TREATING DIABETES EFFECTIVELY AND AFFORDABLY IN 2025

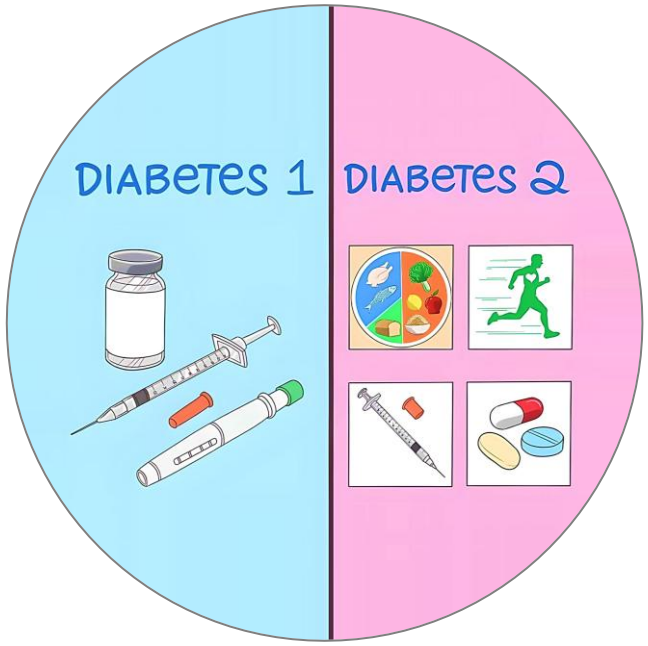
A COMPREHENSIVE APPROACH

ADD PRESENTERS NAME

OVERVIEW

- CLASSIFICATION OF DM
- EPIDEMIOLOGY OF T2DM
- PATHOPHYSIOLOGY OF T2DM
  - The Ominous Octet
- MANAGEMENT OF T2DM
  - General considerations
  - Treatment options
  - Focus on Gliptins

CLASSIFICATION



CLASSIFICATION OF DIABETES

DIFFERENTIATE BETWEEN

- Type 1
  - Auto-immune destruction of cells in islands of Langerhans that produce insulin
  - Also known as insulin-dependent DM
  - Lifelong condition
  - Juvenile or childhood onset
- Type 2
  - Underproduction of insulin OR insulin resistance
  - Much more common
- Gestational diabetes
  - Develops during pregnancy
  - Returns to normal, but with higher life-time risk
- Non-diabetic hyperglycaemia or prediabetes

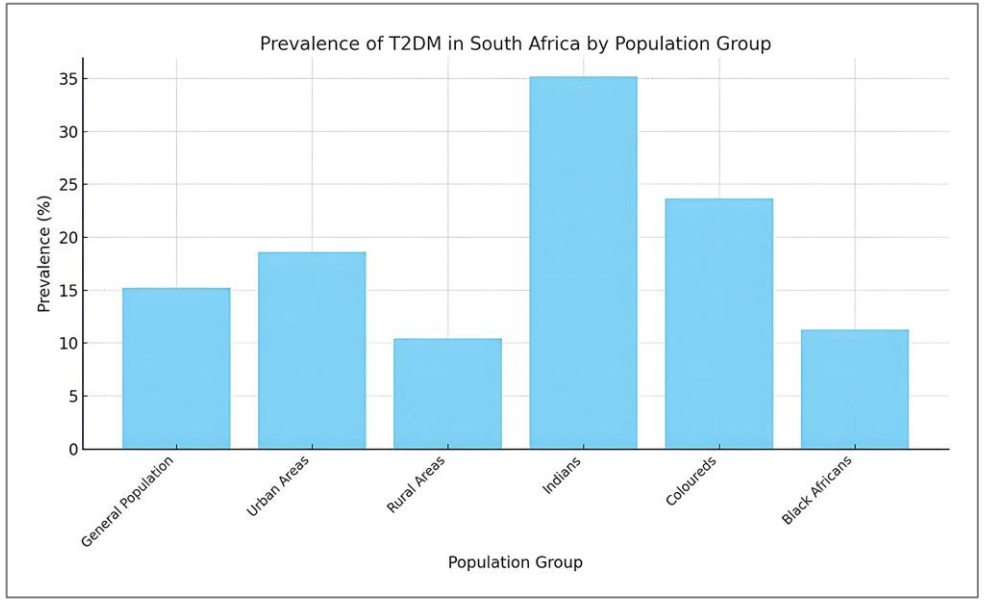
EPIDEMIOLOGY T2DM

BURDEN OF DISEASE – T2DM

SYSTEMATIC REVIEW AND META-ANALYSIS BY PHEIFFER ET AL

- 2021
- T2DM one of top 10 causes of death worldwide
- Prevalence in SA doubled from 2000 to 2009
  - 5,5% to 9%
    (almost 1 in every 10 people)
  - Current rates much higher
- Obesity is a major contributor
  - Excess bodyweight estimated to account for 87% of T2DM cases in SA
  - 69% of women and 39% of men in South Africa overweight or obese

PREVALENCE OF T2DM IN SA



SUBGROUP PREVALENCE

- T2DM prevalence among females was higher (16,78%) compared to males (12,36%), likely attributed to higher rates of obesity and insulin resistance in women. The prevalence increases with age, consistent with global trends.

URBAN VS. RURAL DISPARITIES

- Urban areas showed a higher prevalence (18,63%) compared to rural settings (10,44%). This difference is linked to urbanization's lifestyle changes, such as sedentary behavior and consumption of energy-dense diets.

DIAGNOSTIC TEST SENSITIVITY

- Among diagnostic methods, the Oral Glucose Tolerance Test (OGTT) was 30% more sensitive than Fasting Plasma Glucose (FPG), but FPG detected 36% more cases in some studies, showing variability in detection rates.

IMPAIRED GLUCOSE METABOLISM

- The prevalence of impaired glucose tolerance (IGT) was 9,59%, while impaired fasting glucose (IFG) was 3,55%. Newly diagnosed T2DM accounted for 8,29% of the population.

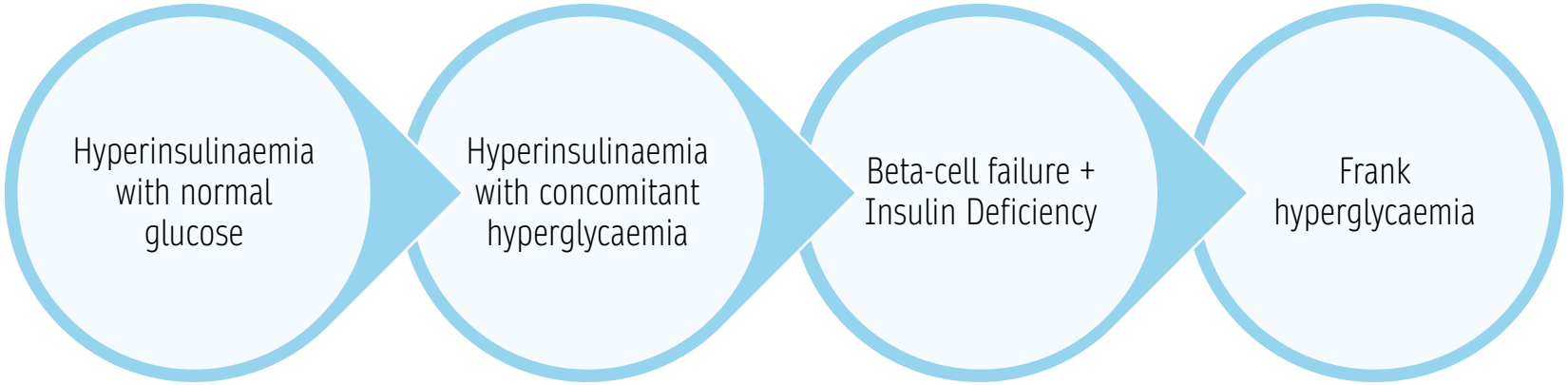
GENDER AND RISK FACTORS

- Women of reproductive age, especially urban Black African women, are identified as high-risk groups due to a 20,3% prevalence of IGT, highlighting the intergenerational risk for obesity and T2DM.

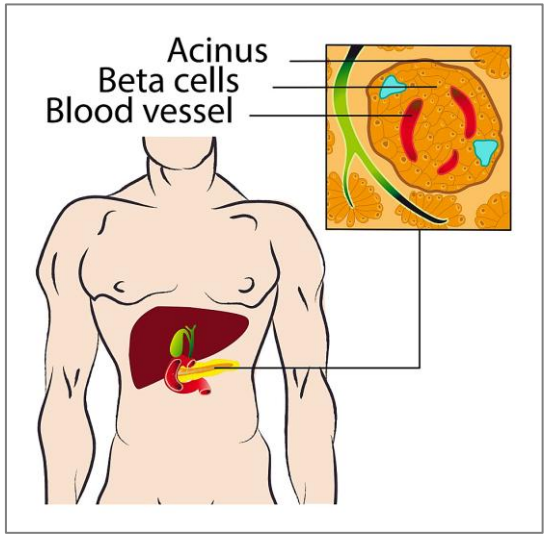
PATHOPHYSIOLOGY T2DM

DEVELOPMENT OF T2DM

- Develops along a spectrum



BETA-CELL DYSFUNCTION IN DIABETES



PROGRESSIVE BETA-CELL FAILURE IS CENTRAL TO T2DM PROGRESSION

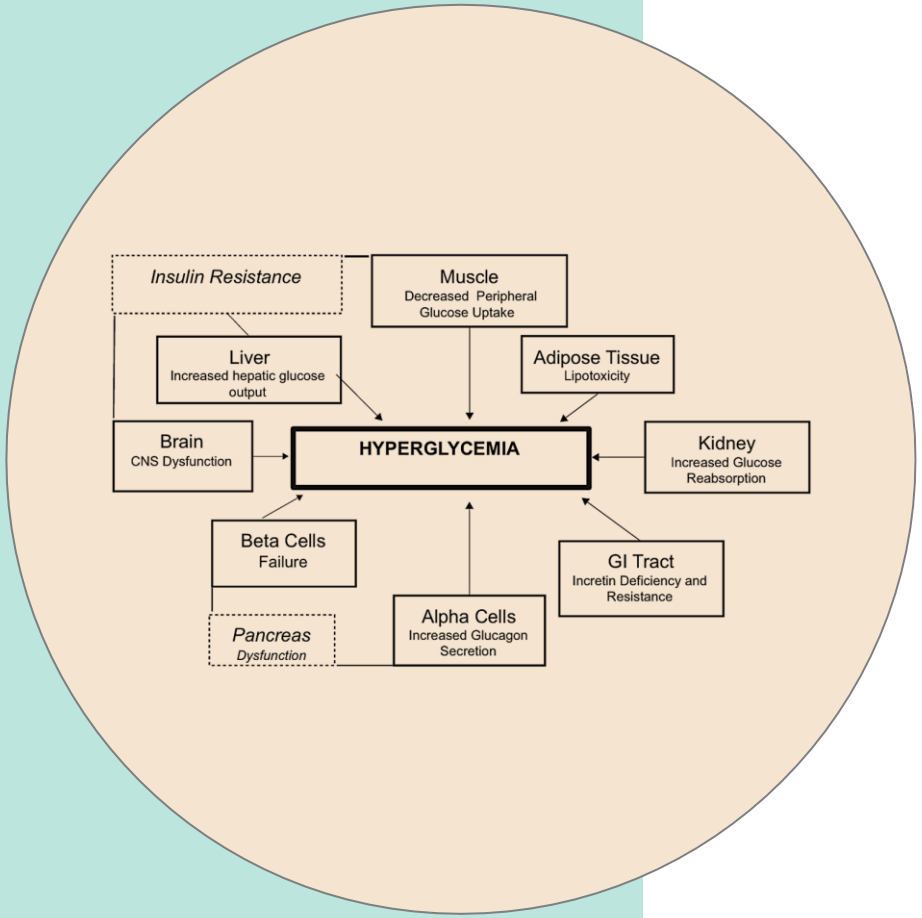
- Declining insulin secretion ultimately disrupts glucose homeostasis

FACTORS

- Genetic predisposition, glucotoxicity, lipotoxicity.

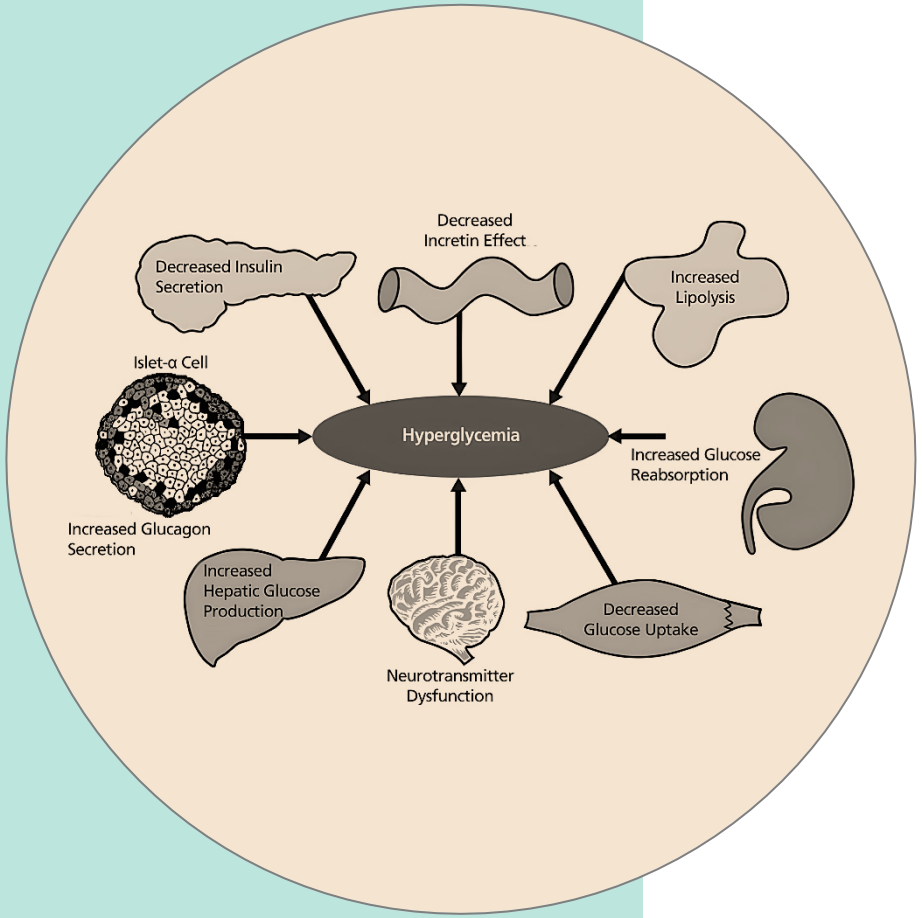
KEY STAGES IN B-CELL DYSFUNCTION

1. Compensation: In response to insulin resistance, beta-cells increase insulin secretion to maintain normal glucose levels. This is achieved through beta-cell hyperplasia and heightened secretory activity.
2. Adaptation: Beta-cells begin to show signs of stress, with reduced functional capacity and impaired glucose-stimulated insulin secretion. Fasting glucose levels may remain near-normal, but postprandial glucose levels begin to rise.
3. Decompensation: Chronic stress from glucotoxicity, lipotoxicity, and oxidative damage leads to beta-cell apoptosis and loss of mass. Insulin secretion becomes inadequate, resulting in persistent hyperglycaemia and the clinical onset of overt diabetes.
4. Failure: In advanced stages, severe beta-cell dysfunction and loss of mass occur, with minimal or no insulin production. Patients may become dependent on exogenous insulin to manage glucose levels.



UNDERSTANDING T2DM: THE OMINOUS OCTET

- Beta-cell dysfunction
- Insulin resistance
- Glucagon dysregulation
- Lipotoxicity
- Incretin deficiency
- Renal glucose reabsorption
- Neurotransmitter dysfunction
- Hepatic glucose production



ORGAN INVOLVEMENT IN THE OMINOUS OCTET

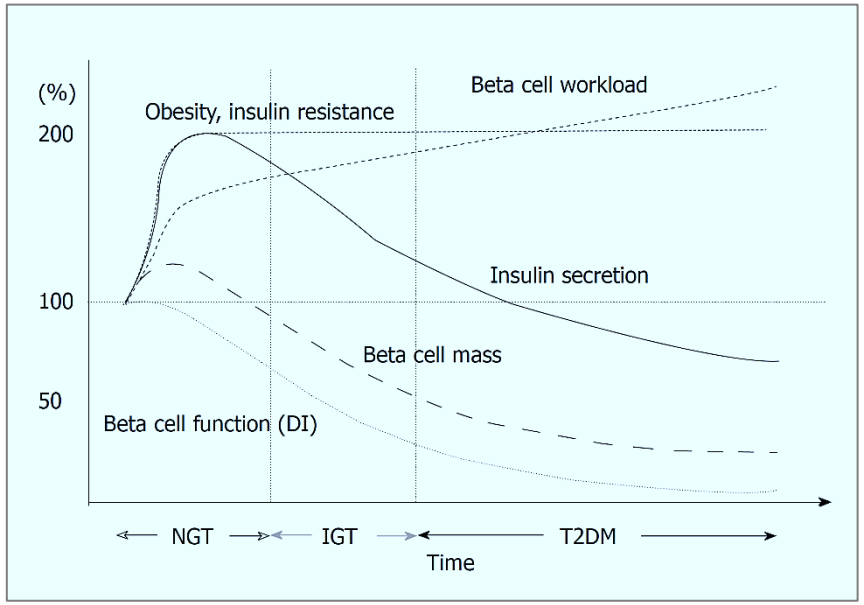
1. LIVER: Insulin resistance and increased glucose production
2. MUSCLE: Insulin resistance and reduced peripheral glucose uptake
3. BRAIN: Insulin resistance and CNS dysfunction
4. ADIPOSE TISSUE: Insulin resistance, lipotoxicity, and proinflammatory markers
5. KIDNEYS: Increased glucose production and reabsorption
6. GI TRACT: Incretin hormone dysfunction and resistance
7. PANCREATIC BETA-CELLS: Failure and dysfunction
8. PANCREATIC ALPHA-CELLS: Hyperglucagonemia

MANAGEMENT

GENERAL CONSIDERATIONS

T2DM MANAGEMENT CHALLENGES

- Diabetogenic environment
  - Obesity, consumption of unhealthy food, reduced physical activity, increased screen time
- Health literacy
  - Understanding effects and side effects; understanding importance of compliance
- Reimbursement issues
- Inertia in screening and management
  - Screen also for complications (eye, kidney, etc.)
- Establishing a constructed, stepwise patient management system



GENERAL CONSIDERATIONS

NEED FOR SUSTAINED GLYCEMIC CONTROL AND BETA-CELL PRESERVATION

- T2DM never develops without beta-cell dysfunction
- Beta-cell dysfunction associated with **Rx failure** and **poor control**
- Not possible to recover B-cell functional mass
- Can reduce its workload
  - LIFESTYLE MODIFICATION and WEIGHT LOSS
  - Improve insulin sensitivity
  - Consider incretin medications over sulfonylureas as secretagogues
    - Low risk of hypoglycaemia
    - Low risk of weight gain

GENERAL CONSIDERATIONS

ECONOMIC CONSIDERATIONS IN TREATMENT SELECTION

- (South) Africa grappling with high rates of HIV/AIDS and TB, maternal and childhood mortality, and injury-related disorders
  - In addition to non-communicable diseases such as T2DM
  - Overburdened and under-resourced health systems
- NDOH Guidelines on Diabetes Management limit options in public sector
- Reimbursement decisions/co-payments limit options in private sector

TREATMENT OF T2DM

AVAILABLE OPTIONS

- Oral antihyperglycaemic agents
  - Sensitisers (metformin, thiazolidinediones)
  - Secretagogues (sulfonylureas, glinides, **gliptins**)
  - Enhancers of glucosuria (SGLT2-inhibitors or gliflozins)
- Injectable antihyperglycaemic agents
  - GLP-1 receptor agonists (semaglutide, liraglutide, exenatide)
  - Dual incretin agonists (tirzepatide)
- Insulin
- Disease modifying medications (teplizumab)

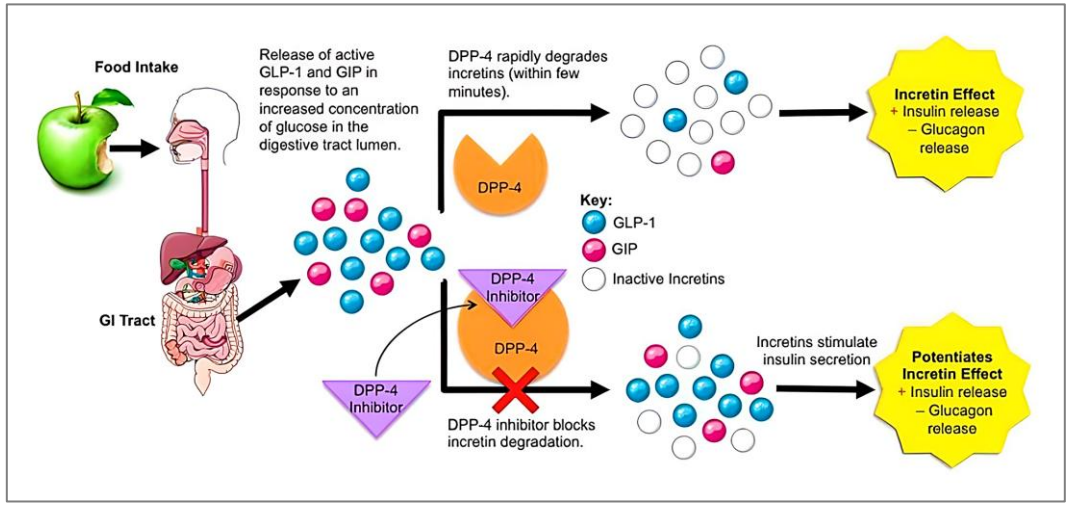
MEDICATIONS FOR LOWERING GLUCOSE

		Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects	
					Effect on MACE	HF
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral
SGLT2 inhibitors		Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
GLP-1 RAs		High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral
Dual GIP and GLP-1 RA		Very high	No	Loss (very high)	Under investigation	Under investigation
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral
Insulin	**Human**	High to very high	Yes	Gain	Neutral	Neutral
	Analogs					

MEDICATIONS FOR LOWERING GLUCOSE

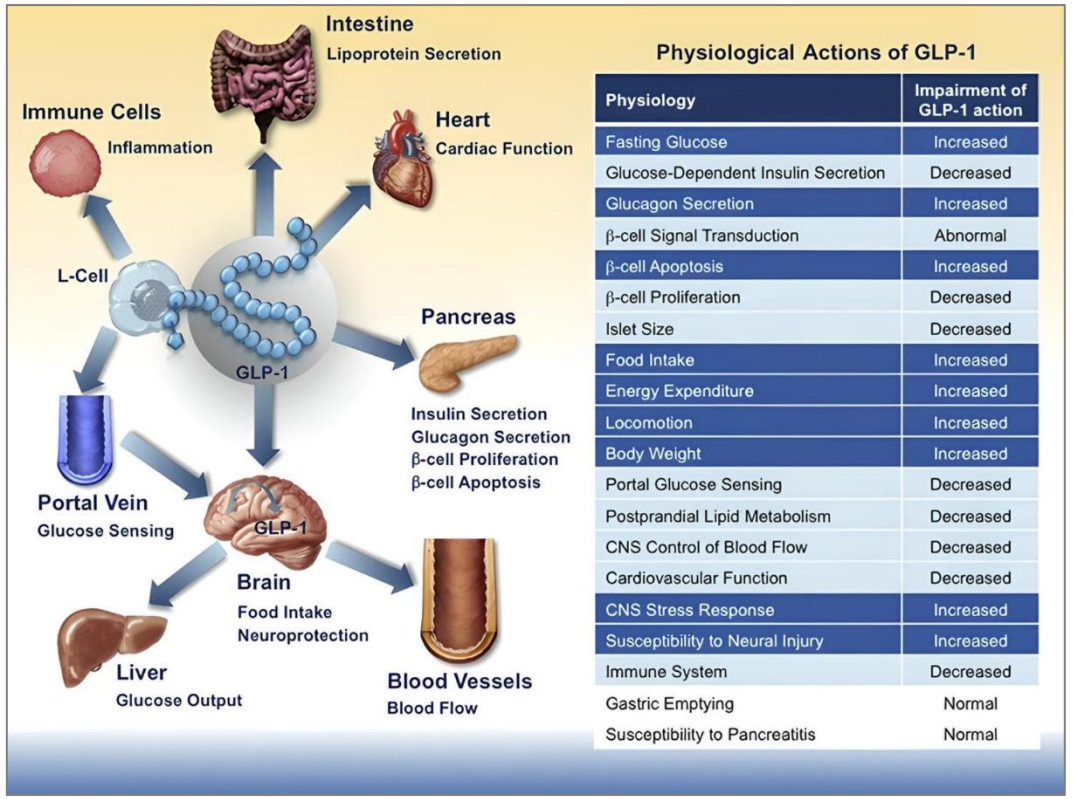
		Renal effects		Oral/SQ	Cost	Clinical considerations
		Progression of DKD	Dosing/use considerations*			
Metformin		Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors		Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs		Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Counsel patients about potential for ileus • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
Dual GIP and GLP-1 RA		Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Not recommended for individuals with history of gastroparesis • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
DPP-4 inhibitors		Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected
Thiazolidinediones		Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)		Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycemia
Insulin	**Human**	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs			SQ	High	

GLIPTINS



GLIPTINS: MECHANISM OF ACTION

- Inhibit DPP-4 enzymes, preventing incretin degradation, in a reversible and competitive manner
- Enhance GLP-1 and GIP activity, boosting insulin release
- Suppress glucagon, reducing hepatic glucose production

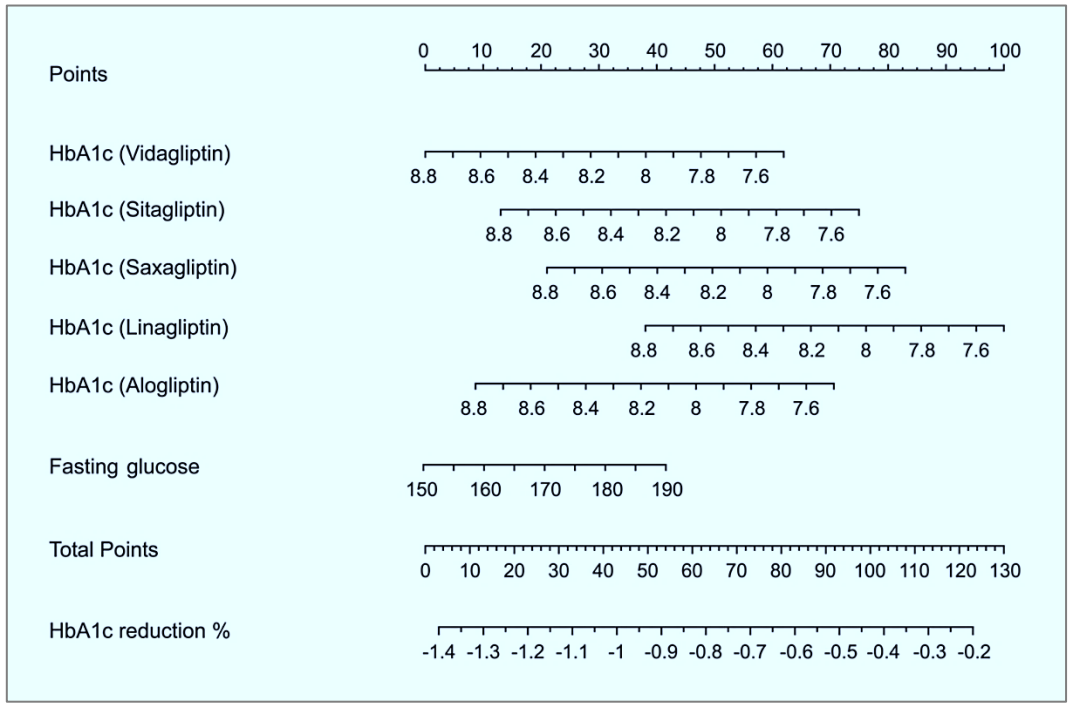


Physiological Actions of GLP-1

Physiology	Impairment of GLP-1 action
Fasting Glucose	Increased
Glucose-Dependent Insulin Secretion	Decreased
Glucagon Secretion	Increased
β-cell Signal Transduction	Abnormal
β-cell Apoptosis	Increased
β-cell Proliferation	Decreased
Islet Size	Decreased
Food Intake	Increased
Energy Expenditure	Increased
Locomotion	Increased
Body Weight	Increased
Portal Glucose Sensing	Decreased
Postprandial Lipid Metabolism	Decreased
CNS Control of Blood Flow	Decreased
Cardiovascular Function	Decreased
CNS Stress Response	Increased
Susceptibility to Neural Injury	Increased
Immune System	Decreased
Gastric Emptying	Normal
Susceptibility to Pancreatitis	Normal

THE SCOPE OF INCRETIN INFLUENCE

- Incretins, primarily GLP-1 and GIP, are gut hormones that enhance glucose-dependent insulin secretion.
- GLP-1 also suppresses glucagon, slows gastric emptying, and promotes satiety, while both are rapidly degraded by DPP-4.
- Therapies like GLP-1 receptor agonists and DPP-4 inhibitors leverage incretin pathways to improve glycaemic control with minimal hypoglycaemia risk.



CLINICAL BENEFITS OF GLIPTINS

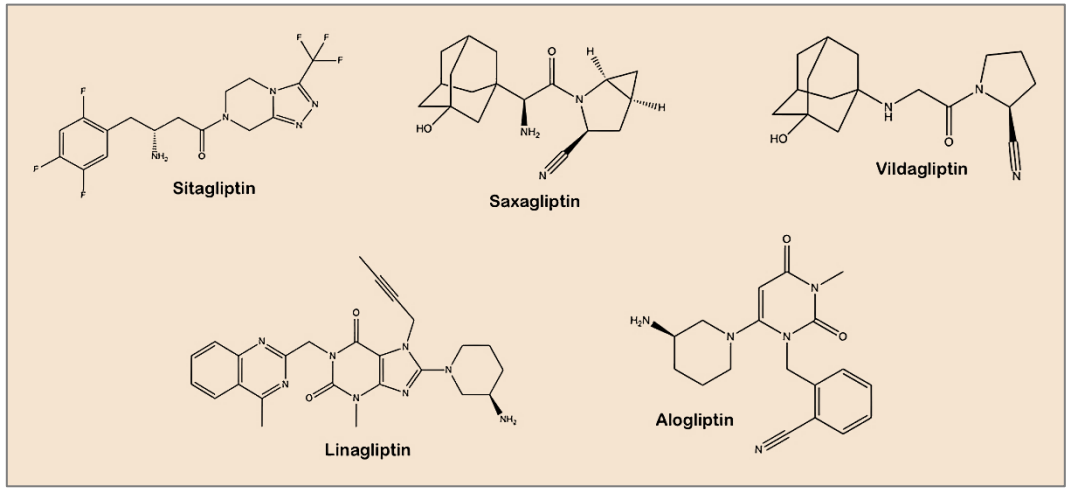
- HbA1c reduction: 0,5% to 1,2%
- Weight neutrality, low hypoglycaemia risk
- Improved beta-cell function and insulin sensitivity

SEMDSA
Society for Endocrinology, Metabolism and Diabetes of South Africa

9.4: Drug summary - DPP-4-inhibitors

Mode of action and pharmacology	DPP-4 inhibitors (gliptins) are capable of inhibiting the degradation of endogenous GLP-1, thereby therapeutically raising circulating GLP-1 levels.			
Glycaemic efficacy and indications	Can be used as monotherapy in selected patients when there is intolerance to metformin (where there is a high risk for hypoglycaemia). Can be used as dual or triple therapy when added to metformin / sulphonylurea / SGLT 2 inhibitor / insulin. HbA_{1c} reduction when used as monotherapy is between 0.5 and 1.1 %.			
Macrovascular and Mortality Outcomes	Cardiovascular outcome safety trials for all 3 DPP-4 inhibitors have been neutral for major adverse cardiovascular events. Saxagliptin was associated with increased rates of hospitalisation for heart failure.			
Hypoglycaemia	Hypoglycaemia rates are not different to placebo except when DPP 4 inhibitors are combined with insulin or insulin secretagogues.			
Non-glycaemic benefits	Weight-neutral.			
Side Effects and Precautions	Small absolute risk for pancreatitis. Increased risk of hospitalisation for heart failure with saxagliptin.			
Contraindications	Acute, chronic or recurrent pancreatitis or high risk for pancreatitis. Pancreatic cancer. All are contraindicated in severe liver disease. Use saxagliptin and vildagliptin with caution in moderate liver disease. Heart failure (saxagliptin).			
Dosing	*eGFR*	**Saxagliptin**	**Sitagliptin**	**Vildagliptin**
	≥50 ml/min	5 mg daily	100 mg daily	50 mg twice a day
	30-50 ml/min	2.5 mg daily	50 mg daily	50 mg daily
	<30 ml/min	2.5 mg daily	25 mg daily	50 mg daily
Cost at maximum dose	Moderate (R260 – 340 per month - single exit pricing as at March 2017)			

SEMDSA 2017 Recommendations for DPP-4 inhibitors	
Consider a DPP-4 inhibitor as initial monotherapy when metformin is contraindicated or not tolerated.	C
Consider a DPP-4 inhibitor as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.	A
Consider a DPP-4 inhibitor as the third glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.	A
Combination DPP-4 inhibitor and insulin therapy should be initiated at specialist level.	C
Be aware of dose adjustments for chronic kidney disease.	C
Circumstances where a DPP-4 inhibitor may be preferred to other treatment options: ◦ As the 2nd add-on drug when gliclazide MR is contraindicated or not tolerated. ◦ As the 3rd add on drug for most patients if HbA_{1c} targets are potentially achievable. ◦ Older patients with multiple comorbidities. ◦ Patients with stage-4 chronic kidney disease (can be used without risk of hypoglycaemia). ◦ If a fixed-dose combination tablet will improve adherence, compliance and/or cost-effectiveness.	C
Circumstances where a DPP-4 inhibitor may not be the preferred option: ◦ Very high HbA_{1c} and the glycemic target is not likely to be achieved with a DPP-4 inhibitor. ◦ History of pancreatitis or pancreatic tumour. ◦ History of heart failure or high risk of heart failure (saxagliptin). ◦ Liver disease: moderate (do not use saxagliptin or vildagliptin) or severe (do not any DPP-4 inhibitor).	C



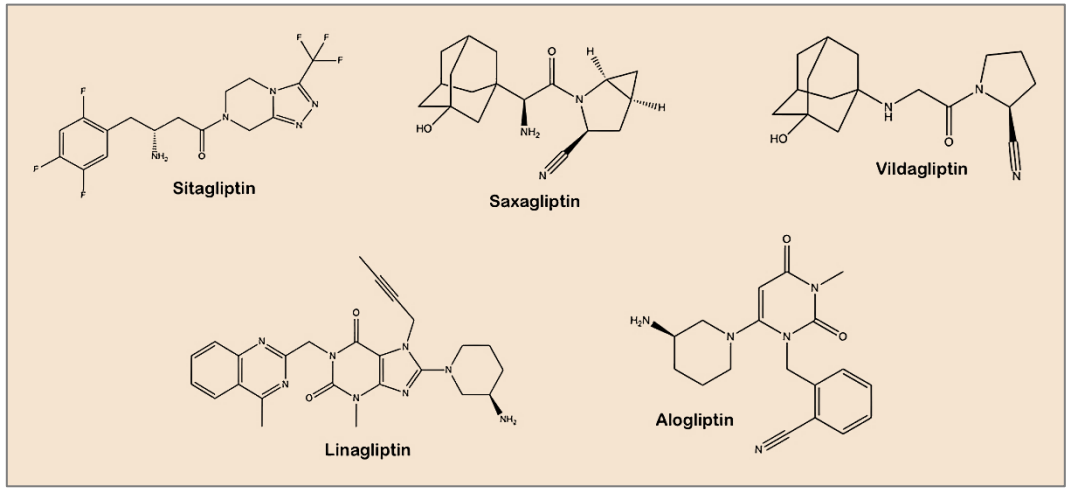
DPP4-INHIBITORS: STRUCTURE

PEPTIDOMIMETICS

- Vildagliptin, saxagliptin
- Lesser selectivity toward DPP-4 compared to DPP8/9
  - Greater possibility of side effects (e.g., allergic skin manifestations)
- Forms reversible covalent enzyme-inhibitor complexes resulting in persistent DPP4 inhibition (exceeding half-life of molecule)

NON-PEPTIDOMIMETICS

- Sitagliptin, linagliptin, alogliptin
- Greater selectivity toward DPP-4 compared to DPP8/9
- Non-covalent extracellular interactions resulting in potent, immediate inhibition



COMPARATIVE DATA ON GLIPTINS

SITAGLIPTIN ADVANTAGES

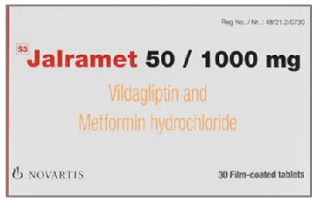
- Lower risk of hypoglycaemia with glucose-dependent insulin secretion
- Convenient once-daily dosing, improving adherence
- Favourable cardiovascular safety profile in multiple studies
- Effective across diverse populations

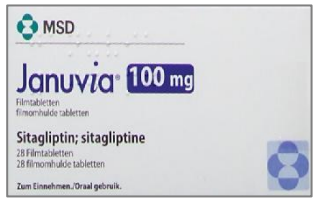
VILDAGLIPTIN ADVANTAGES

- Comparable cardiovascular safety profile
- Massive cohort of data

LINAGLIPTIN

- Favourable safety profile, no dose adjustment in renal impairment





CONTINUATION: SITAGLIPTIN VS. VILDAGLIPTIN

- RENAL DOSE ADJUSTMENTS
  - Sitagliptin
    - Safer across a wider range of renal impairments
  - Vildagliptin
    - Requires more cautious use with renal limitations
- HEPATIC SAFETY PROFILE
  - Sitagliptin
    - Safe even in mild to moderate hepatic impairment
  - Vildagliptin
    - Contraindicated in any hepatic impairment
- SELECTIVITY FOR DPP4 ENZYME
  - Sitagliptin
    - Superior selectivity, reducing off-target effects
  - Vildagliptin
    - Less selective, leading to potential non-specific interactions

Table 1: Pharmacokinetic profile of DPP-4 inhibitors/gliptins[14-18,28-34,40-43]

	Chemistry	Metabolism	Elimination route
Sitagliptin (US, FDA approved)	Non-peptidomimetic (β-amino acid-based)	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin (EU, approved)	Peptide-like	Hepatically hydrolyzed to inactive metabolite	Renal (22% as parent, 55% as metabolite)
Alogliptin (Japan, approved)	Non-peptidomimetic (modified pyrimidinedione)	Not appreciably metabolized	Renal (>70% unchanged as parent)
Saxagliptin (US FDA approved)	Peptide-like	Some metabolism to active metabolite	Renal (12-29% as parent, 21-52% as metabolite)
Linagliptin (US, FDA approved)	Non-peptidomimetic (xanthine)	Not appreciably metabolized	Biliary (unchanged as parent); <6% via kidney

Table 2: Pharmacokinetic profile continued[14-18,28-34,40-43]

	Dosing	Compound t½ (half-life)	DPP-4 inhibition	Drug interactions
Sitagliptin (launched)	100 mg qd	8-24 h	Max ~97%; >80% 24 h post-dose	None known
Vildagliptin (launched)	50 mg bid	1½-4½ h	Max ~95%; >80% 12 h post dose	None known

Table 3: DPP-4 inhibitor *in vitro* selectivity, (fold selectivity for DPP-4 vs. other enzymes)[14-18,28-34,40-43]

	FAPα	DPP-8	DPP-9
Vildagliptin	285	270	32
Sitagliptin (highly selective)	>5 550	>2 660	>5 550

ADDITIONAL KEY INSIGHTS

COMBINATION THERAPIES

- Sitagliptin
  - Flexible combinations, safer in hepatic and renal impairments
- Vildagliptin
  - Effective in triple therapy with SU and Metformin

RECEPTOR SELECTIVITY AND PHARMACOKINETICS

- Sitagliptin
  - Highly selective (>5,550-fold), renal excretion
- Vildagliptin
  - Less selective, renal and hepatic excretion

BENEFITS OF DPP4-INHIBTORS

COST AND ACCESSIBILITY

- Comparable cost to traditional therapies
- Long-term savings from reduced complications
- Potential for improved adherence due to fewer side effects

SAFETY AND TOLERABILITY

- Minimal risk of hypoglycemia
- No significant weight gain
- Rare side effects
  - Headache, nasopharyngitis

GLIPTINS VS. SULFONYLUREAS

REDUCED RISK OF HYPOGLYCAEMIA

- DPP-4 inhibitors: Have a glucose-dependent mechanism of action, enhancing insulin secretion only when blood glucose levels are elevated. This minimizes the risk of hypoglycaemia.
- Sulfonylureas: Stimulate insulin secretion irrespective of blood glucose levels, increasing the risk of hypoglycaemia, especially in elderly or renally impaired patients.

WEIGHT NEUTRALITY

- DPP-4 inhibitors: Typically associated with weight neutrality, making them a better option for patients concerned about weight gain.
- Sulfonylureas: Often lead to weight gain due to sustained insulin secretion.

BETA-CELL PRESERVATION

- DPP-4 inhibitors: May support beta-cell preservation by reducing the stress of continuous insulin production.
- Sulfonylureas: Prolonged stimulation can exhaust pancreatic beta cells, accelerating their decline in function over time.

CARDIOVASCULAR SAFETY

- SU associated with hypoglycemia-induced adrenergic responses and possible negative effects on ischemic preconditioning.

RENAL AND HEPATIC TOLERANCE

- DPP-4 inhibitors: Most are safe and well-tolerated in patients with renal impairment (dose adjustments may be needed for some agents like Sitagliptin).
- Sulfonylureas: Pose a higher risk of hypoglycemia in renal impairment due to prolonged drug clearance.

CONVENIENCE AND PATIENT ADHERENCE

- DPP-4 inhibitors: Administered as once-daily doses with a favorable safety profile, which can improve adherence.
- Sulfonylureas: While also available as once-daily doses, the risk of hypoglycemia can reduce patient confidence and adherence.

LACK OF RISK FOR PANCREATIC EXHAUSTION

- DPP-4 inhibitors: Enhance the natural incretin effect, working in tandem with physiological insulin needs.
- Sulfonylureas: Overstimulate beta cells, potentially hastening pancreatic burnout.

NEW DATA ON DPP4I

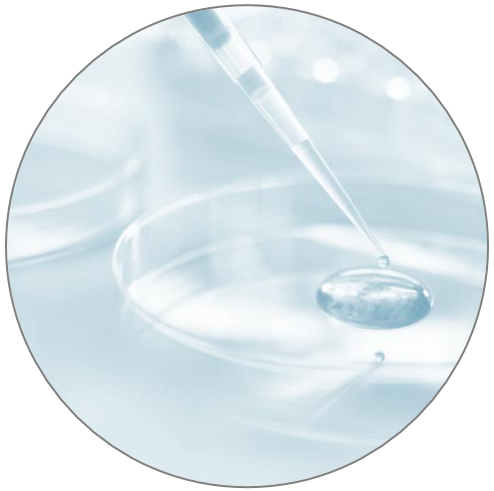
- Emerging evidence on DPP4i impact on BRCA2 stability and DNA repair
- Role in promoting DNA damage repair mechanisms
- Potential therapeutic implications for metabolic and oncological diseases

SUMMARY

- Gliptins as an effective T2DM therapy
- Addressing multiple facets of T2DM pathophysiology

QUESTIONS

Open floor for discussion and questions



THANK YOU

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