 2021

International Diabetes Federation


Type 1 diabetes
Type 2 diabetes
100
10·0
7·5
5·0
2·5
0
Prevalence rate (%)
2000
2020
2040
Year

Burden of Diabetes Mellitus worldwide

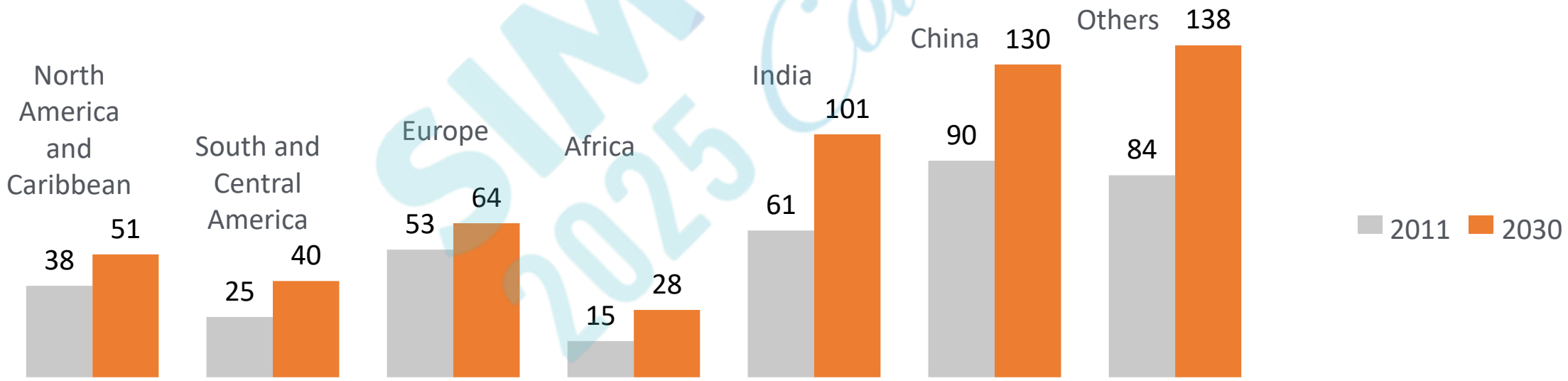
- 1990: Global age standarized prevalance was 3.2%
- 2021: 6.1% (90.5% increase from 1990)
- 2050: 9.5% (61.2% increase from 2021)

The Lancet 2023 402203-234DOI: (10.1016/S0140-6736(23)01301-6)

Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021. Results. Institute for Health Metrics and Evaluation. 2024

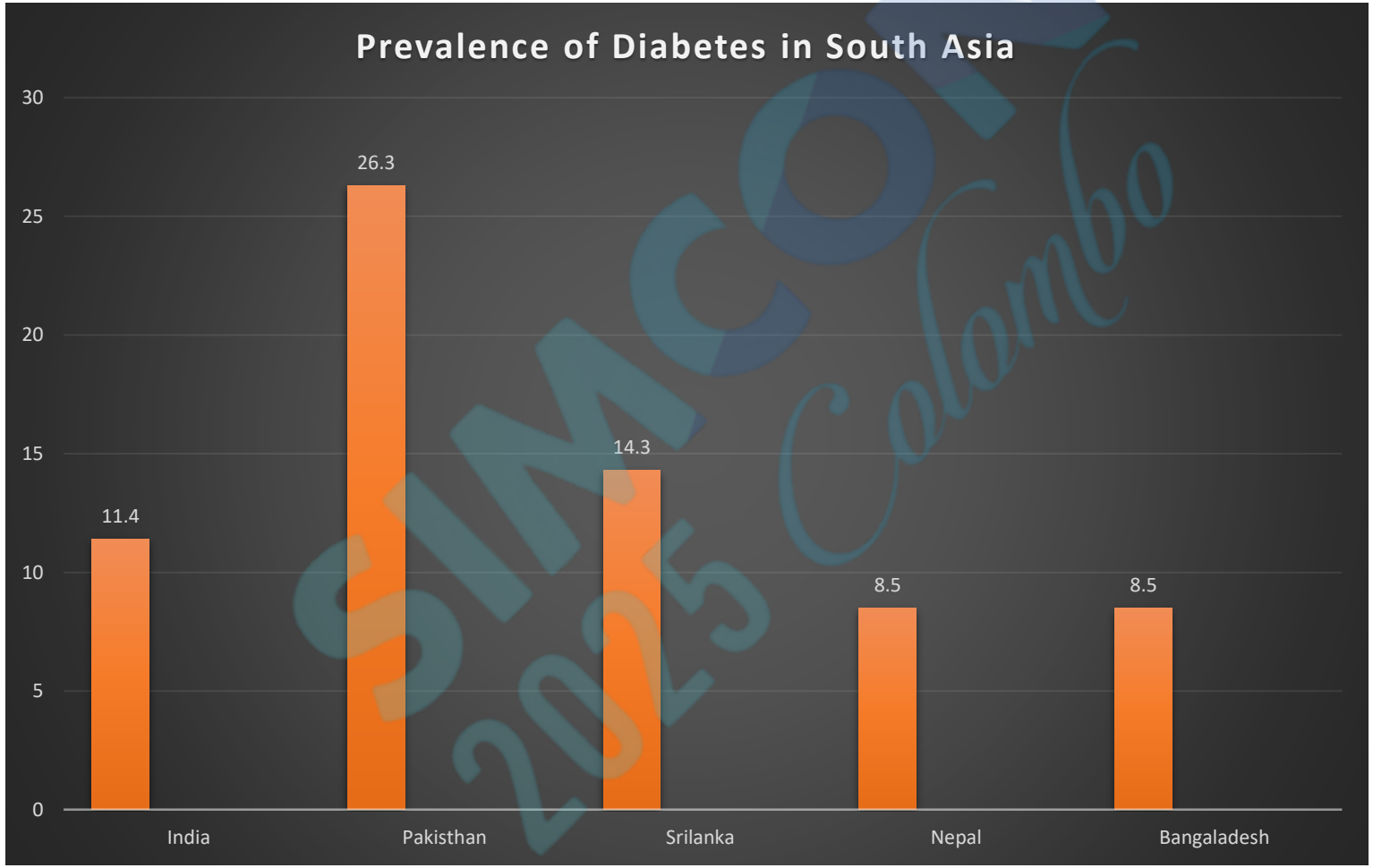
Diabetes

- **Every 10 seconds... Two people develop diabetes**
- The number of patients with diabetes worldwide is expected to increase from 366 million in 2011 to 552 million in 2030



- International Diabetes Federation. IDF Homepage. International Diabetes Federation 2011. Available from: http://www.idf.org/.

Prevalence of DM in South Asia



BMJ 2025; 390 doi: https://doi.org/10.1136/bmj-2024-079801 (Published 12 August 2025)

BMJ Journals

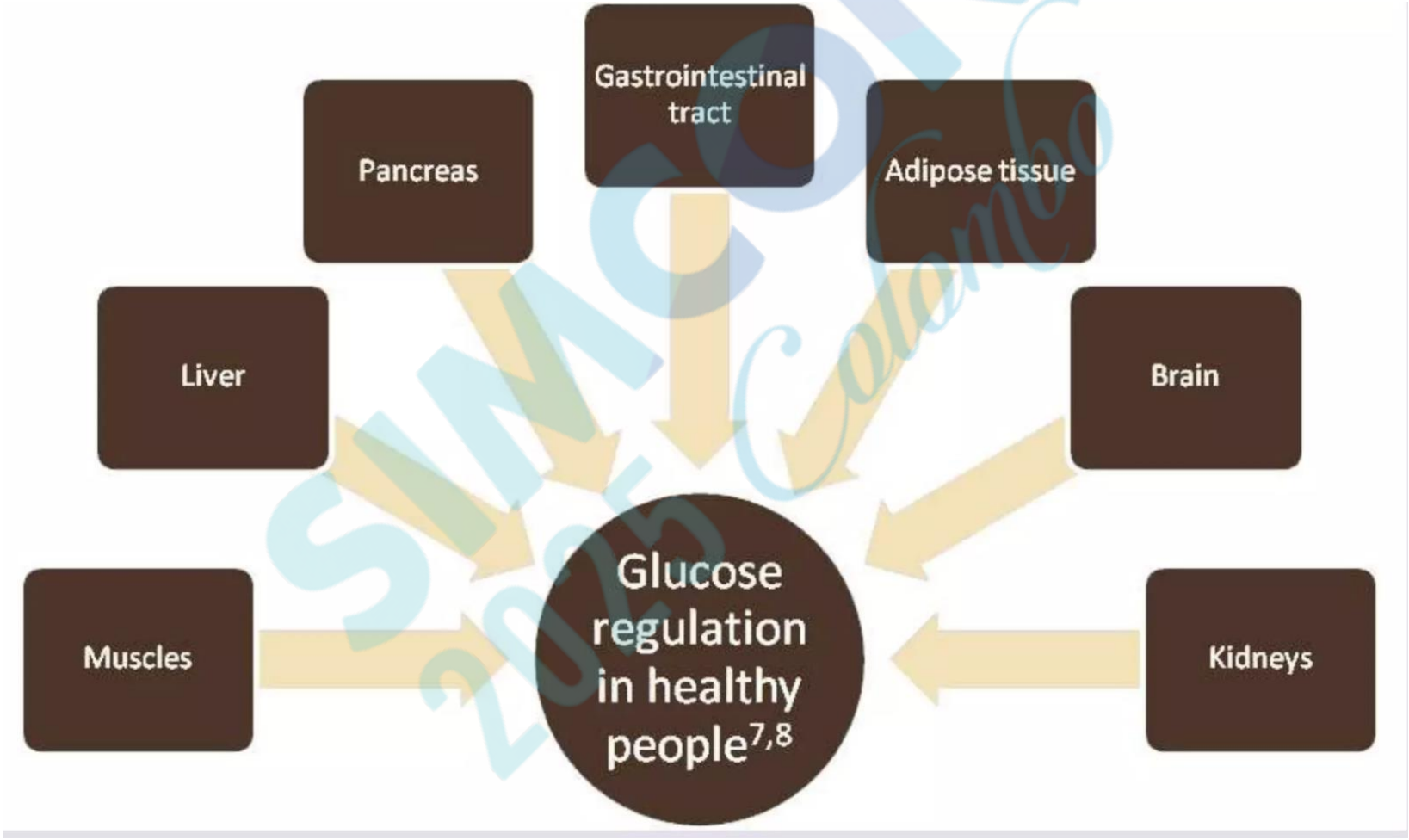
BMJ Open Diabetes Research & Care

Prevalence of diabetes and pre-diabetes in Sri Lanka: a new global hotspot–estimates from the Sri Lanka Health and Ageing Survey 2018/2019

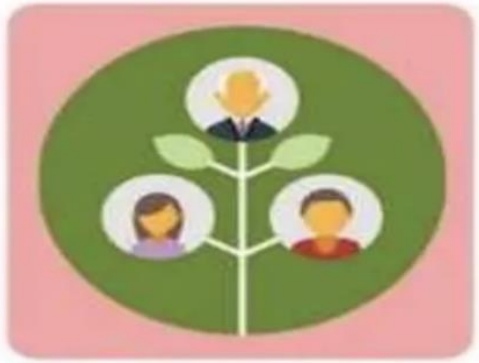
Author affiliations • Ravindra Prasan Rannan-Eliya [1], Nilmini Wijemunige [1], Prasadini Perera [2], Yasodhara Kapuge [1], ... 14 Show all authors

Sri Lanka has a very high diabetes prevalence, significantly higher than previous estimates of 8%–15% and higher than current global estimates for any other Asian country.

Physiology of glucose regulation in healthy people



Risk factors that increase the chances of diabetes



Family History of Diabetes

Obesity

Age - 30 years and above

Sedentary Lifestyle

Unhealthy Diet

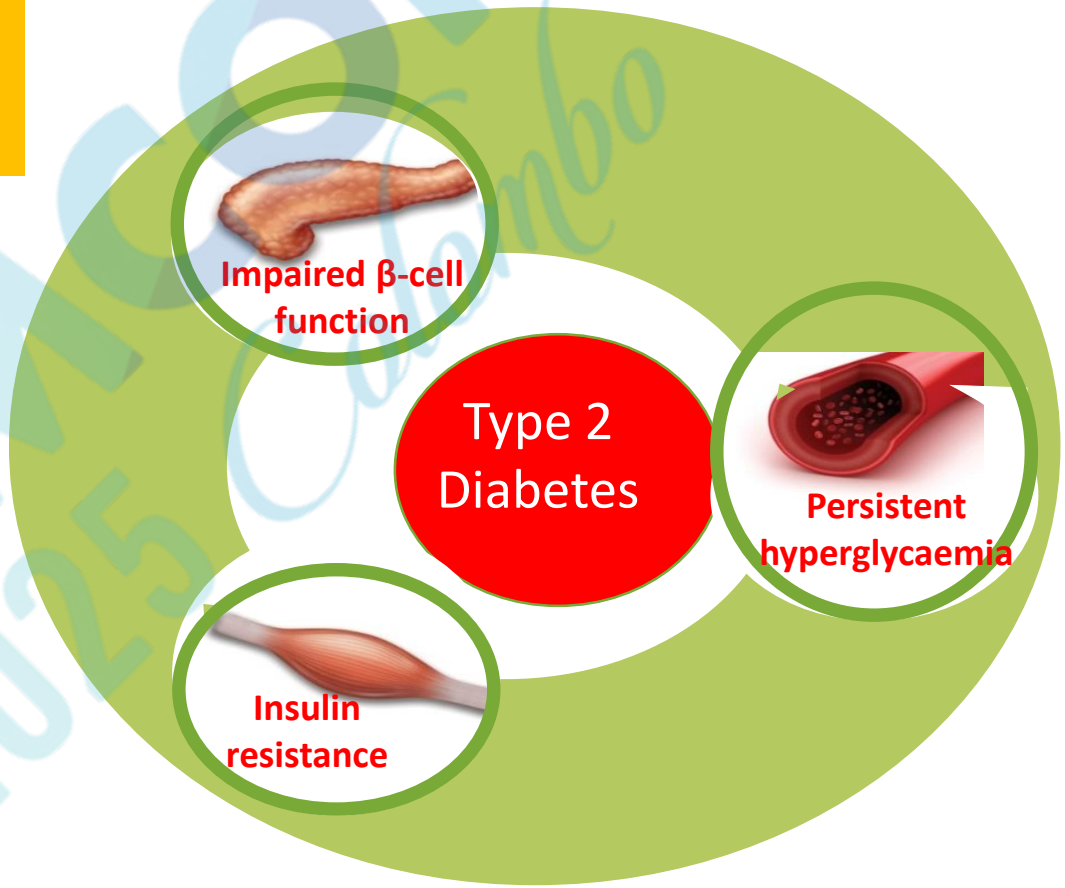
High Blood Pressure

Stress

History of Gestational Diabetes

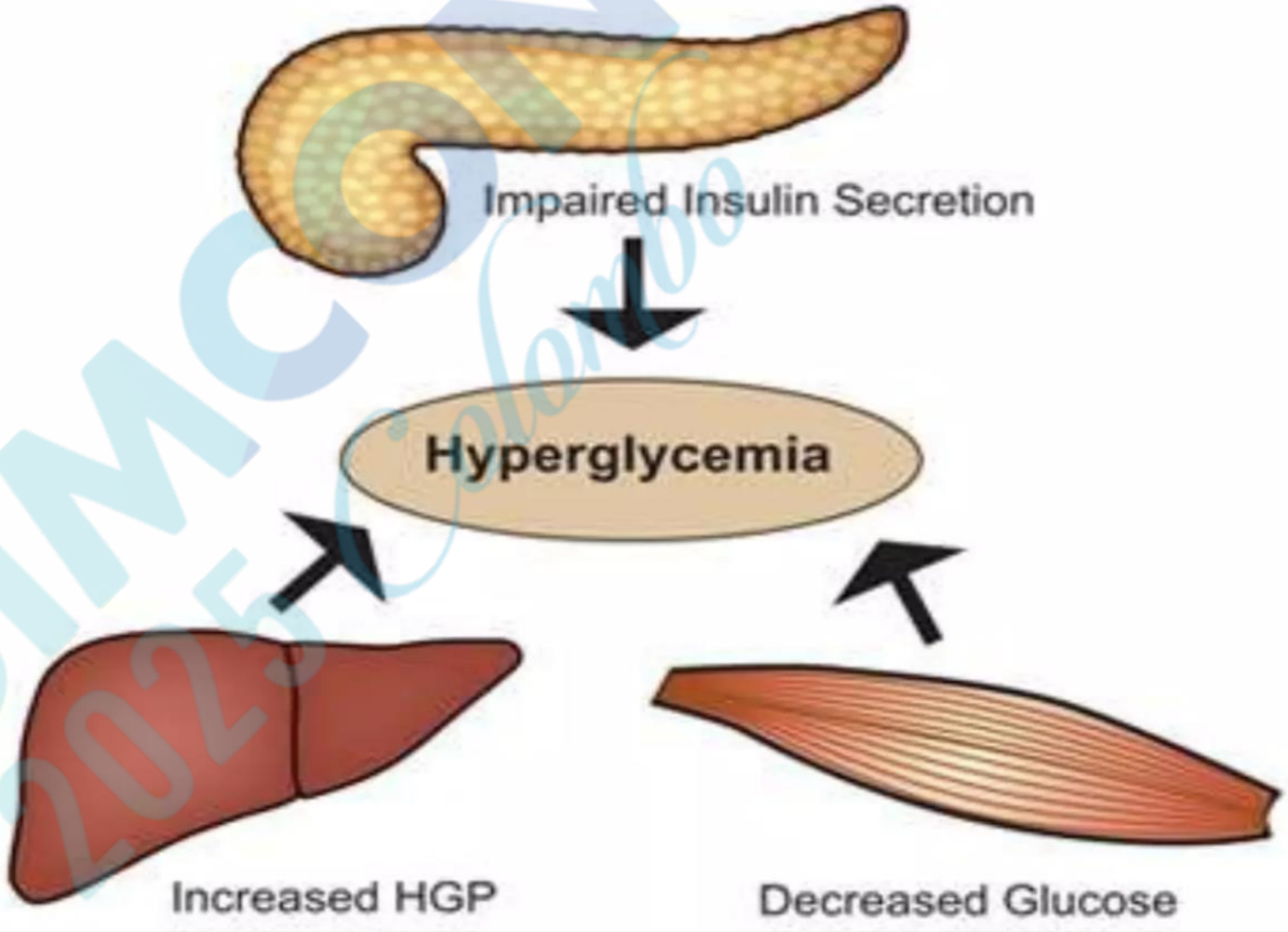
Pathophysiology of Diabetes

T2D is a dysregulation of glucose homeostasis characterized by persistent hyperglycaemia, impaired β-cell function and insulin resistance

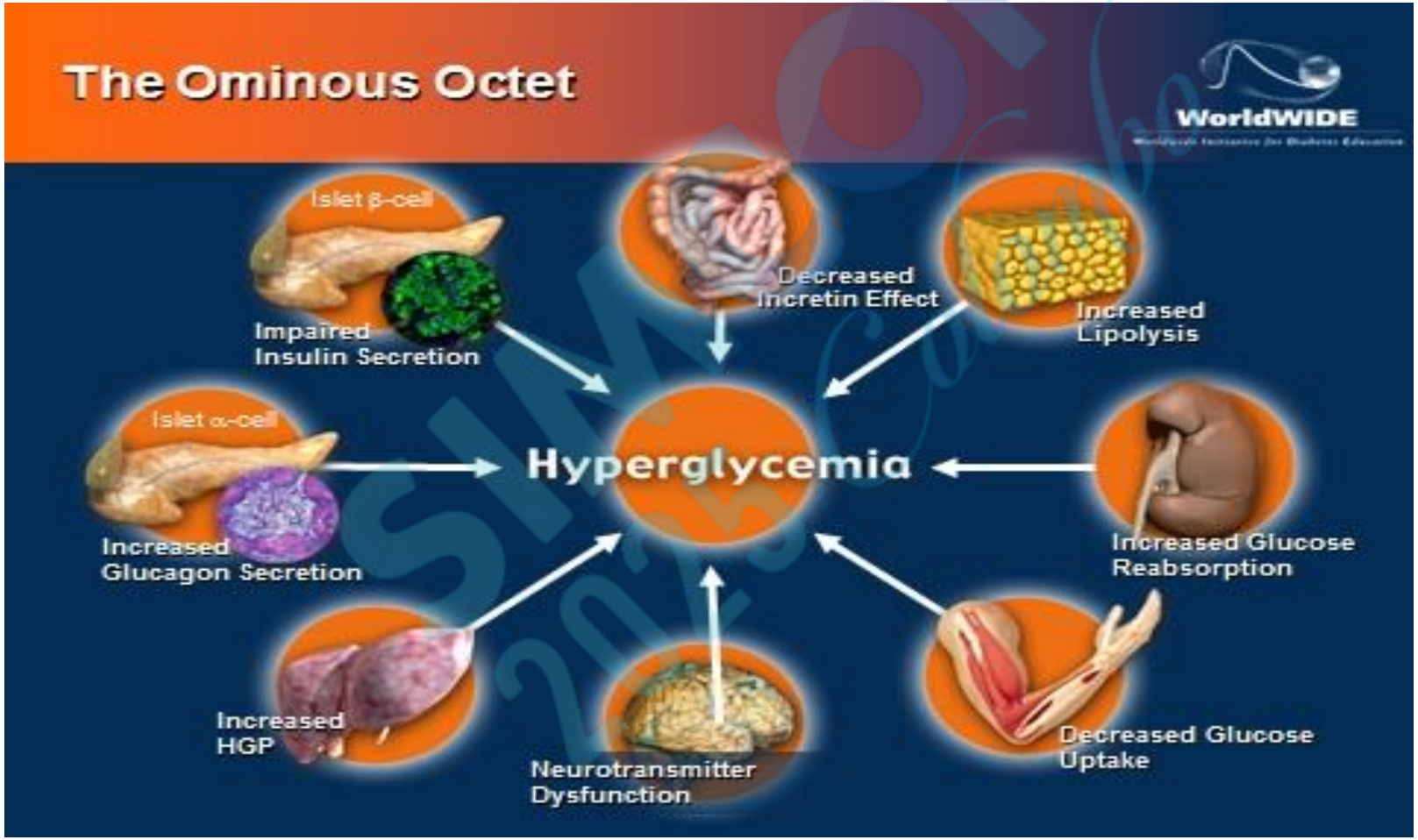


- DeFronzo RA. *Diabetes*. 2009;58:773–795; Poitout V, Robertson RP. *Endocrinology*. 2002;143:339–342; Robertson RP, et al. *Diabetes*. 2003;52:581–587.

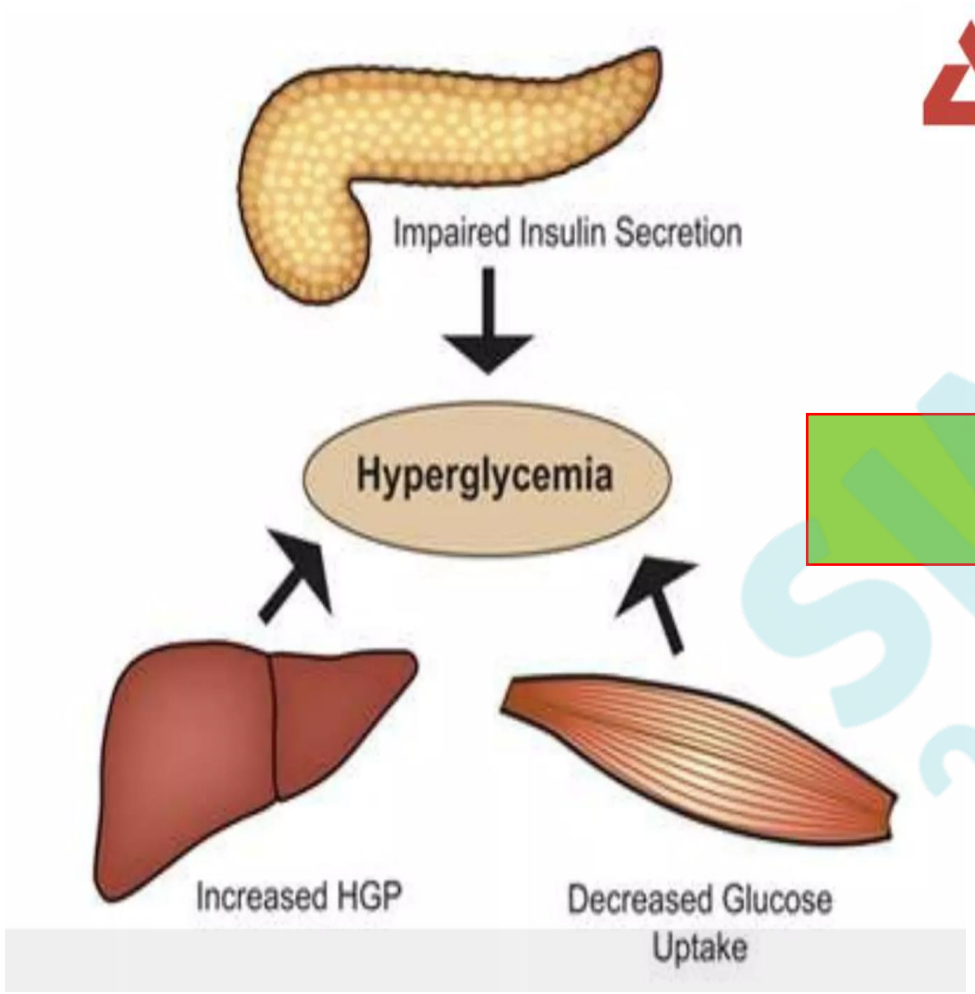
Theory of DM/ Triumvirate



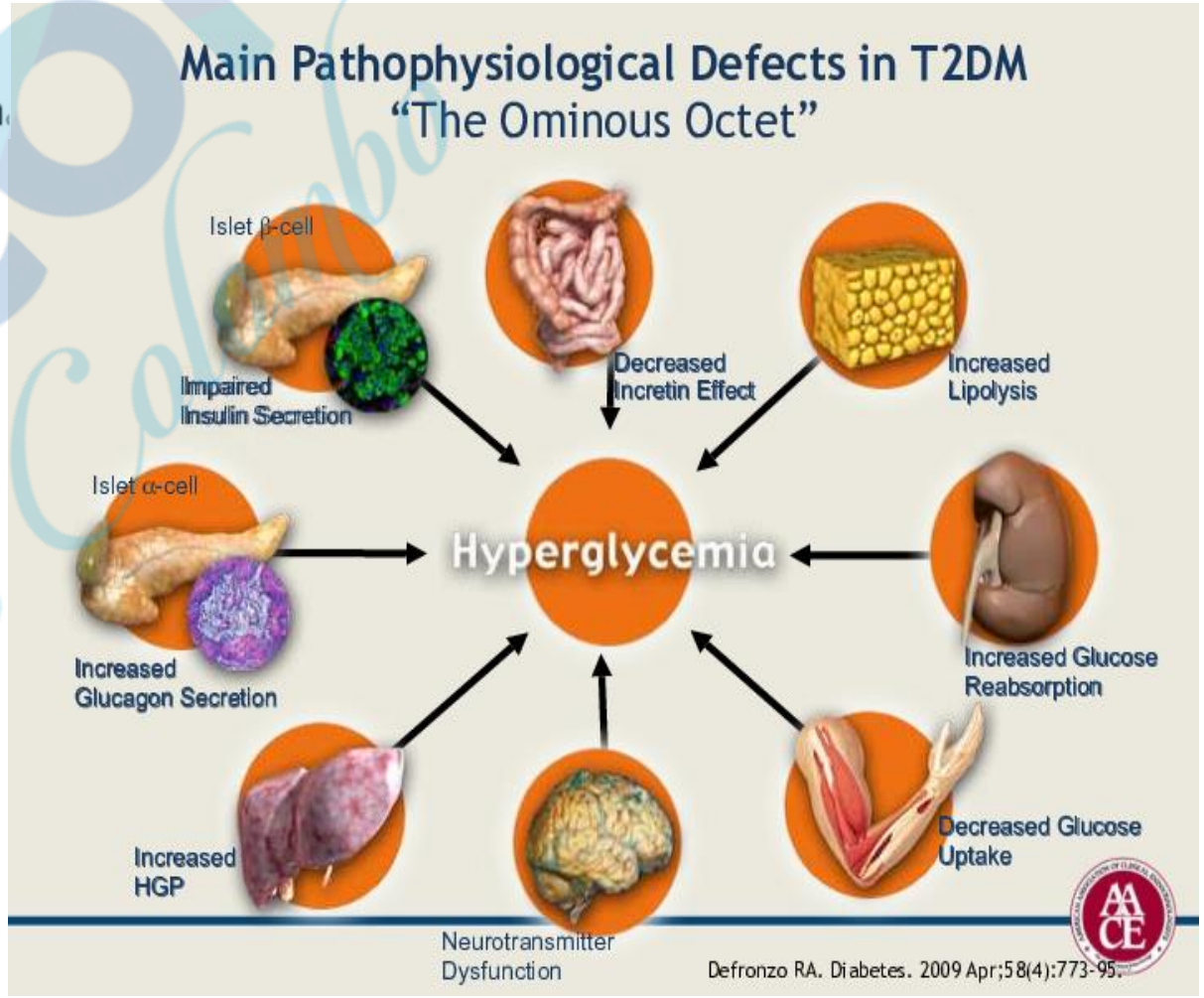
Theory of DM /Ominous octet



From the triumvirate to the ominous octet



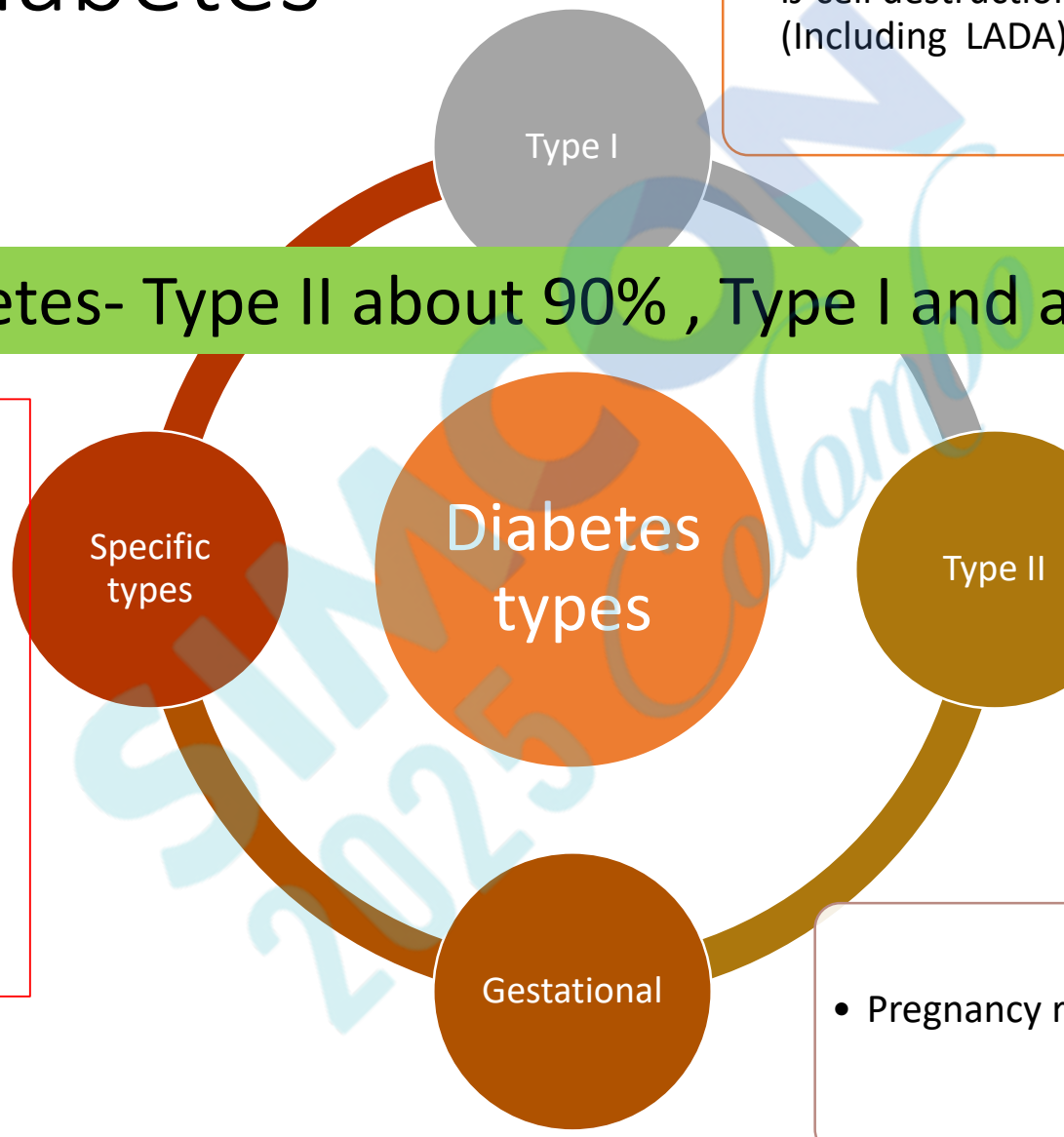
American Diabetes Association.



Diagnosis of Diabetes

	HbA1C	FBG (mg/dl)	OGTT (mg/dl)
Diabetes	≥6.5	≥126	≥200
Prediabetes	5.6-6.4	100-125	140-199
Normal	<5.6	≤99	≤139

Types of Diabetes



- Due to autoimmune ß-cell destruction (Including LADA)

Total volume of diabetes- Type II about 90% , Type I and all other combined 10%

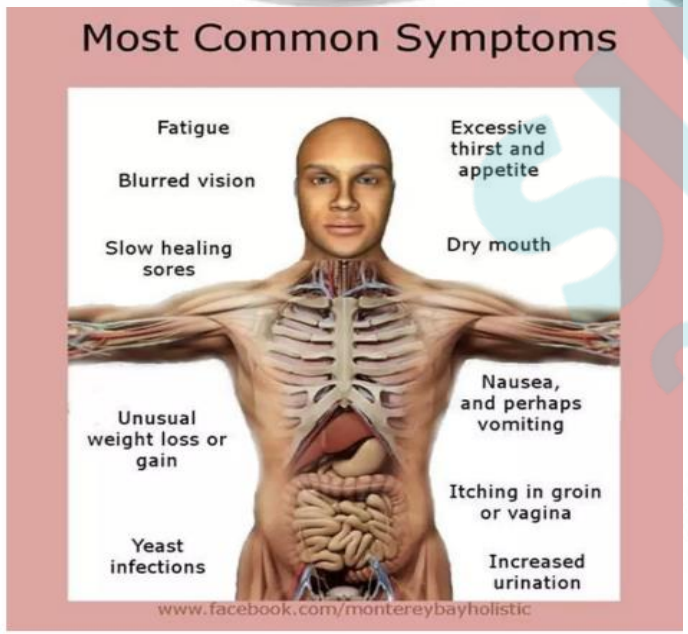
- Monogenic diabetes syndromes : Neonatal diabetes and maturity-onset diabetes of the young
- Diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and
- Drug- or chemical-induced diabetes (glucocorticoid use, ART, or after organ transplantation)

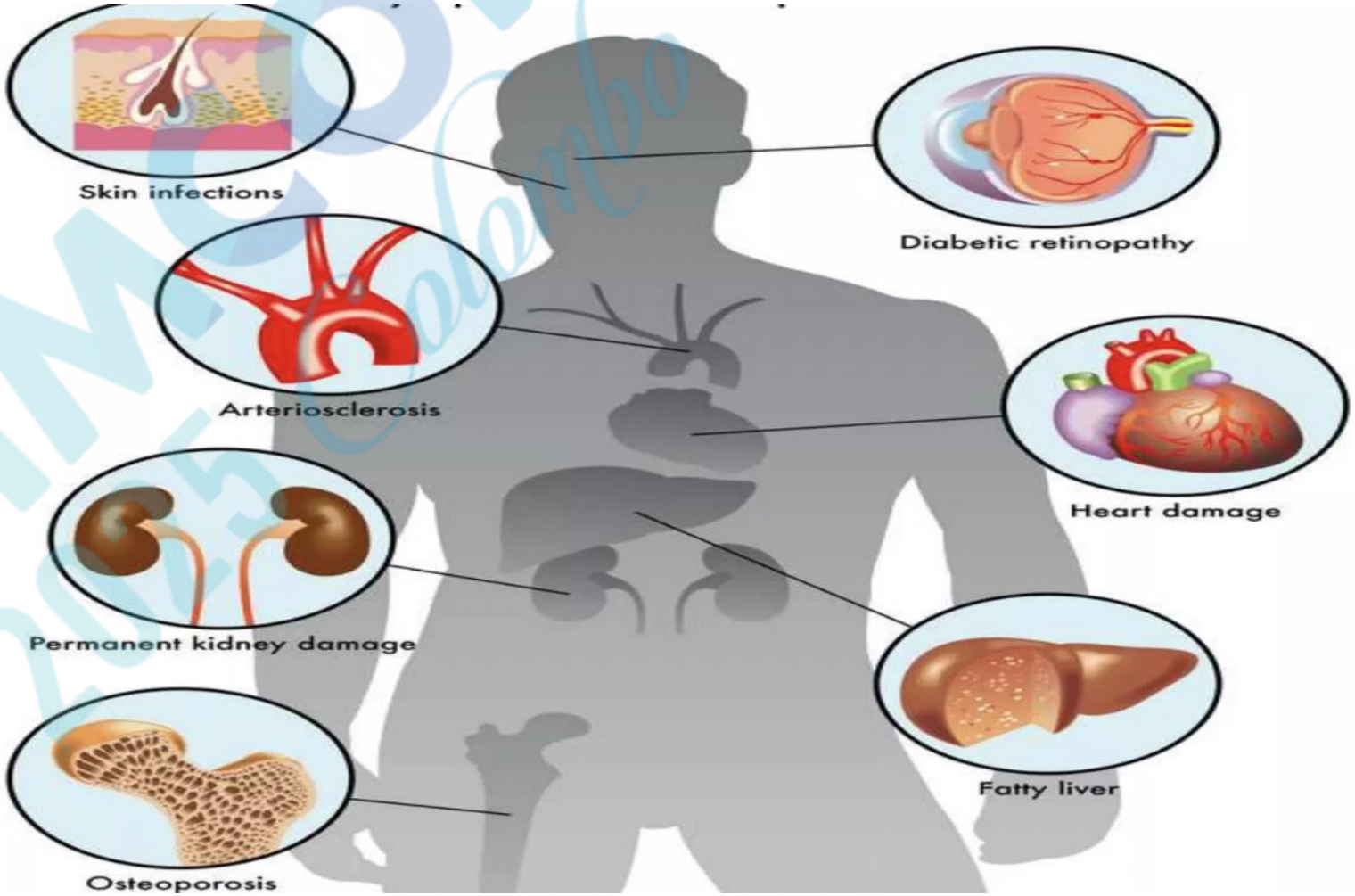
- Insulin resistance

- Pregnancy related

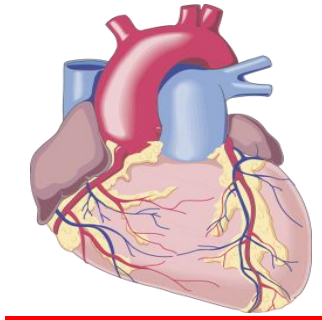
Clinical symptoms of Diabetes

Metabolic disease, Multi-systems disease

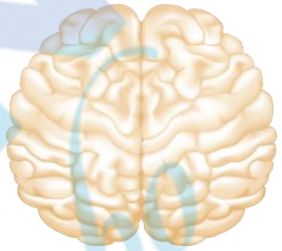




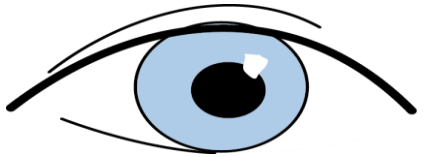
Diabetes- Multisystem , Metabolic disease significantly increase risk of



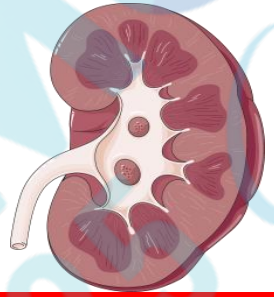
Heart disease by 2–4 fold[2]



Stroke
by more than 2–4 fold[2]



62 new patients will have severe vision loss due to diabetes[2]



137 new patients will need dialysis[2]

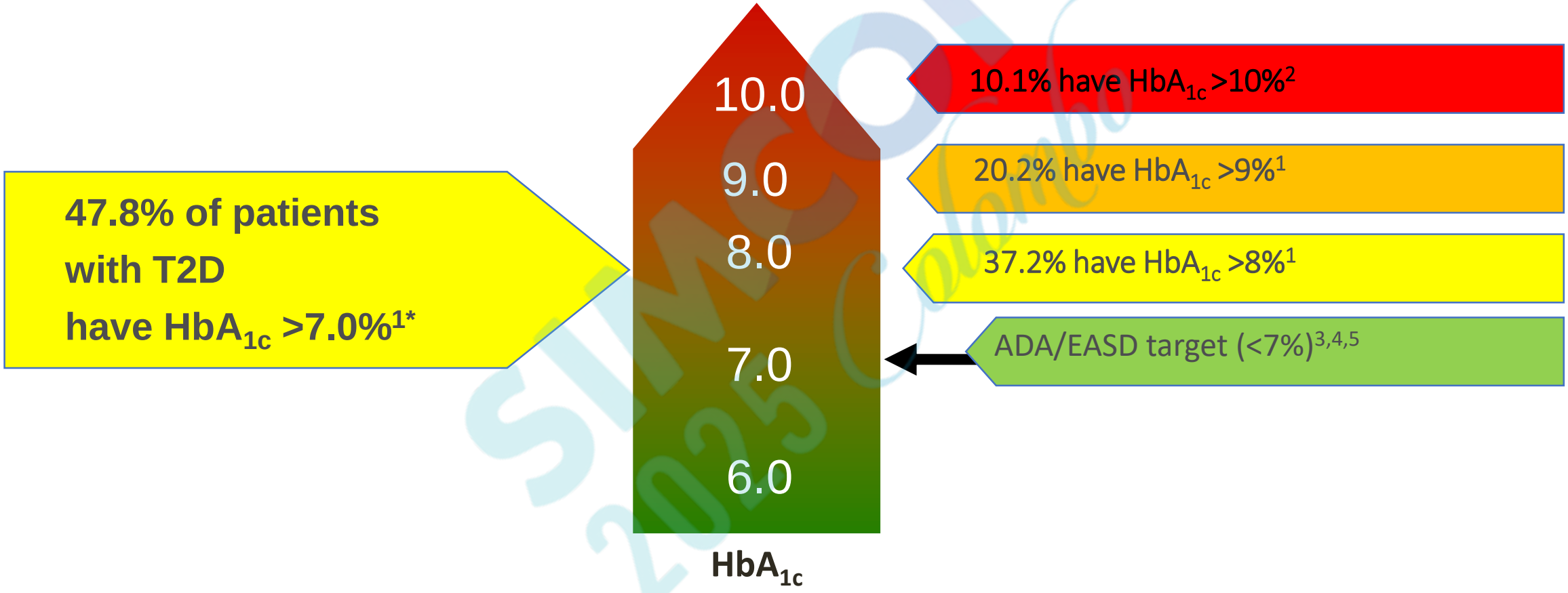
186 new patients will have an amputation[2]

Every 10 seconds, one person dies from diabetes-related complications[1]

1. International Diabetes Federation. Diabetes Atlas, Fifth Edition: www.diabetesatlas.org. Accessed 25 June 2012. Estimated based on mortality data;
2. Adapted from: CDC 2011 National Diabetes Fact Sheet: http://www.cdc.gov/diabetes/pubs/estimates11.htm#12. Accessed June 2011.

Glycaemic Goals in Diabetes

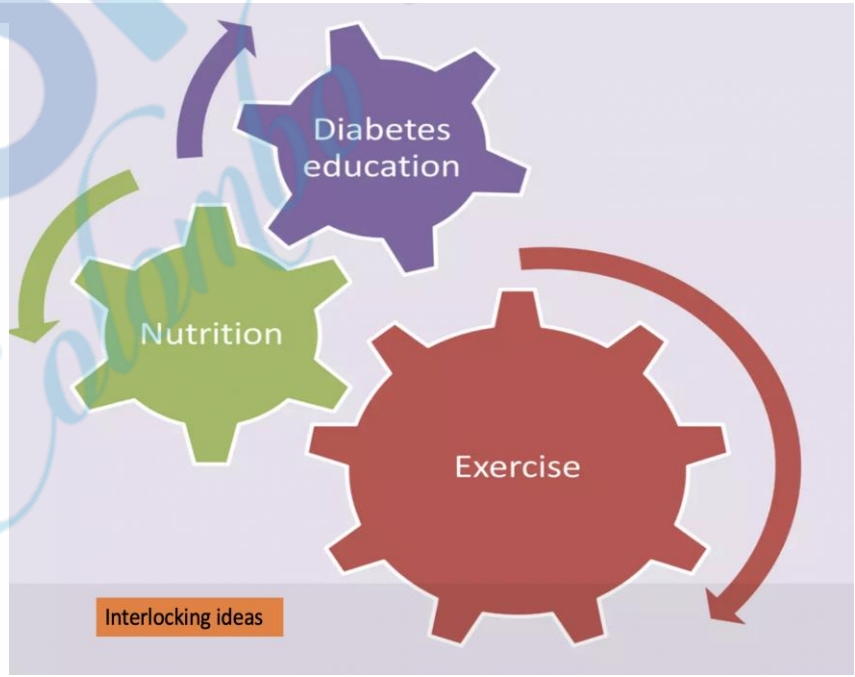
The majority of patients in USA with T2D remain far above glycaemic goals



*.Adapted from

1. Saydah SH, et al. *JAMA*. 2004;291:335–342.
2. Dodd AH, et al. *Curr Med Res Opin*. 2000;291:1605–1613;
3. Oluwatowoju I, et al. *Diabet Med*. 2010;27:354–359;
4. ADA. *Diabetes Care*. 2013;36:S11–S66;
5. Inzucchi SE, et al. *Diabetes Care.* 2012;35:1364–1379;

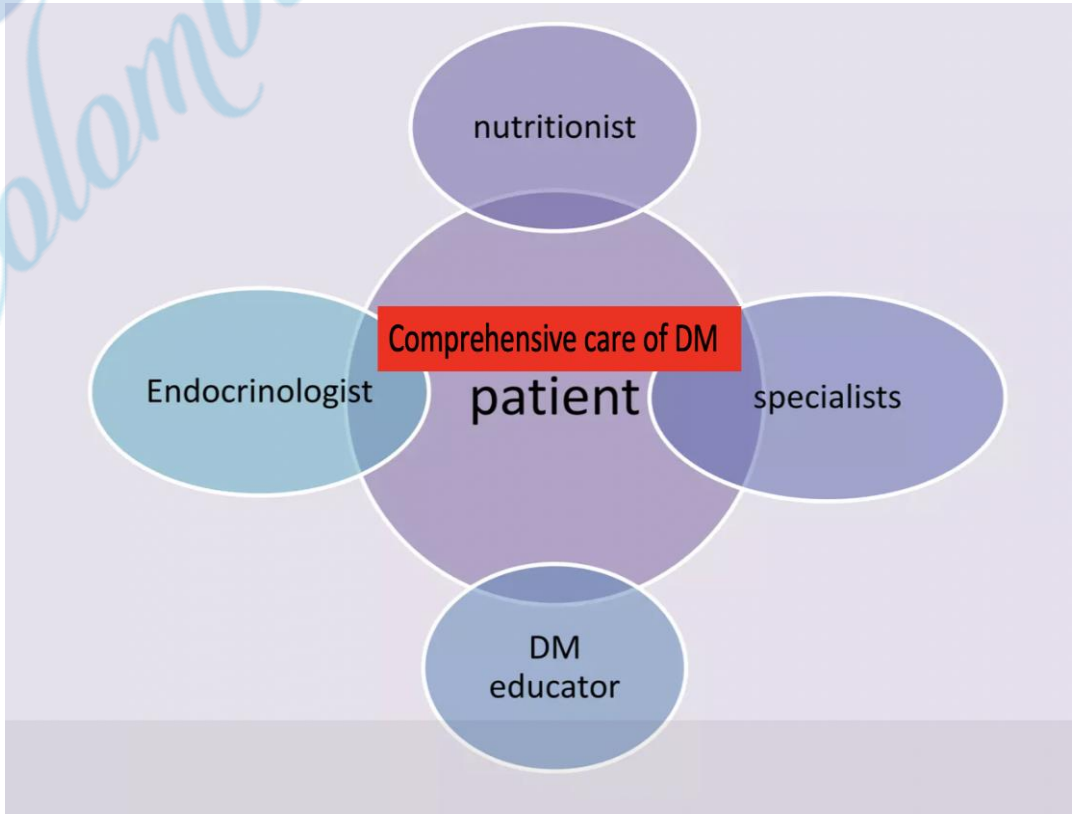
Management of Diabetes



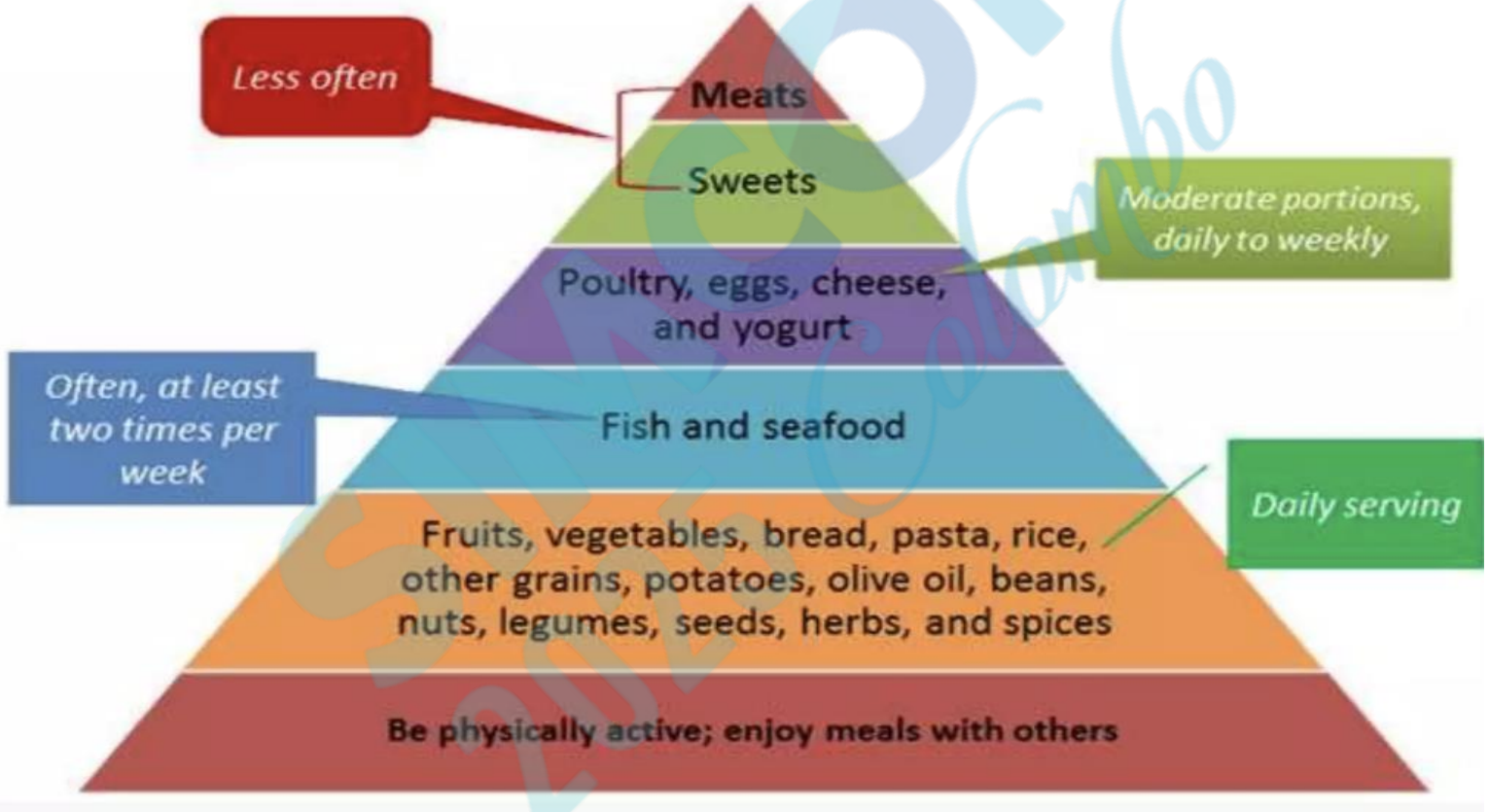
- High financial consequences of managing diabetes
  - Medical expenses
  - Lost productivity

Management of Diabetes

- Trials
  - DCCT-Diabetes and control and complications trial
  - UKPDS-United kingdom prospective study
- Treatment
  - Medical nutrition therapy
  - Physical activity
  - Monitoring
  - Medications
  - Self management education



Medical nutrition therapy of DM



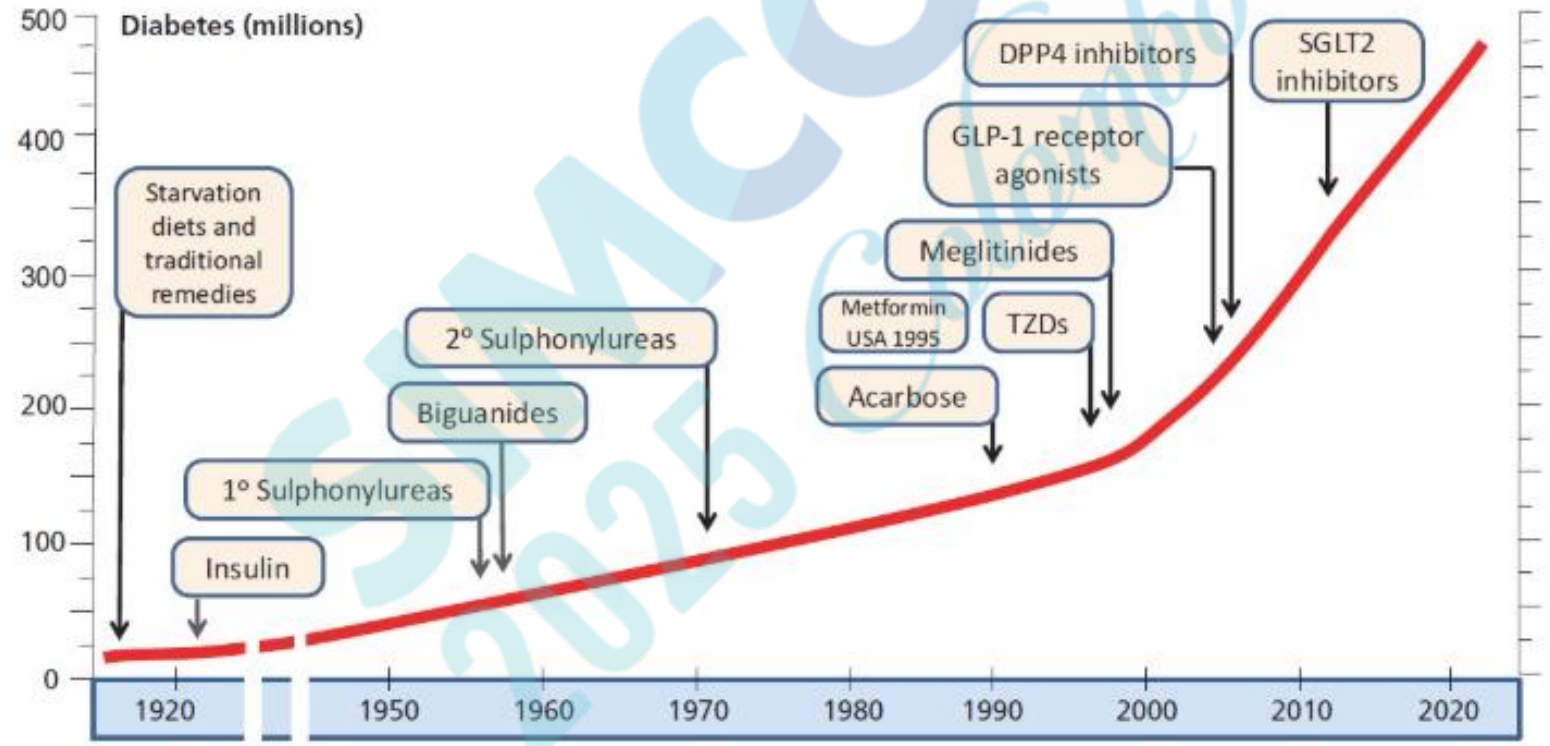
Antidiabetic agents

Class	Compound
Biguanides	• Metformin
Sulfonylureas (2nd generation)	• Glimepiride • Glipizide • Glyburide
Thiazolidinedione	• Pioglitazone
α-Glucosidase inhibitors	• Acarbose • Miglitol
Meglitinides	• Nateglinide • Repaglinide
DPP-4 inhibitors	• Alogliptin • Linagliptin • Saxagliptin • Sitagliptin
SGLT2 inhibitors	• Bexagliflozin • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin
GLP-1 RAs	• Dulaglutide • Exenatide • Exenatide (ER) • Liraglutide • Semaglutide
Dual GIP and GLP-1 RA	• Tirzepatide
Bile acid sequestrant	• Colesevelam
Dopamine-2 agonist	• Bromocriptine
Amylin mimetic	• Pramlintide

Standards of care in Diabetes 2025, Diabetes Care: diabetesjournals

Evolution of antidiabetic medicines

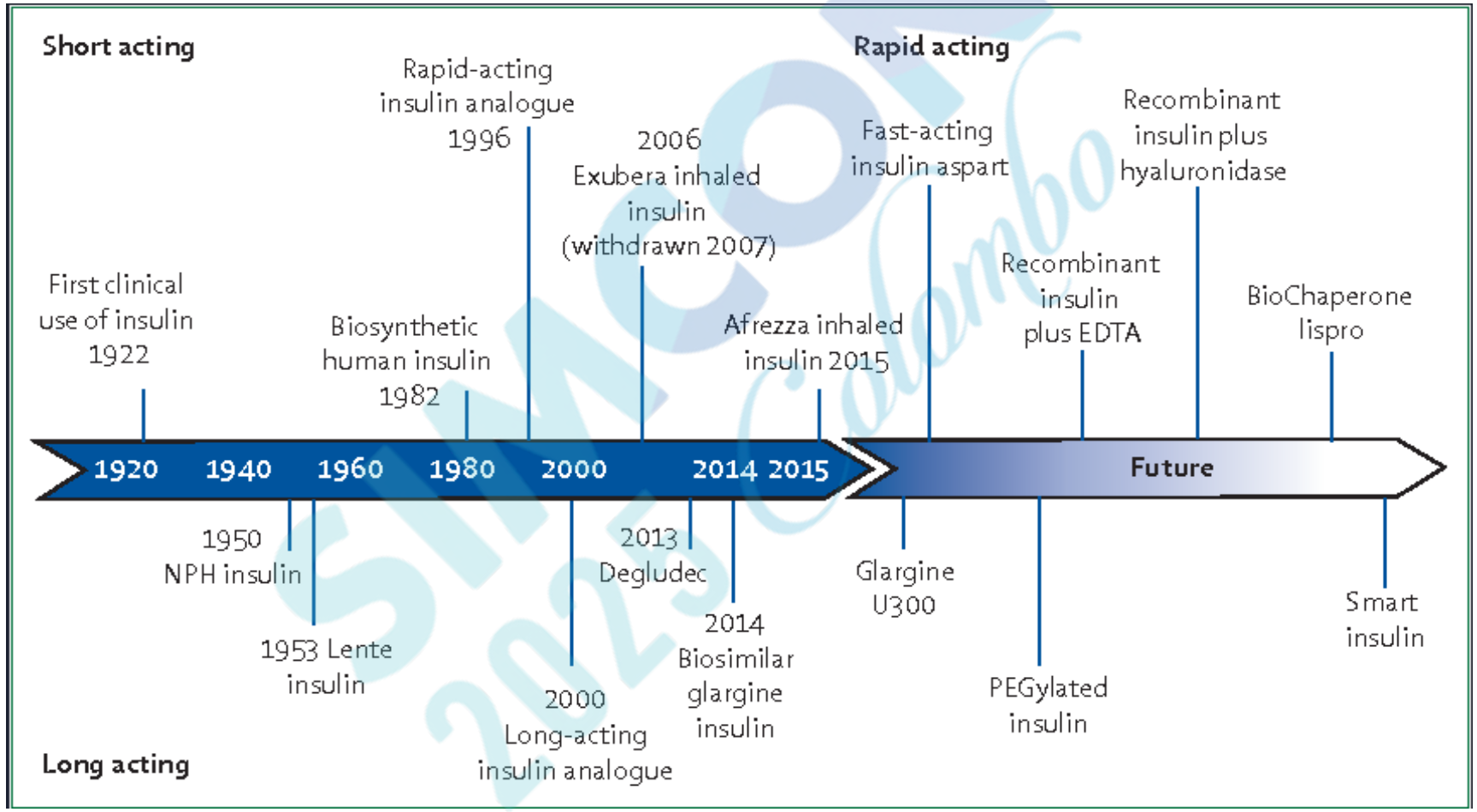
Figure 1. Timeline showing the introduction of different classes of glucose-lowering agents. The red line indicates the estimated global prevalence of people with diabetes (in millions), >90% of whom are believed to have T2DM



DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; TZD, thiazolidinedione; 1°, first; 2°, second.

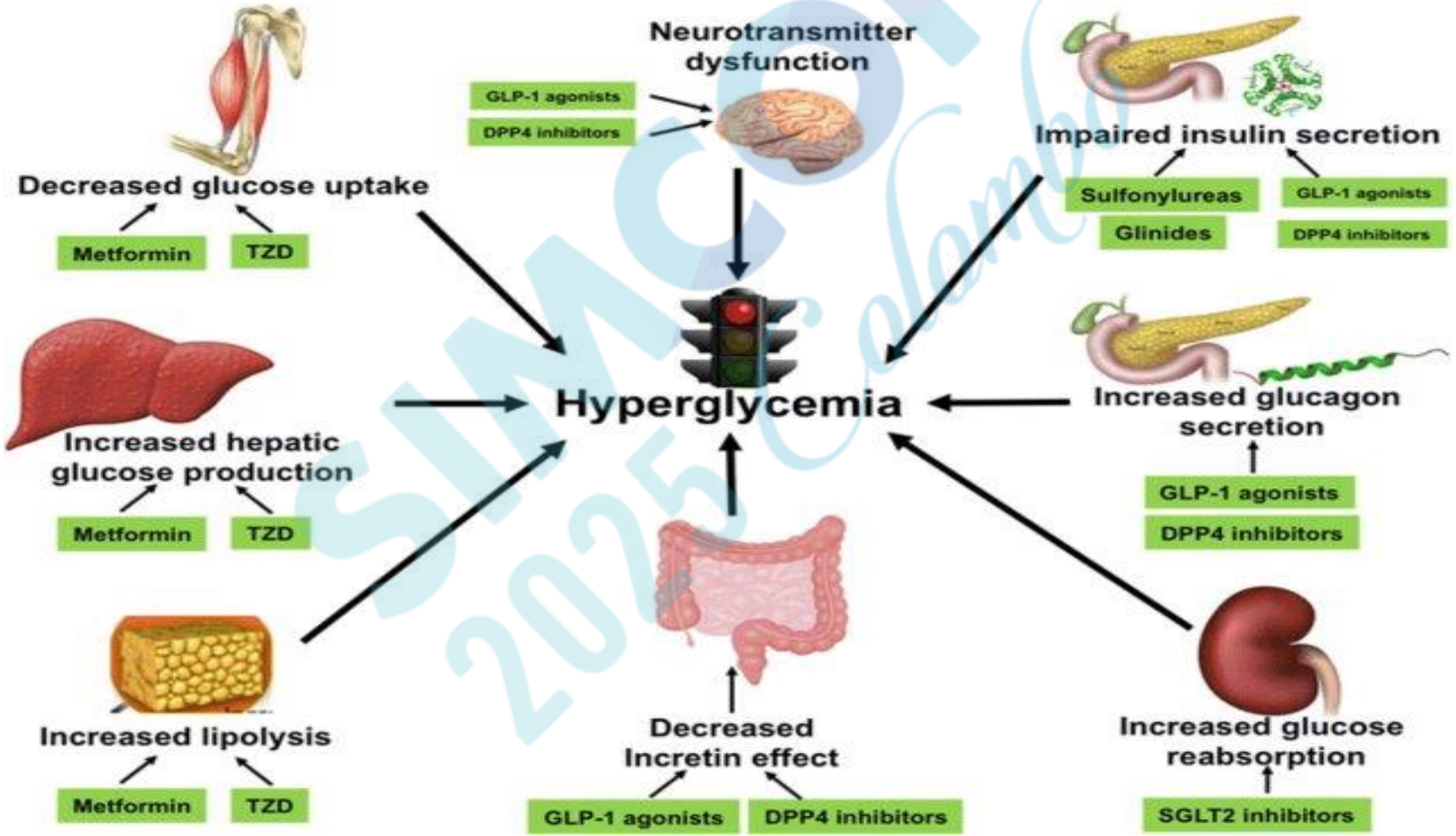
2022;22:112-120The origins of type 2 diabetes medications, Clifford J Bailry, Br J Diabetes

Evolution of insulin therapy



New forms of insulin and insulin therapies for the treatment of type 2 diabetes, Cahn, Avivit et al. The Lancet Diabetes & Endocrinology, Volume 3, Issue 8, 638 - 652

Different site actions of OHA



Why Novel Approach ?

- Glucose homeostasis: it’s more than just β-cell function

- Current therapy has limitations
  - Remains unmet the needs
  - requirement for new therapies

- Role of new therapies:
  - SGLT2 or SGLT1/2 inhibitors
  - GLP-1 RA
  - Diabetic technology
  - Novel approach for Insulin delivery

Novel Approach

- **Diabetic technology**
  - BGM devices
  - CGM (continuous glucose monitoring)
  - Insulin pens
  - CSII (continuous subcutaneous insulin infusion)
  - AID (Automated insulin delivery)

Standards of care in Diabetes 2025, Diabetes Care: diabetesjournals

Treatment

NOVEL APPROACHES IN INSULIN DELIVERY

Inhaled insulin Insulin delivery to the lungs is the first reported alternative to subcutaneous injection. The first inhalable insulin, Exubera, was approved by U.S. FDA in the year 2006 and is available in 1-mg and 3-mg doses.

Oral insulin The oral route of administration is regarded the most convenient way because of its ease of administration. However, the difficulties with the oral delivery include degradation of the insulin at the acidic pH of the stomach and by different enzymes in the stomach. Several pharmaceutical companies are developing carriers to protect insulin from degrading in the stomach.

Buccal insulin Mucous membrane of the inner lining of cheek is an excellent source of insulin delivery due to its rich blood supply, expansive smooth muscle, visibility and accessibility.

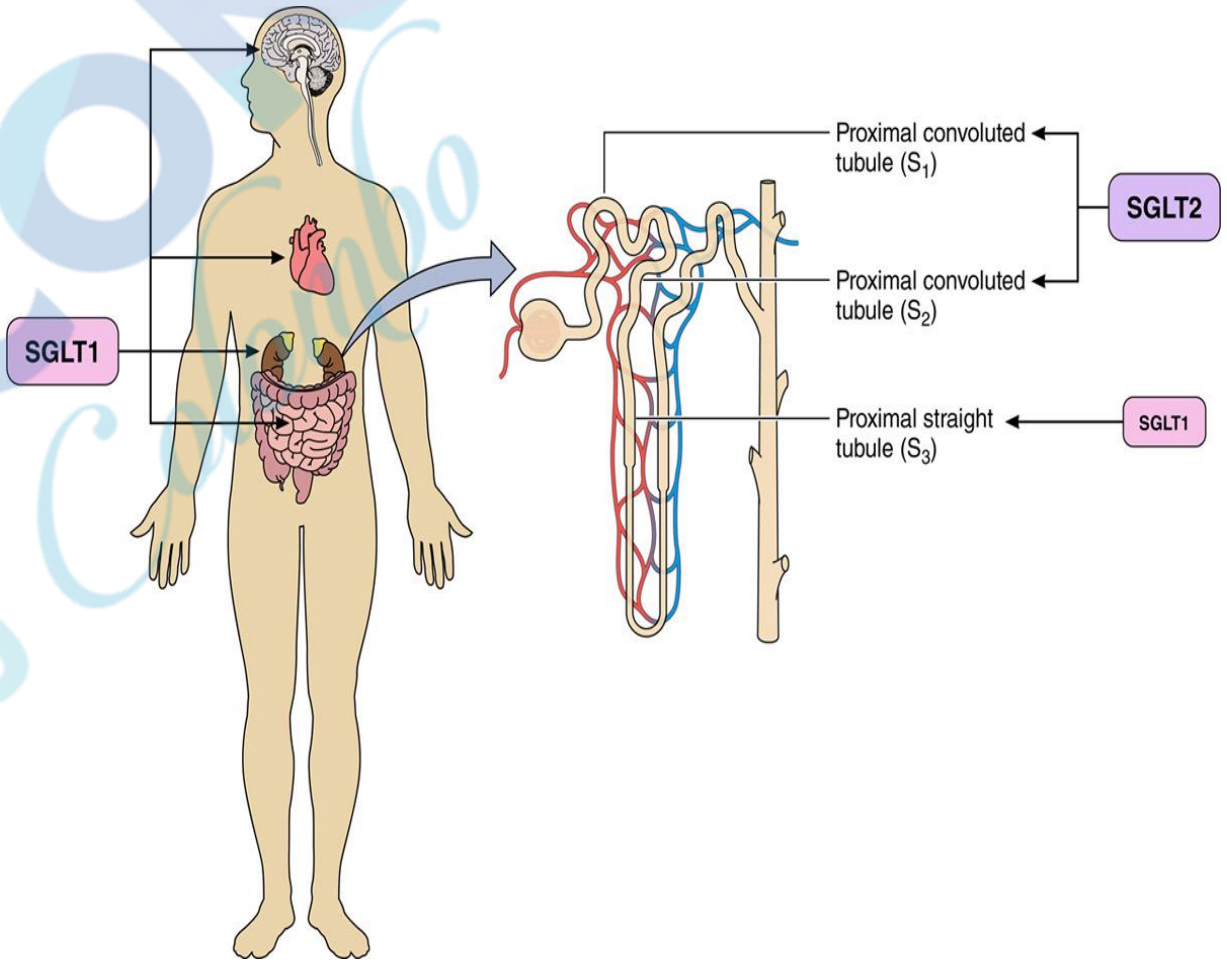
New Drugs in Type 2 diabetes

- Extracted from bark of apple trees
- Inhibits both SGLT1 and SGLT2

New Drugs in Type 2 diabetes

Gliflozins or **flozins**

- Considered as promising therapeutic target to treat diabetes and obesity
  - **Inhibits both SGLT1 and SGLT2**
  - SGLT1 is primarily expressed in intestinal epithelium, whose inhibition reduces dietary glucose uptake
  - SGLT2 is highly expressed in kidney - regulating glucose reabsorption



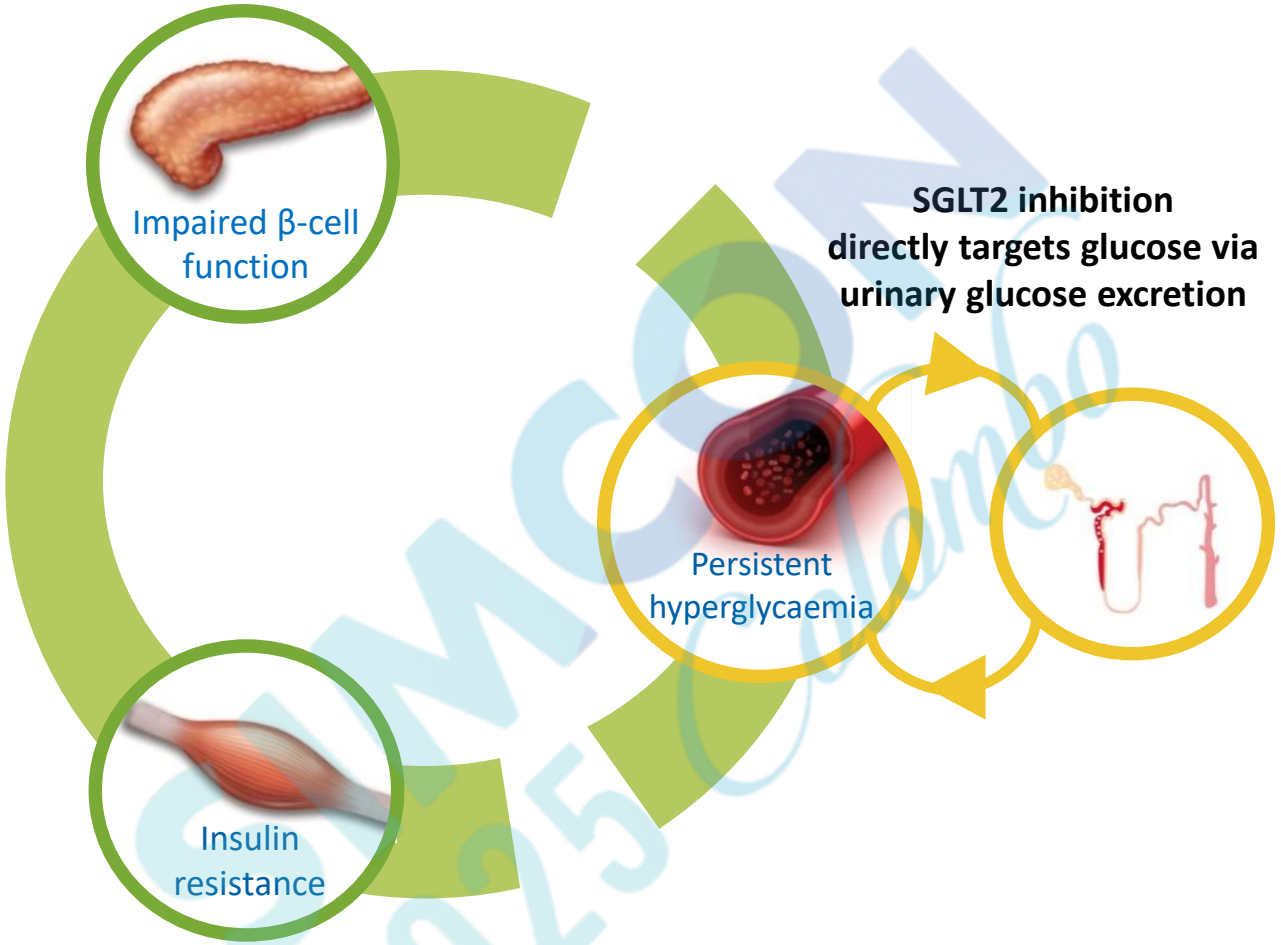
SGLT inhibitors

More recent SGLT2 inhibitors:

- Sergliflozin
- Remogliflozin — Development stopped

- Dapagliflozin
- Canagliflozin
- Empagliflozin — Registered in EU and US

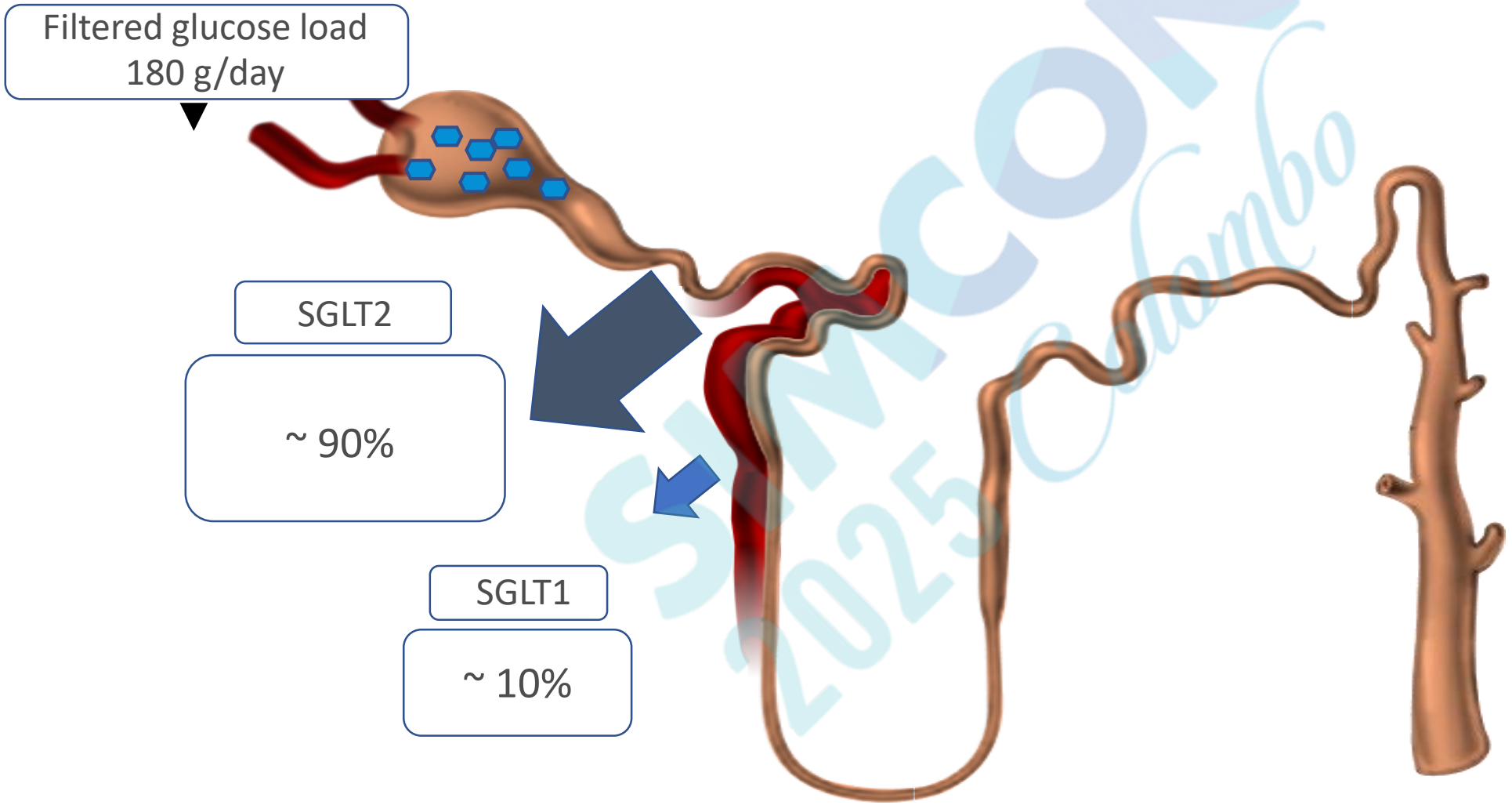
Abdul-Ghani M et al Curr Diab Rep 2012; 12: 230-238



SGLT2 inhibition lowers glycaemia independently of β-cell function and insulin resistance[1–4]

1. DeFronzo RA. *Diabetes*. 2009;58:773–795.
2. Poitout V, Robertson RP. *Endocrinology*. 2002;143:339–342.
3. Robertson RP, et al. *Diabetes*. 2003;52:581–587.
4. DeFronzo RA. *Diabetes Obes Metab*. 2012;14:5–14.

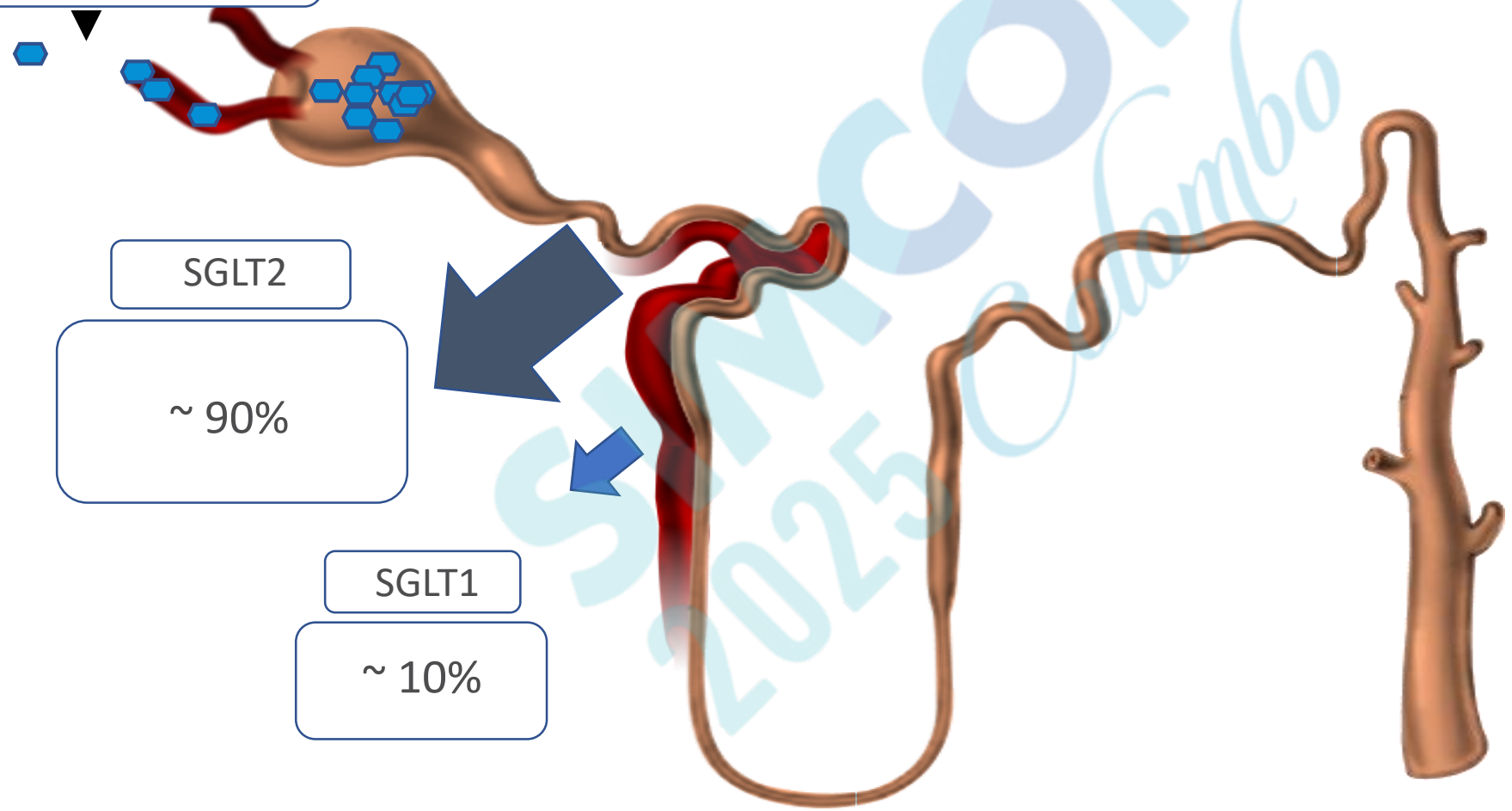
Renal glucose re-absorption in healthy individuals



Gerich JE. *Diabet Med*. 2010;27:136–142.

Renal glucose re-absorption in patients with hyperglycaemia

Filtered glucose load > 180 g/day



SGLT2

~ 90%

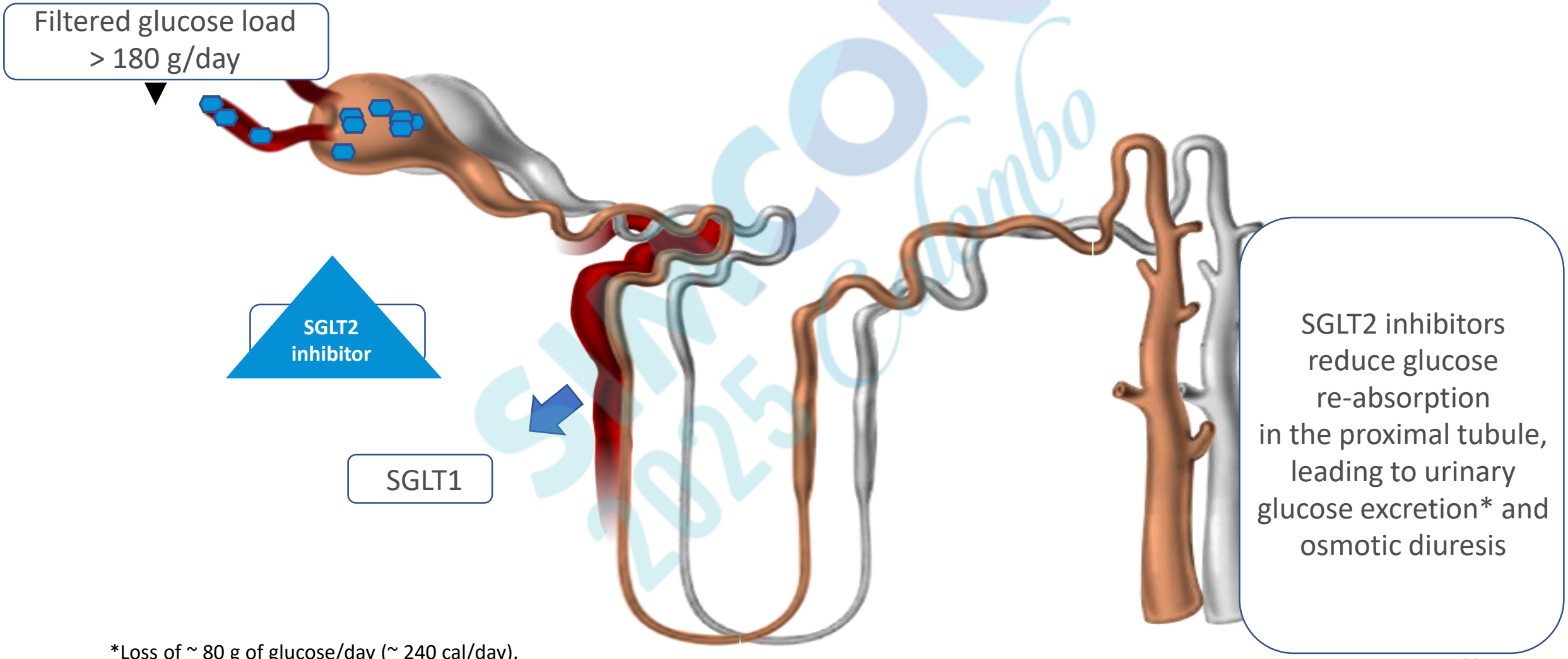
SGLT1

~ 10%

When blood glucose increases above the renal threshold (~ 10 mmol/l or 180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion

Gerich JE. *Diabet Med*. 2010;27:136–142.

Urinary glucose excretion via SGLT2 inhibition



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*Loss of ~ 80 g of glucose/day (~ 240 cal/day).
Gerich JE. *Diabet Med*. 2010;27:136–142.

New Drugs in Type 2 diabetes

Gila monster

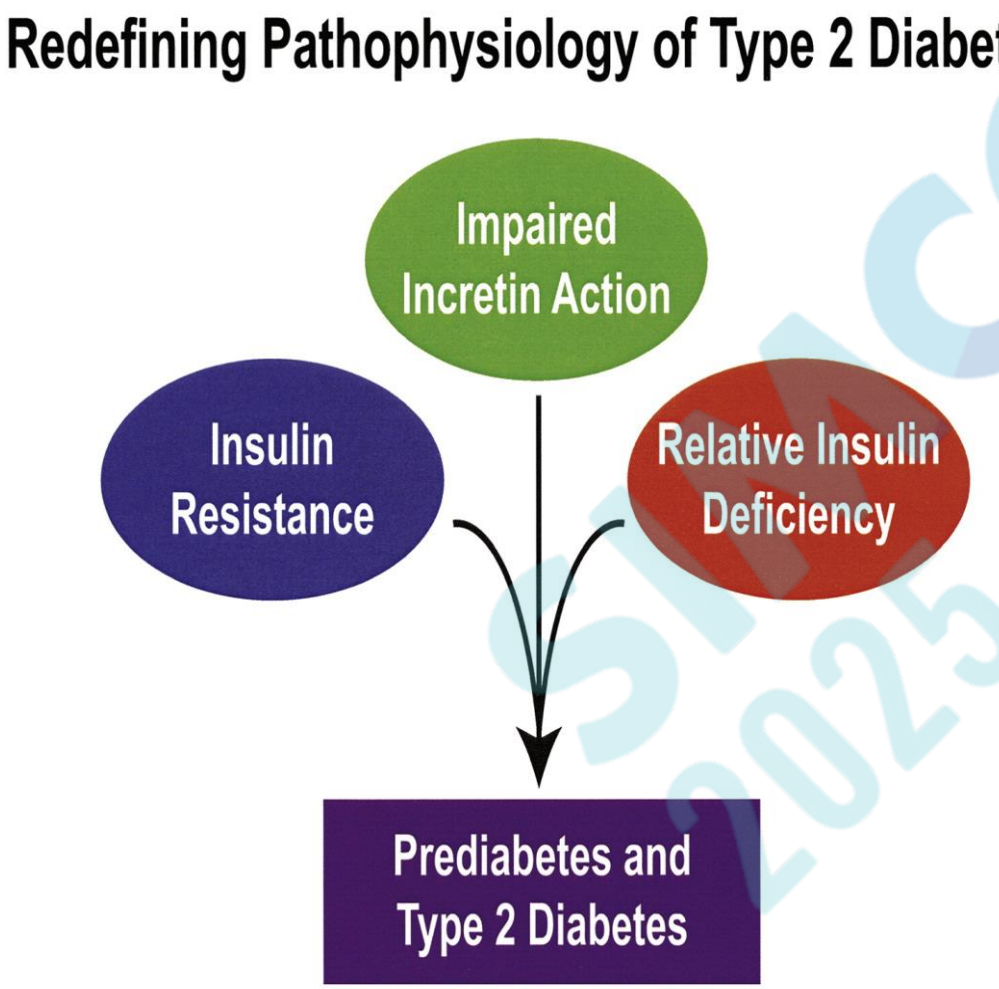
Incretin mimetics

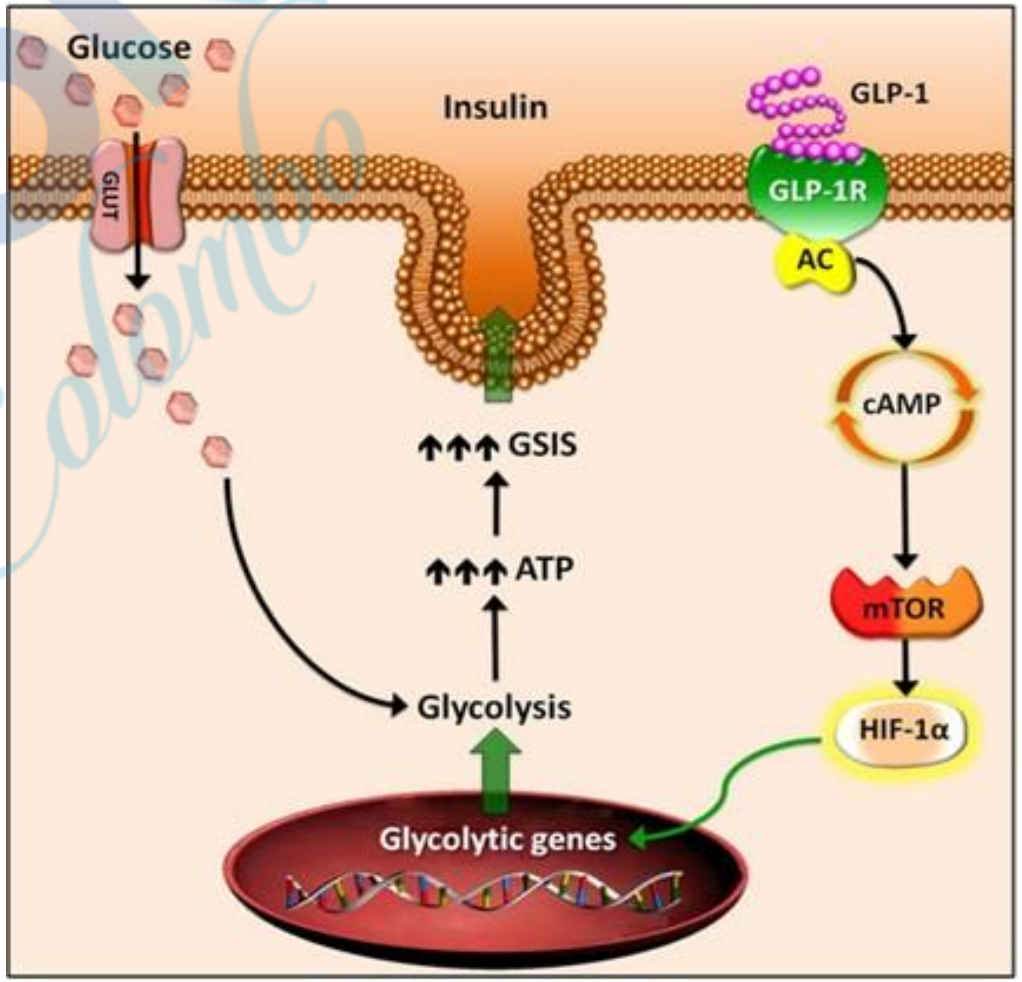
Exenatide

- The first incretin-related therapy available for patients with type 2 diabetes.
- Naturally occurring peptide from the saliva of the Gila Monster.
- Has an approximate 50% amino acid homology with GLP-1.
- Binds to GLP-1 receptors and behaves as GLP-1.

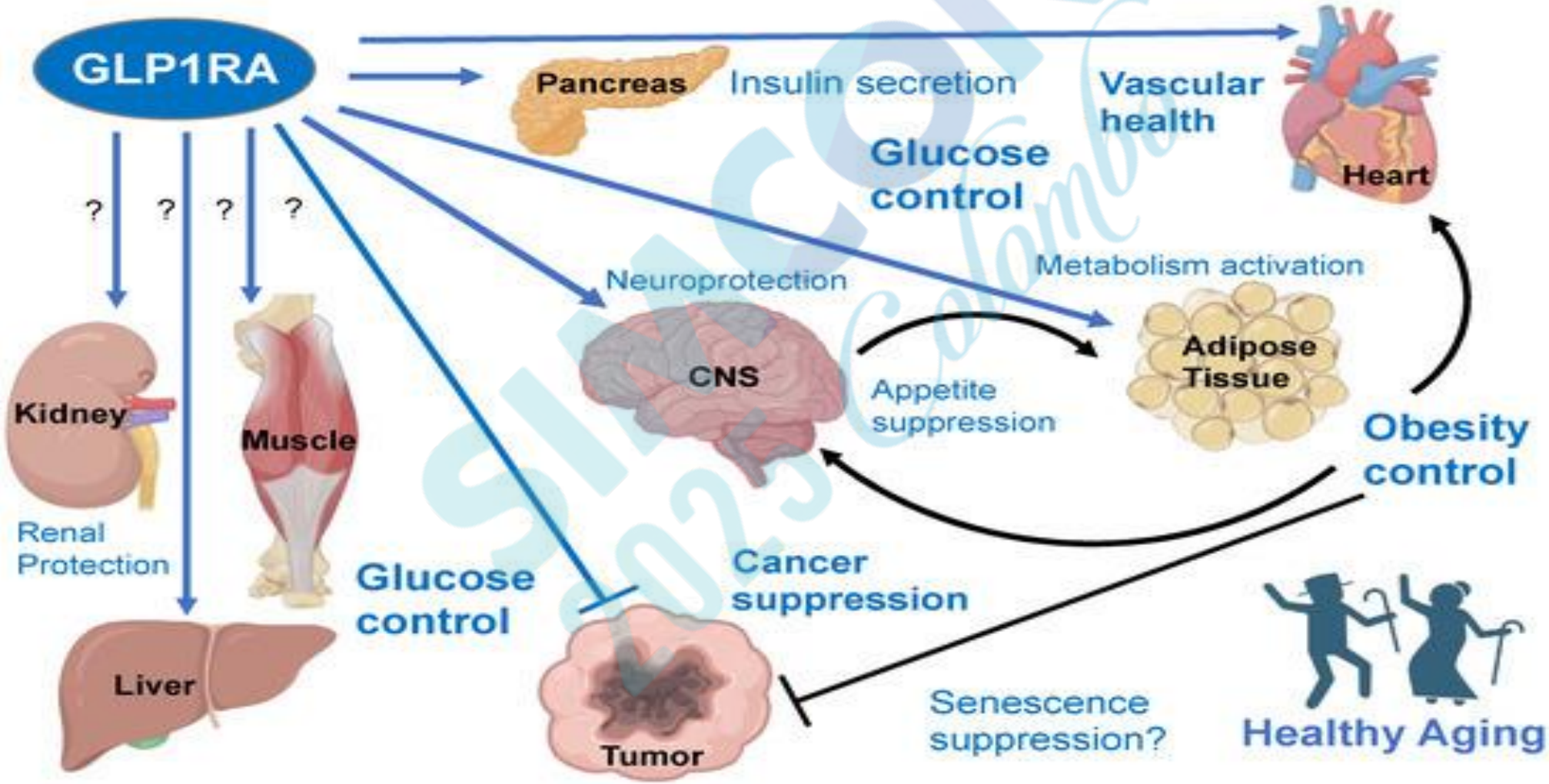
- Stimulates insulin production and delays gastric emptying

Impaired Incretin Action





GLP1RA


GLP1RA
Pancreas
Insulin secretion
Vascular health
Heart
Glucose control
? ? ? ?
Neuroprotection
Metabolism activation
Kidney
Muscle
CNS
Adipose Tissue
Appetite suppression
Obesity control
Renal Protection
Glucose control
Cancer suppression
Liver
Tumor
Senescence suppression?
Healthy Aging

Diabetic technology

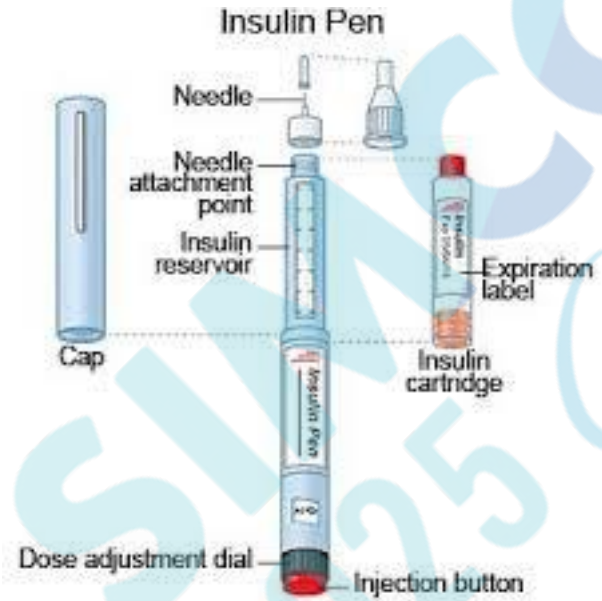
- BGM devices

Diabetic technology

- CGM (continuous glucose monitoring)

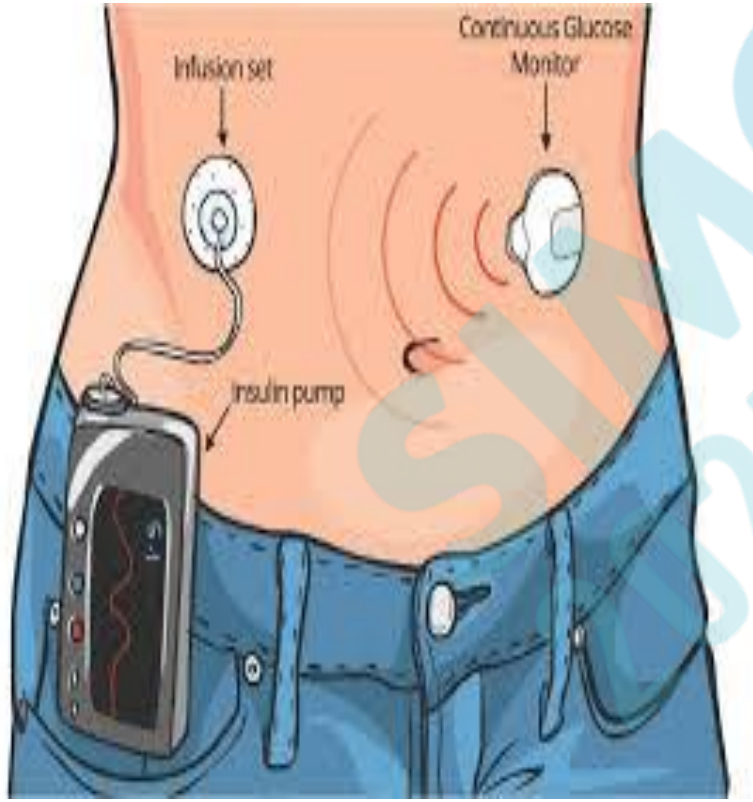
Diabetic technology

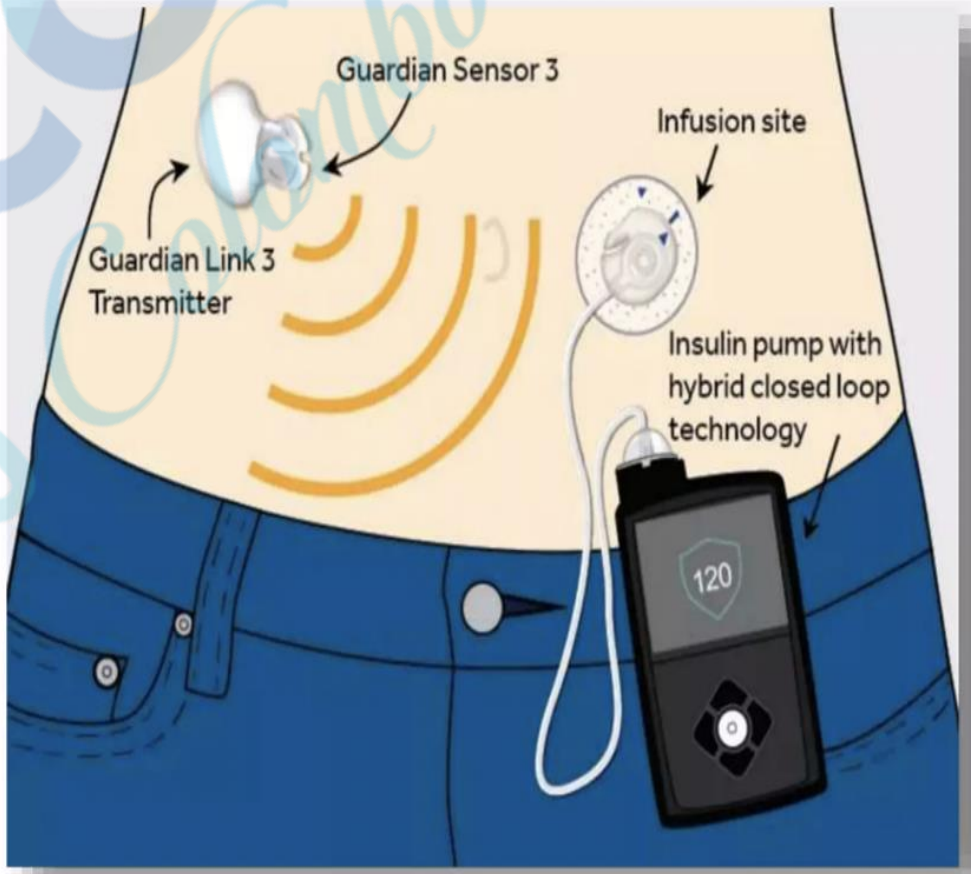
- Insulin pens



Diabetic technology

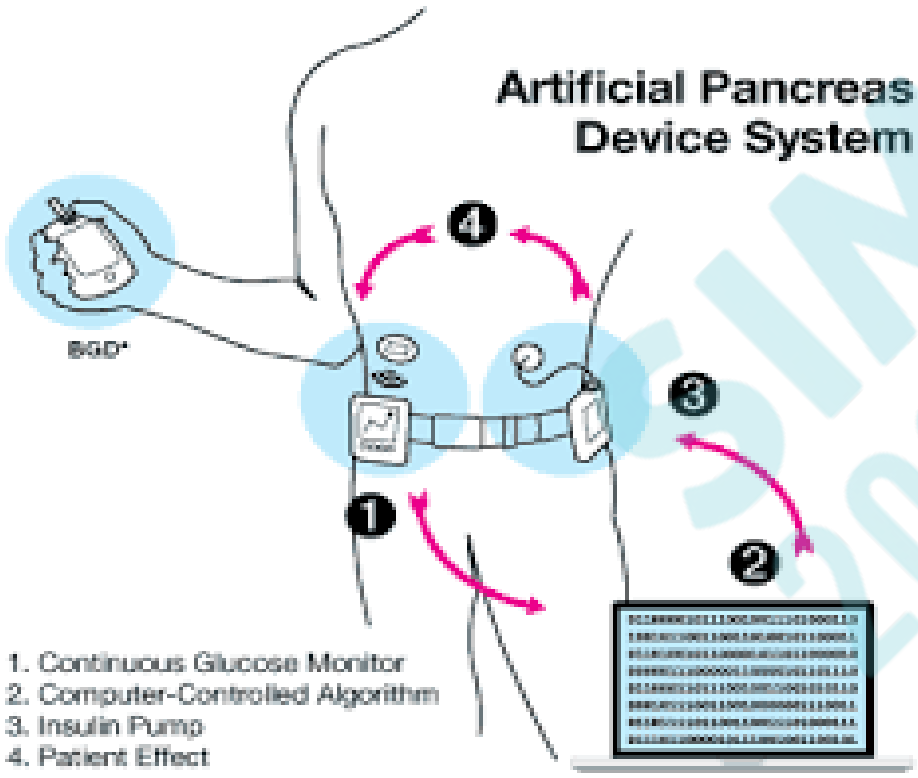
- CSII (continuous subcutaneous insulin infusion)

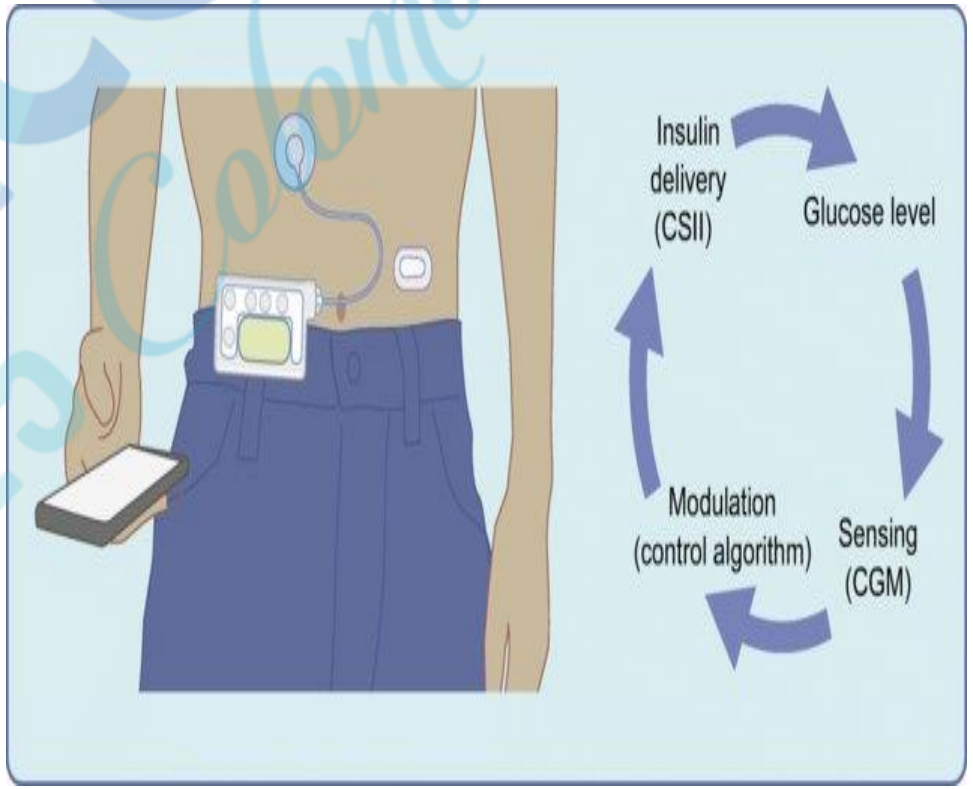




Diabetic technology

- AID (Automated insulin delivery)





Newer targets for diabetes in 2025?

- **Inhibitors of 11β-hydroxysteroid dehydrogenase** 1, which reduce the glucocorticoid effects in liver and fat

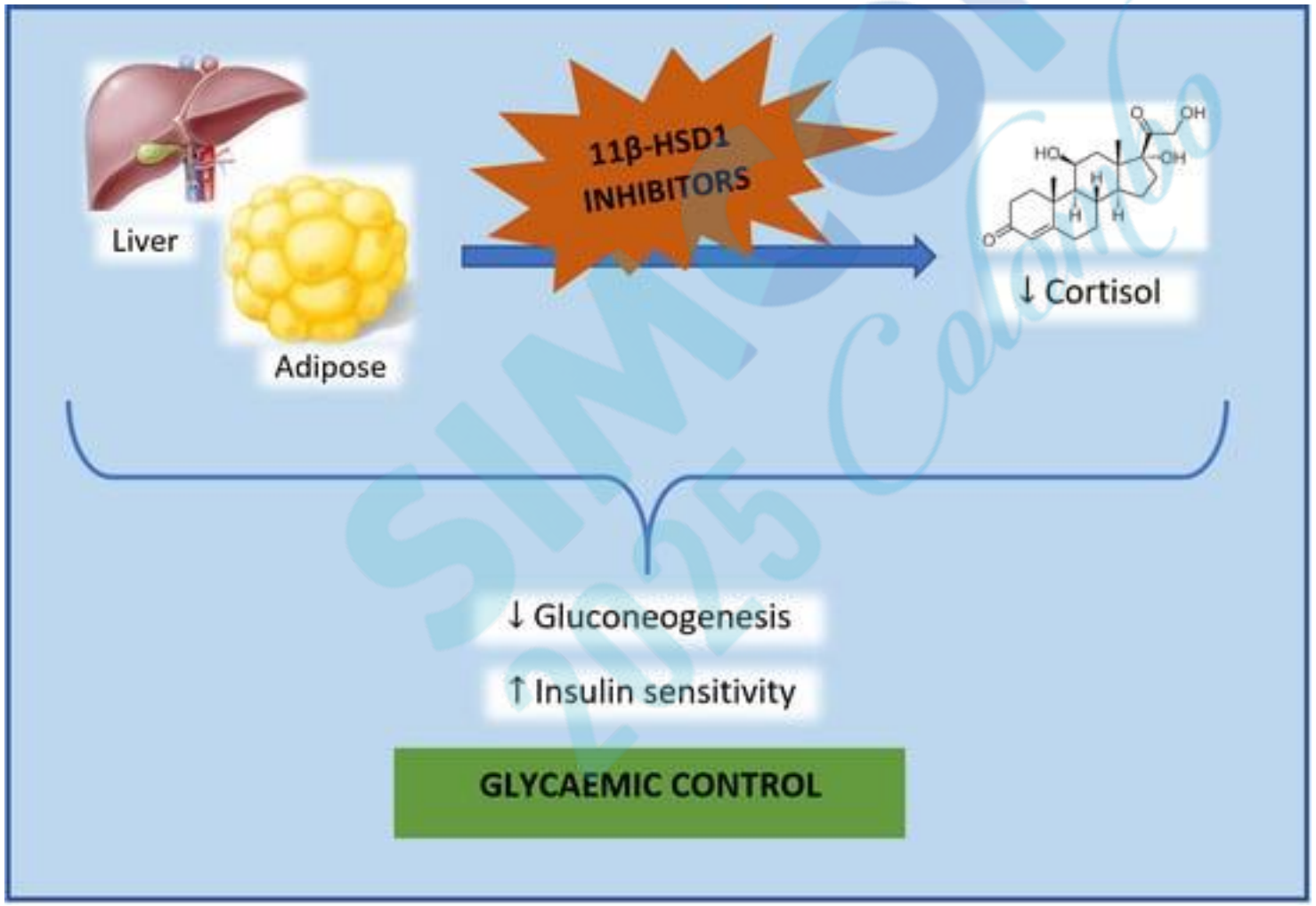
- Insulin-releasing **glucokinase activators** and **pancreatic-G-protein-coupled fatty-acid-receptor agonists**

- **Glucagon-receptor antagonists**

- **Metabolic inhibitors** of hepatic glucose output

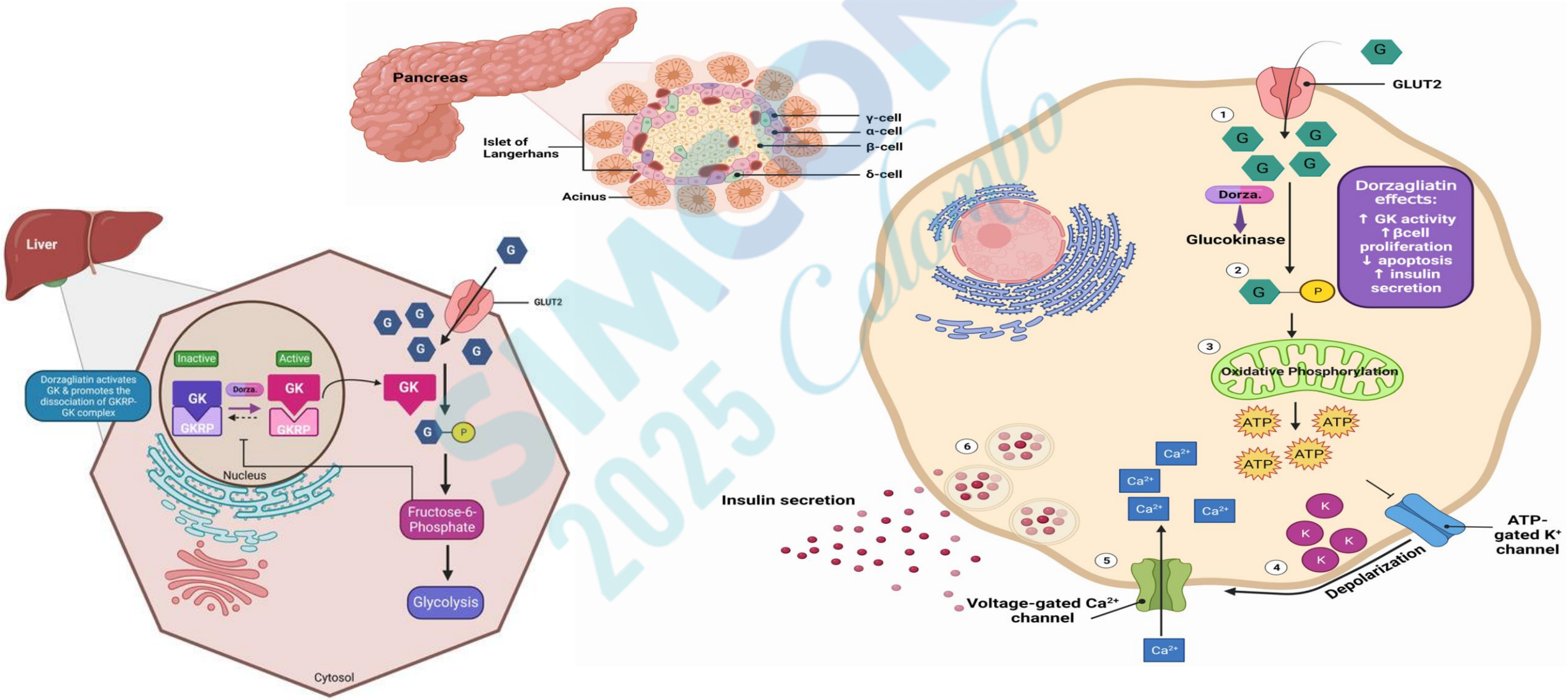
Newer targets for diabetes in 2025?

Inhibitors of 11β-hydroxysteroid dehydrogenase 1

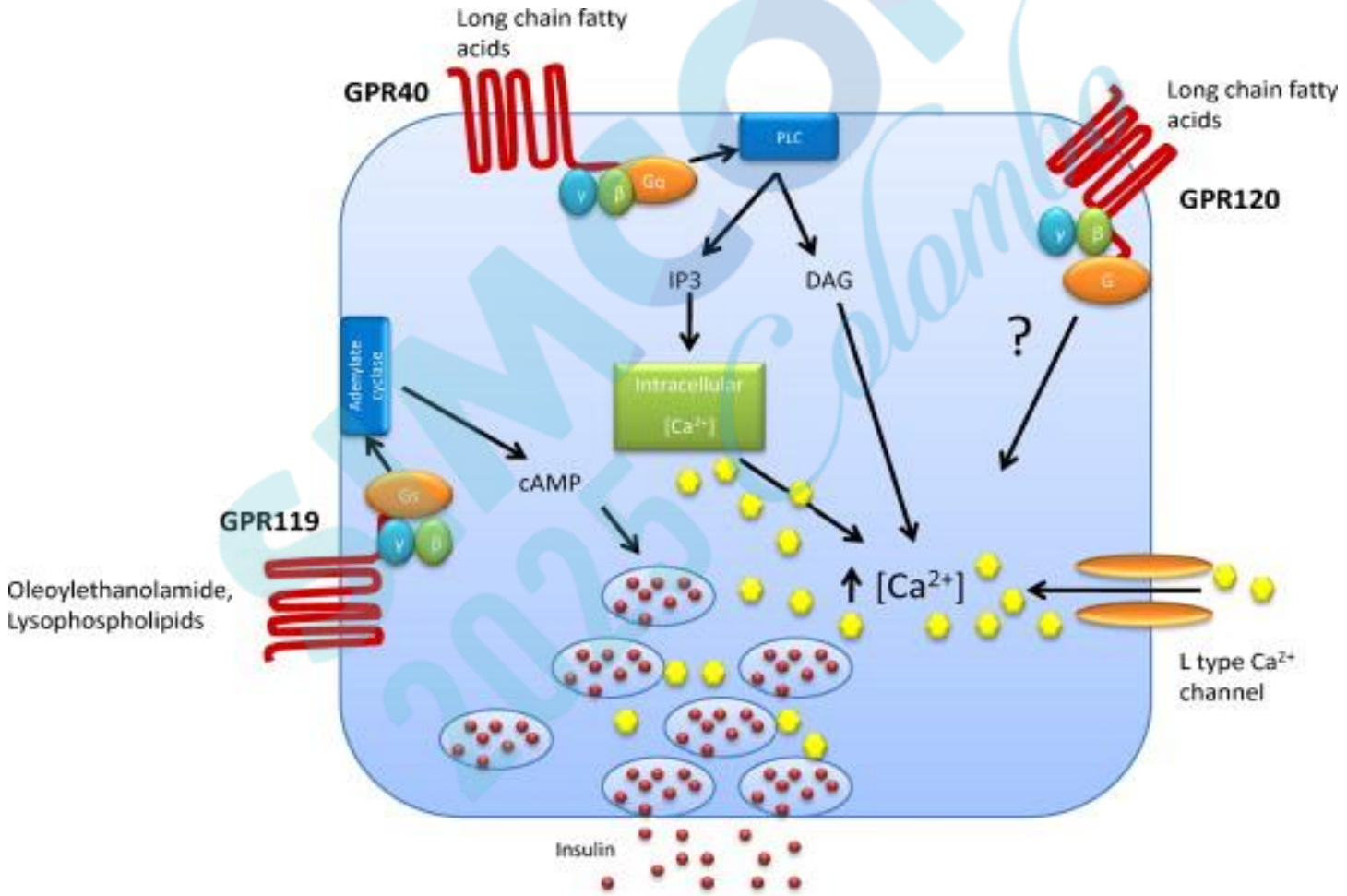


Reduce the glucocorticoid effects in liver and fat

Newer targets -**glucokinase activators**

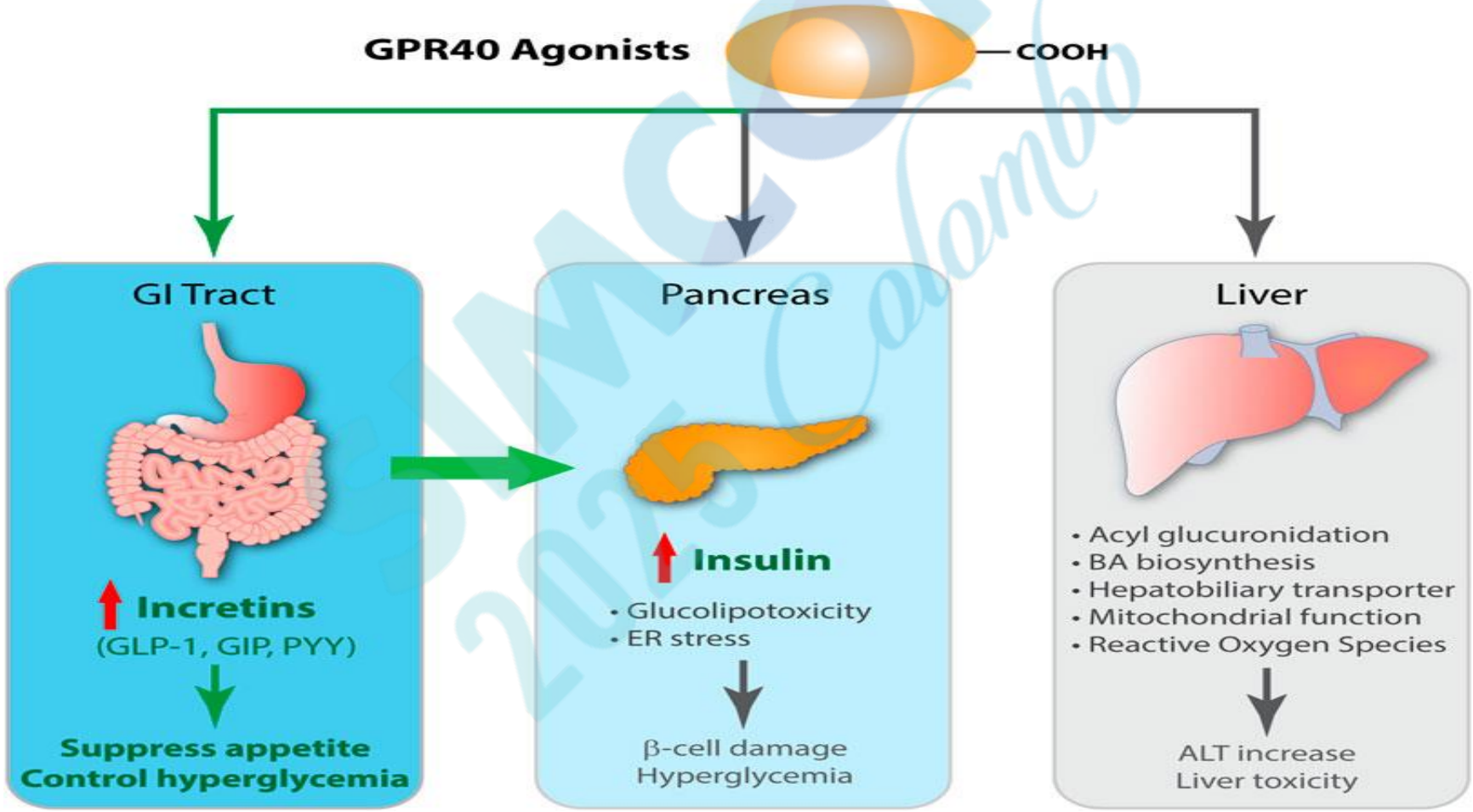


Newer targets **pancreatic-G-protein-coupled fatty-acid-receptor agonists**



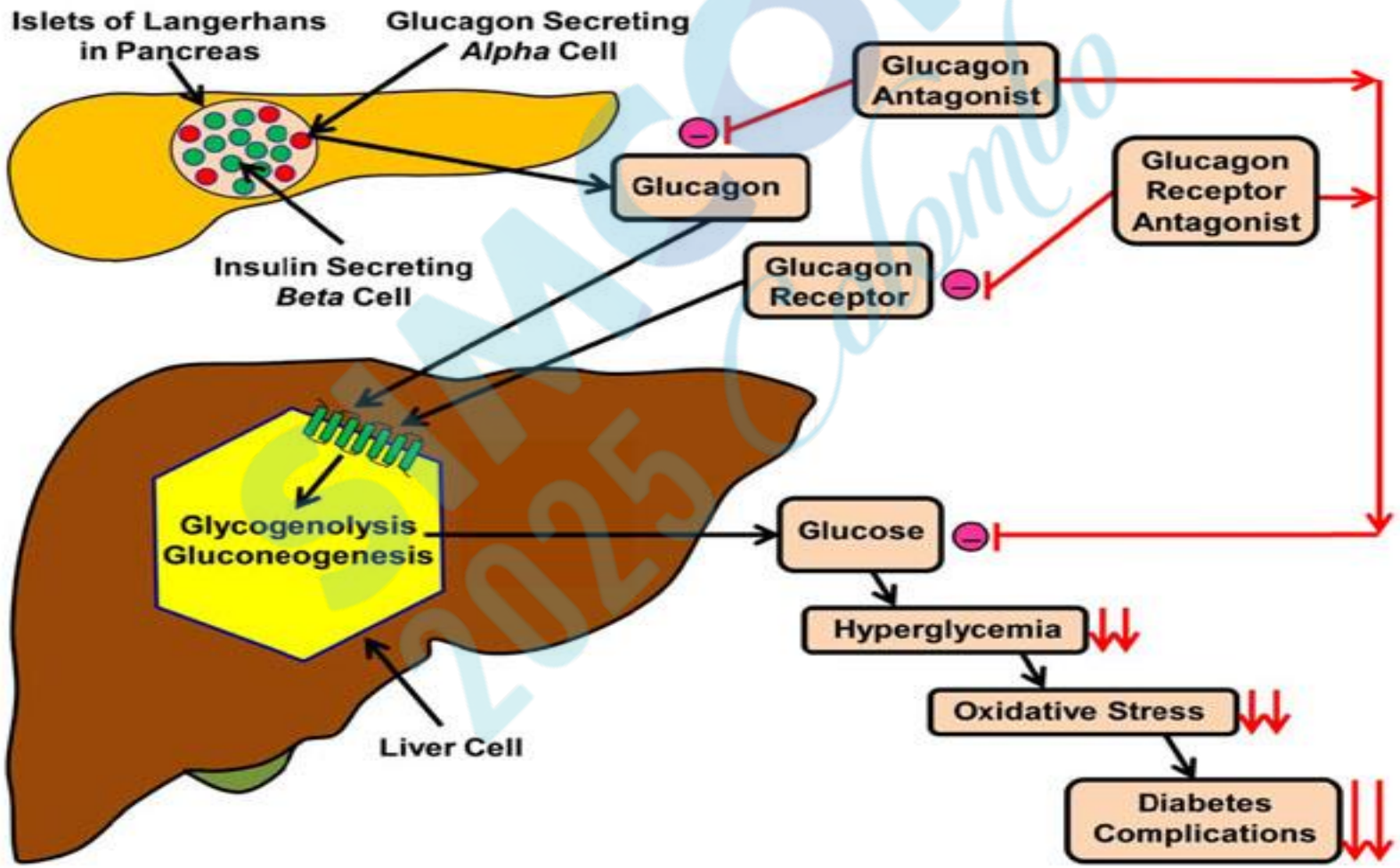
Newer targets

Pancreatic-G-protein-coupled fatty-acid-receptor agonists

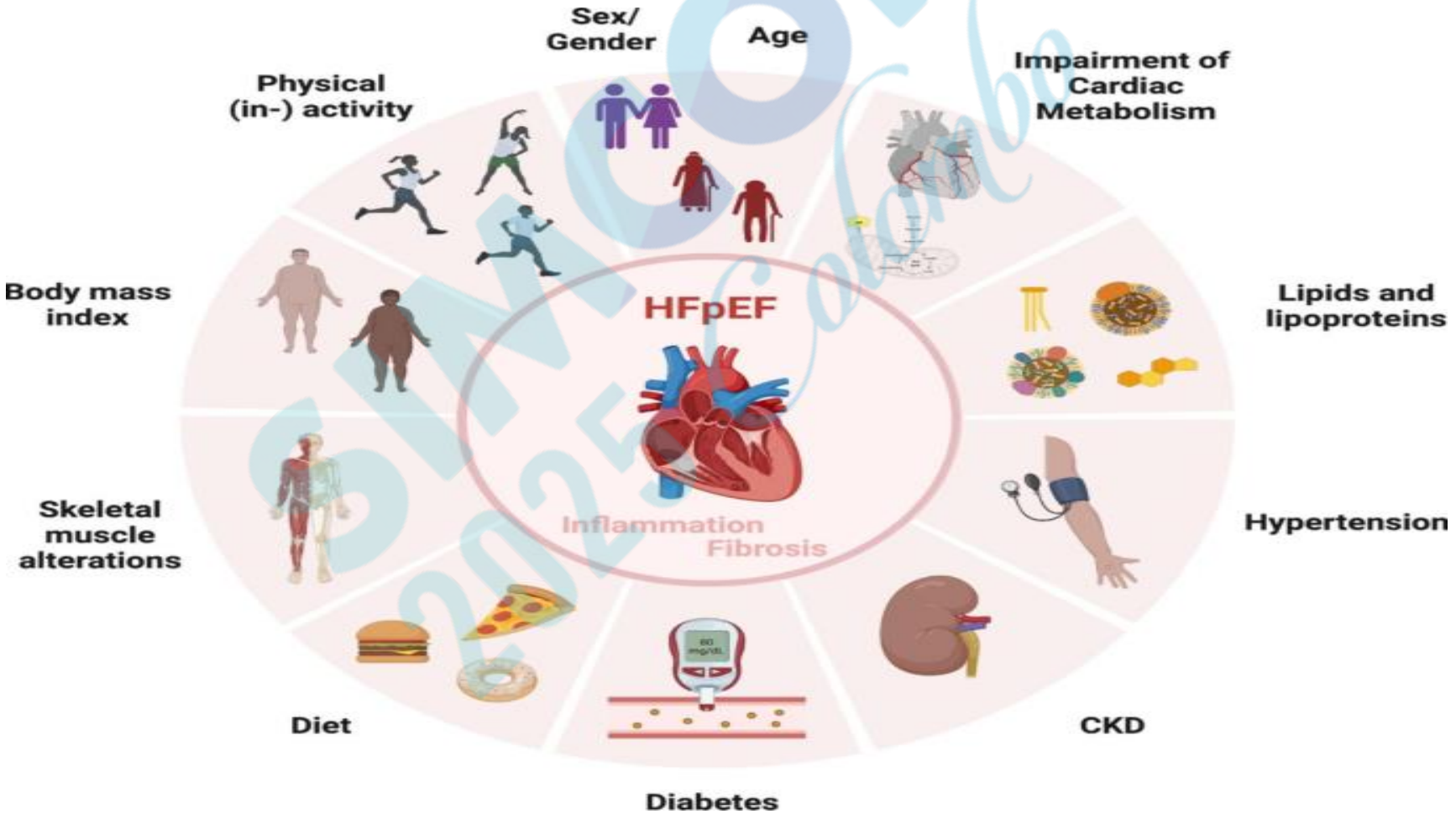


Newer targets

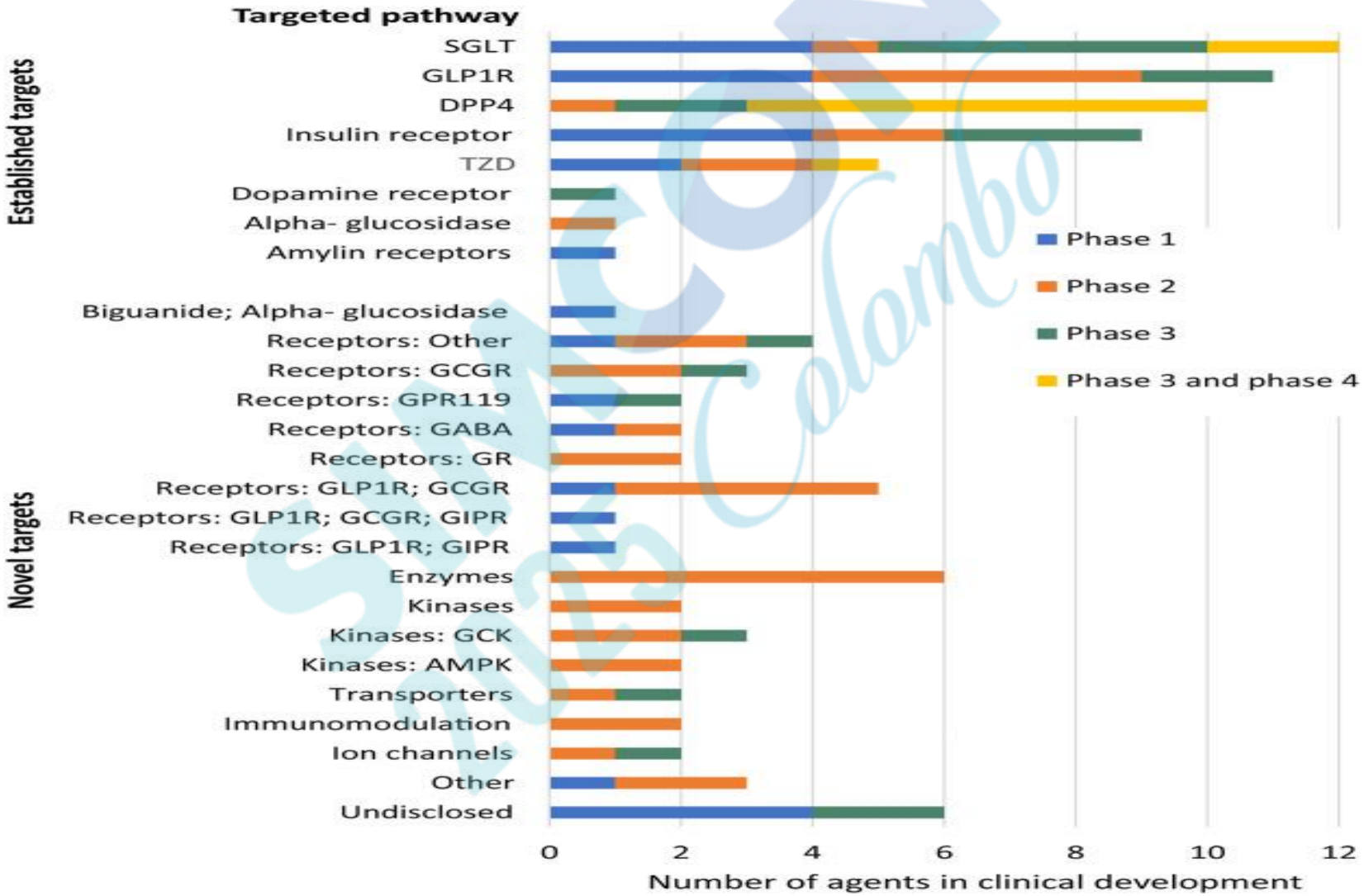
Glucagon-receptor antagonists



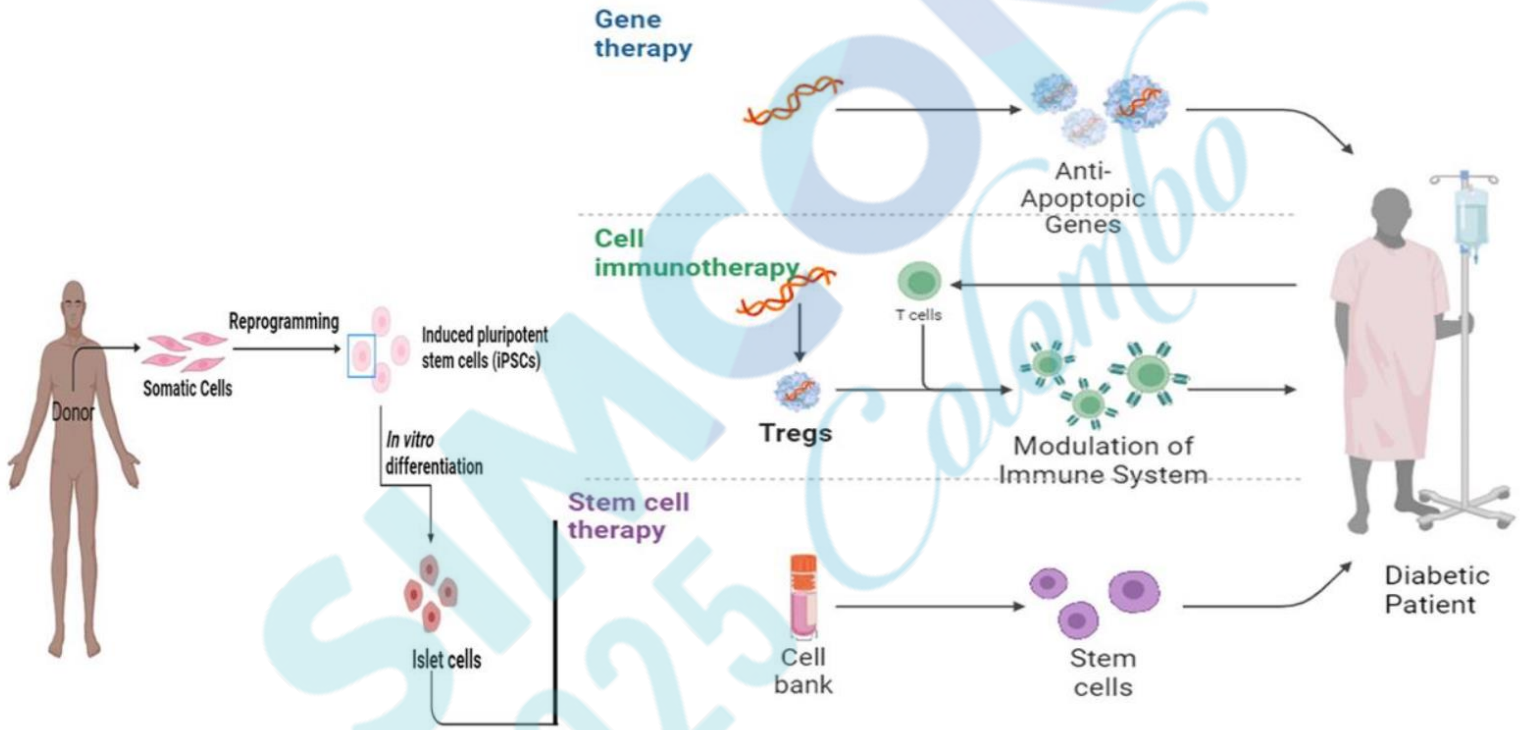
The non-steroidal mineralocorticoid receptor antagonist finerenone



Novel targets for anti diabetic agents

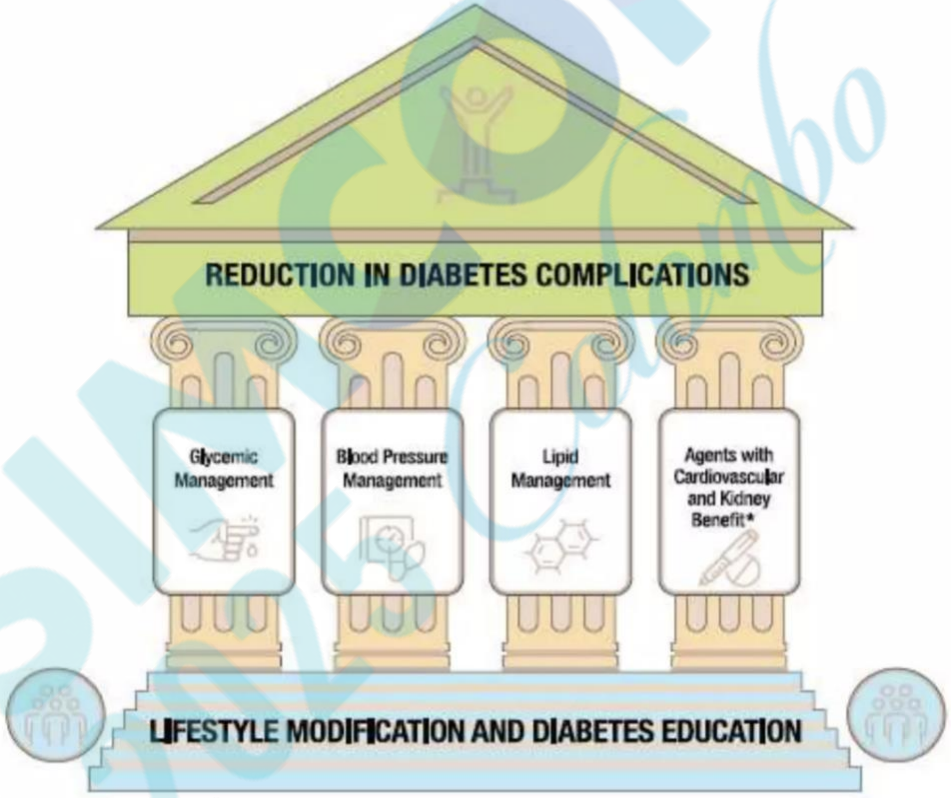


Newer targets



The impact of Embryonic stem cells, gene therapy and Immunotherapy in diabetes management

Cardiovascular disease and risk management

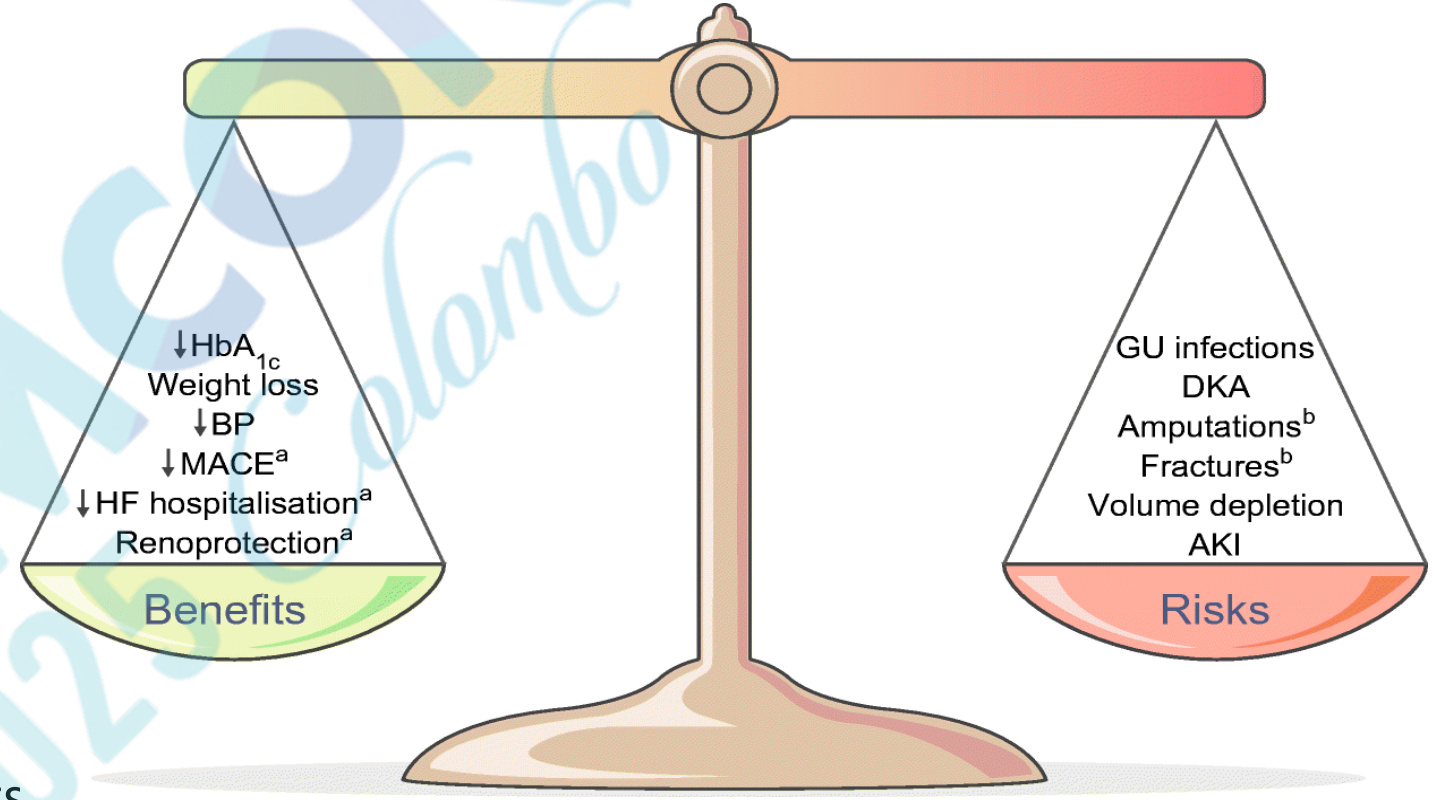


Foot care


Wear socks with loose garters
Wear covered shoes that fit well and protect the feet
DO wear these shoes
Avoid socks with tight garters
Avoid shoes that cramp the feet
DON'T wear these shoes

Summary

- DM-
  - Multisystem Disease
  - Metabolic disease
- Management
  - Conservative approach
  - Physical therapy
  - Diabetic educations
  - Old Drugs therapy
  - Newer drugs therapy
  - Diabetic technology
  - Reductions in risk managements
  - Reductions in complications



Thank you