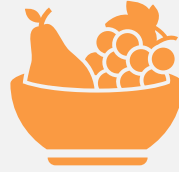




Diabetic Medications.

Clinical Presentation by Miracle Nkemjika

Overview



If lifestyle modifications (weight loss, dietary modification, and exercise) do not sufficiently reduce HbA1c levels (target level: ~ 7%), pharmacological treatment with diabetes medications should be initiated. These drugs can be classified according to their mechanism of action as-



insulinotropic or noninsulinotropic.



They are available as monotherapy or combination therapies, with the latter involving two or more diabetes medications and/or insulin.

Insulinotropic Medications :-

Stimulates the secretion of insulin from pancreatic β cells (also called Secretagogues).

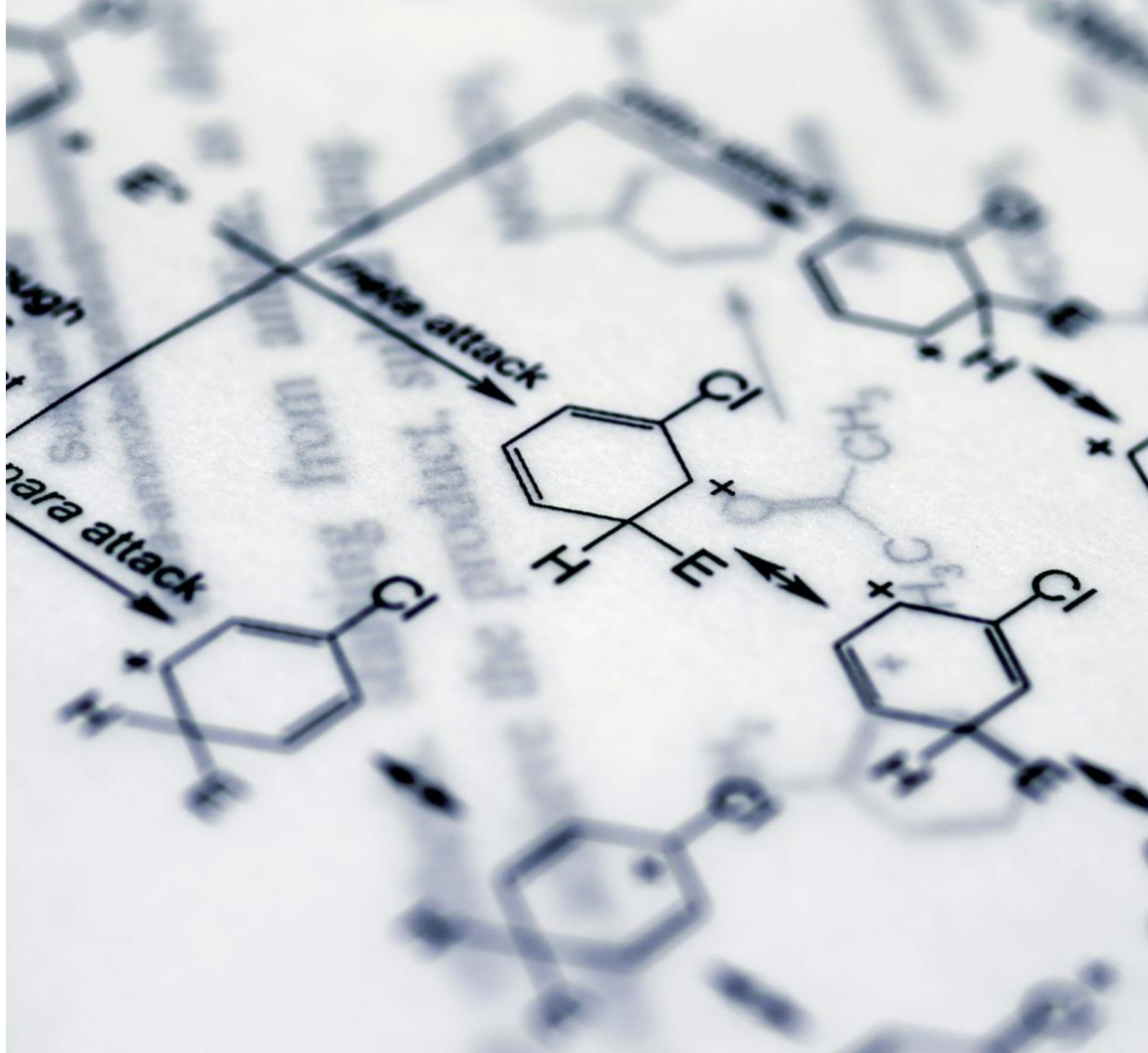
They are further divided to either be -

- Glucose-dependent (GLP-1 agonists, DPP-4 inhibitors): Insulin secretion is stimulated by elevated blood glucose levels (postprandially).
- Glucose-independent (sulfonylurea, meglitinides): Insulin is secreted regardless of the blood glucose level, even if blood glucose levels are low $\rightarrow$ risk of hypoglycemia

Depend on residual β -cell function.

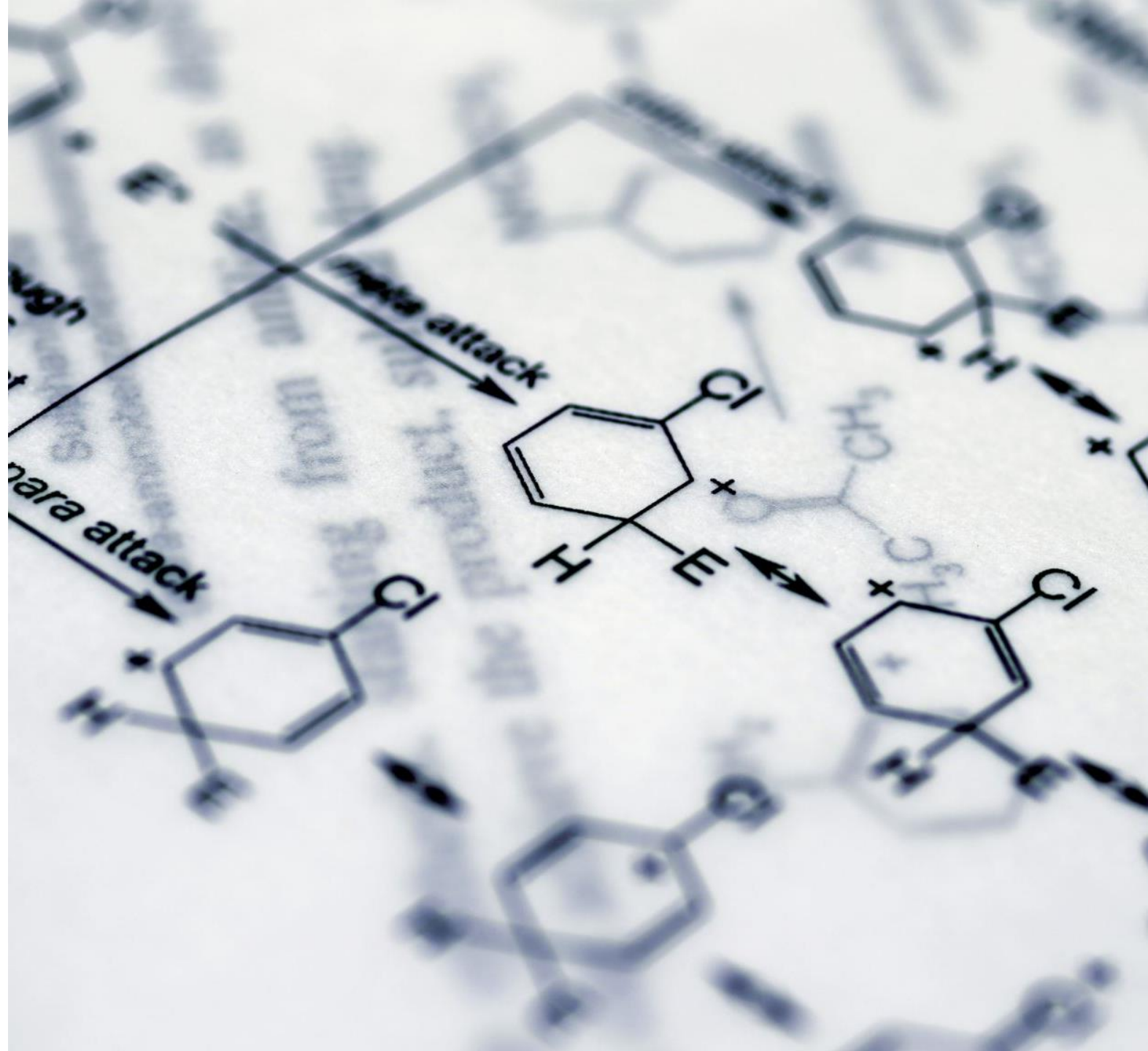
Glucagon – like peptide 1 agonist drugs :-

- These drugs Mimics incretins.
- Active agents
- Exenatide
- Liraglutide (a rapid release formular , administered daily)
- Albiglutide (an extended release formular administered once a week).
- Dulaglutide
- Semaglutide
- Lixisenatide.



Mechanism of Action of GLP-1s

- Clinical profile
- Mechanism of action
 - Incretin effect: food intake
→ activation of enteroendocrine cells in the gastrointestinal tract
→ release of GLP-1 → GLP-1 degradation via the enzyme DPP-4 → end of the GLP-1 effect
 - Incretin mimetic drugs bind to the GLP-1 receptors and are resistant to degradation by DPP-4 enzyme
→ ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)



Clinical Characteristics

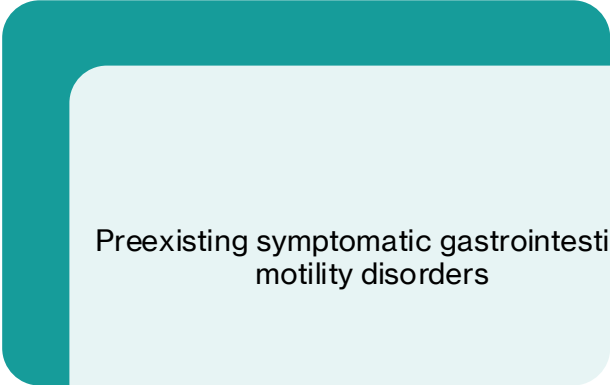
- Glycemic efficacy: lowers HbA1c by 0.5–1.5% over 3 months
- Subcutaneous injection (semaglutide also available as oral drug)
- Weight loss (may be wanted)
- No risk of hypoglycemia.

Side Effects

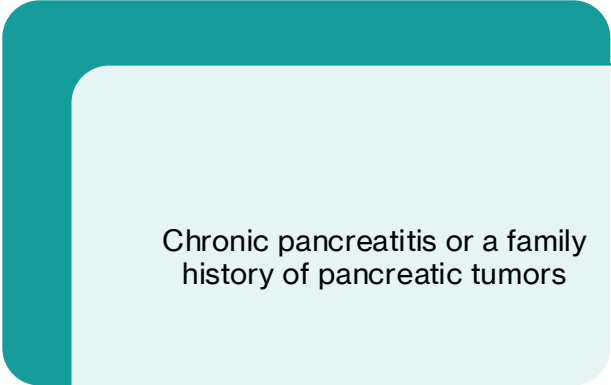
- Side effects
 - Gastrointestinal symptoms
 - Nausea, vomiting
 - Strong feeling of satiety (often desired)
 - Pancreatitis and potentially pancreatic cancer [18]
 - Potential risk of medullary thyroid cancer (MTC): further investigation required



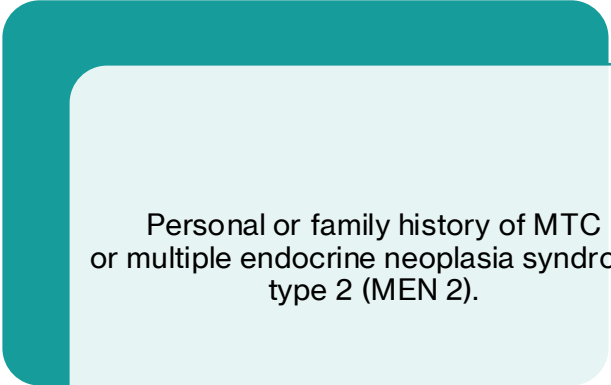
Contraindications.



Preexisting symptomatic gastrointestinal motility disorders



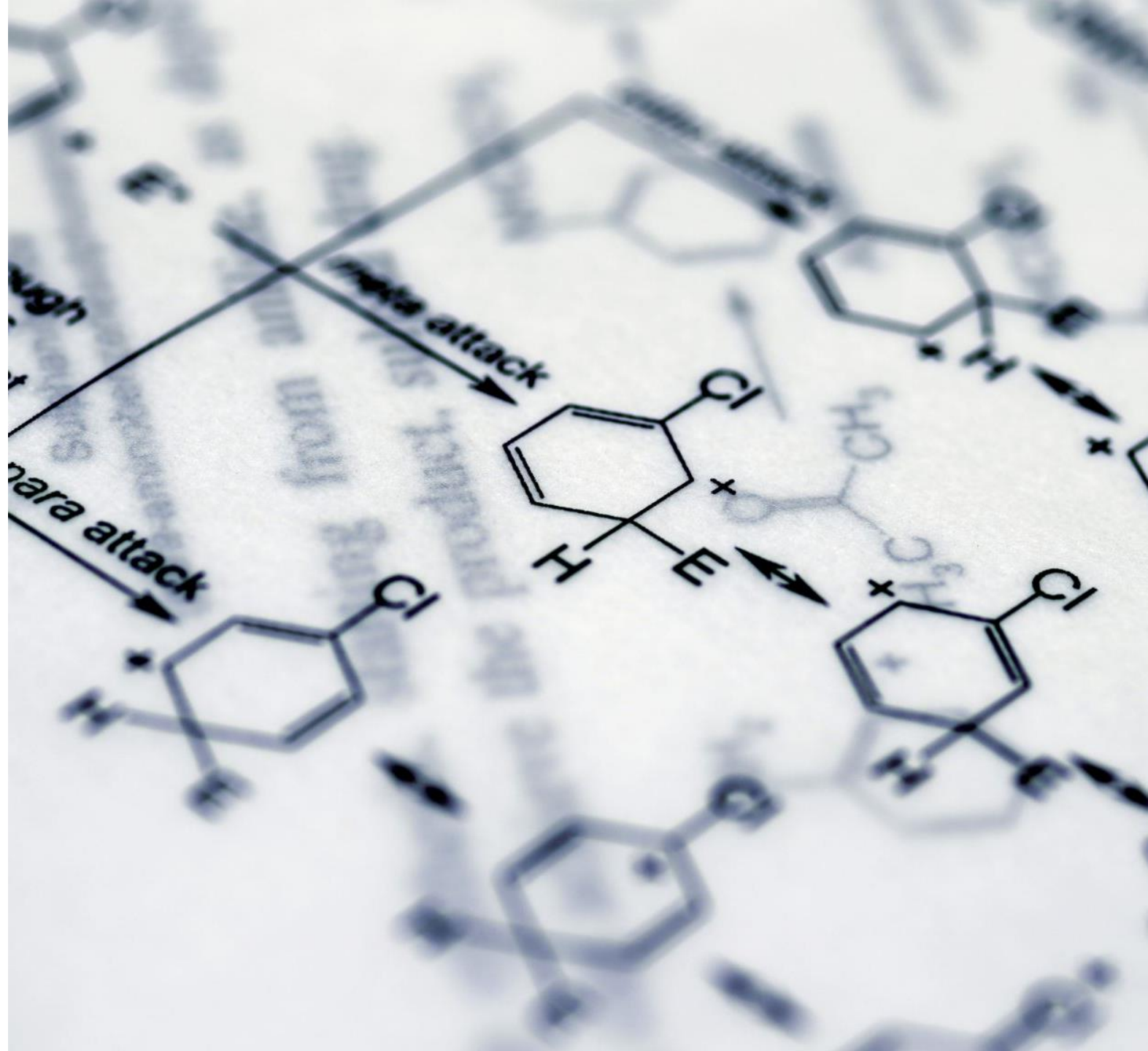
Chronic pancreatitis or a family history of pancreatic tumors



Personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2).

Dipeptidyl- Peptidase 4 inhibitors.

- Active agents
- Sitagliptin
- Saxagliptin
- Linagliptin
- Mechanism of action: indirectly increase the endogenous incretin effect by inhibiting the DPP-4 that breaks down GLP-1 → ↑ insulin secretion, ↓ glucagon secretion.



Clinical Characteristics:-

- Glycemic efficacy:
lowers HbA1c by 0.5–0.75% over 3 months
- No risk
of hypoglycemia unless insulin and/or insulinotropic drugs are used simultaneously because insulin release is glucose-dependent
- Usually no weight changes



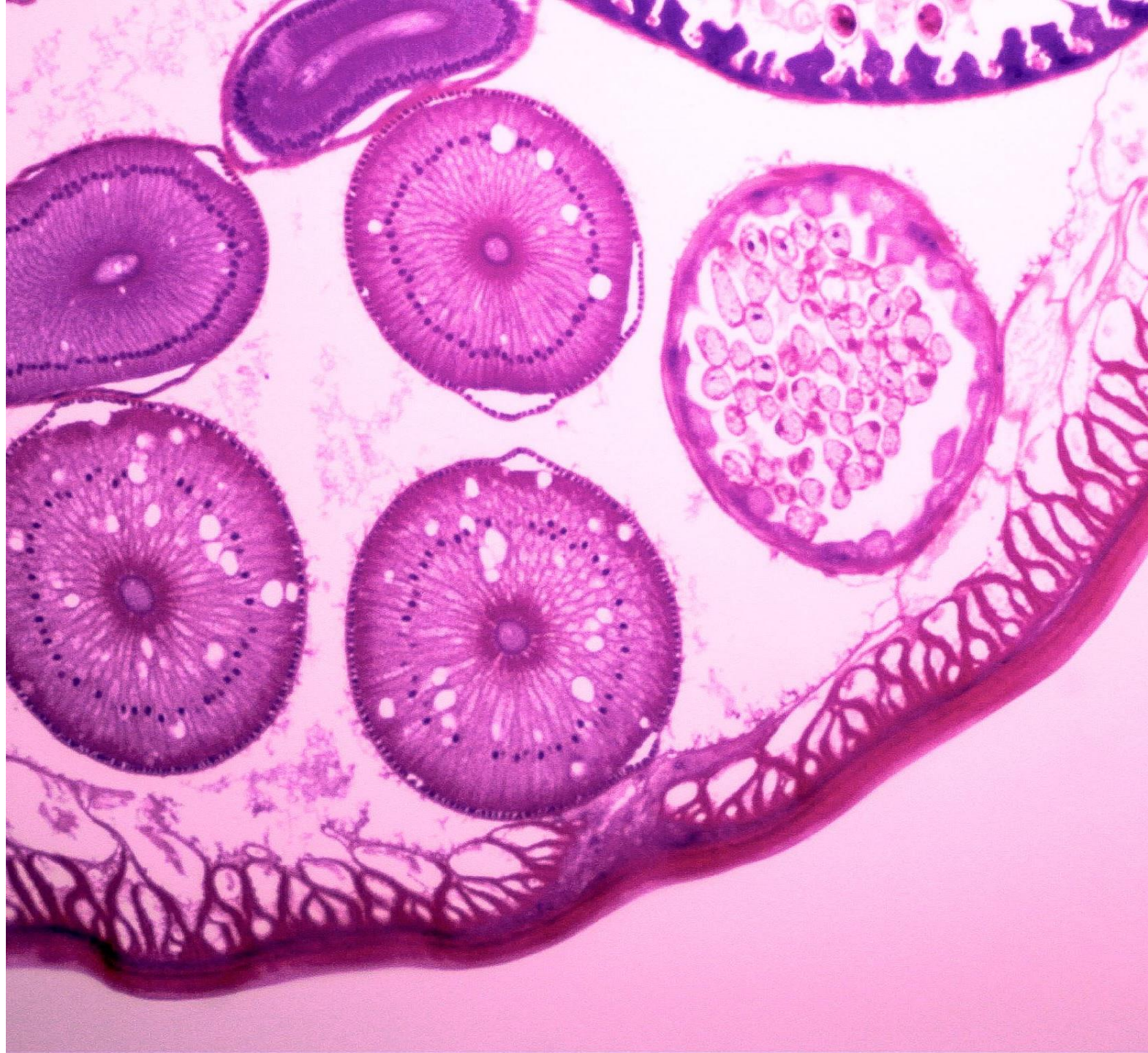


Side Effects:-

- Gastrointestinal symptoms: diarrhea, constipation(milder than in GLP-1 agonist exposure)
- Arthralgia
- Nasopharyngitis and upper respiratory tract infection (Sitagliptin).
- Urinary infections (mild)
- ↑ Risk of pancreatitis
- Worsening renal function, acute renal failure
- Headaches, dizziness.
- Bullious Pemphigoid (Drug – associated).
- Arthralgia / Joint pain.

Contraindications

- Liver failure
- Renal failure (Sitagliptin and saxagliptin are not contraindicated in patients with moderate to severe renal failure, but a dose adjustment is required. However, sitagliptin in combination with metformin is contraindicated in patients with renal impairment because of the risk of lactic acidosis.)
- Hypersensitivity.



Glucose – independent – Sulfonylureas:

Active agents

First generation

- Chlorpropamide
- Tolbutamide

Second generation

- Glyburide (long-acting agent)
- Glipizide (short-acting agent)
- Glimepiride

Mechanism of Action:

- Block ATP-sensitive potassium channels of the pancreatic β cells $\rightarrow$ depolarization of the cellmembrane $\rightarrow$ calcium influx $\rightarrow$ insulin secretion
- Extrapankreatic effect: $\downarrow$ hepaticgluconeogenesis, $\uparrow$ peripheral insulin sensitivity.

Clinical Characteristics:

Glycemic efficacy: lowers HbA1c by 1.2% over 3 months

Low cost.

Indications –

Patients who are not overweight, do not consume alcohol, and adhere to a consistent dietary routine

Generally not frequently used

Important Side Effects:

- Life-threatening hypoglycemia; increased risk under the following circumstances:
 - Simultaneous intake of CYP2C9 inhibitors(e.g., amiodarone, trimethoprim, fluconazole)
 - Patients with renal failure
 - Decreased carbohydrate intake (diets or periods of fasting)
 - Elevated glucose utilization (e.g., unaccustomed physical activity)
 - Sulfonylurea overdose

Side Effects:-

Alcohol intolerance (first-generation agents): disulfiram-like reaction

Weight gain

Hematological changes: granulocytopenia, hemolytic anemia

Allergic skin reactions

Sulfonylureas are associated with more cardiovascular (macrovascular) complications than metformin.

β -cell apoptosis: Studies suggest that sulfonylureas induce β -cell apoptosis in human islet cells.



Contraindications:

- Beta blockers (can mask hypoglycemic symptoms while lowering serum glucose levels)
- Severe cardiovascular comorbidity
- Obesity
- Sulfonamide allergy (particularly long-acting substances)
- Severe liver and kidney failure.
- NOTE!- Beta-blockers may mask the warning signs of hypoglycemia (e.g., tachycardia) and decrease serum glucose levels even further (see hypoglycemia). Since sulfonylureas also increase the risk of hypoglycemia, the combination of these two substances should be avoided.

Glucose independent drug- Meglitinides.

Active agents

Repaglinide

Nateglinide

Mechanism of action (similar mechanism of action to that of sulfonylureas)

- Blockage of ATP-sensitive potassium channels of the pancreatic beta cells → depolarization of the cell membrane → calcium influx → insulin secretion
- Meglitinides should be taken shortly before meals.

Clinical Characteristics:

- Glycemic efficacy: lowers HbA1c by 0.75% over 3 months
- Tolerated well by patients with chronic kidney disease
- More expensive than sulfonylurea.
- Indications: It is particularly suitable for patients with postprandial peaks in blood glucose levels, but overall rarely prescribed.



Important Side Effects:

- Life-threatening hypoglycemia, especially in patients with renal failure (less of a risk than with sulfonylureas)
- Weight gain
- Hepatotoxicity (rare)
- Contraindications: severe liver failure
- Interactions: sulfonylureas. (Meglitinides and sulfonylureas have the same mechanism of action. Simultaneous exposure to both drugs increases the risk of hypoglycemia).

Non – insulinotropic Drugs .

Effective in patients with nonfunctional β cells

Not dependent on residual insulin production

Agents: biguanides (metformin), SGLT-2 inhibitors, thiazolidinediones, α -glucosidase inhibitors, amylin analogues.

METFORMIN (Biguanides):

Active agent

Metformin.

Mechanism of action: enhances the effect of insulin

- Reduction in insulin resistance via modification of glucose metabolic pathways
 - Inhibits mitochondrial glycerophosphate dehydrogenase (mGPD)
→ ↓ hepatic gluconeogenesis and intestinal glucose absorption
 - Increases peripheral insulin sensitivity → ↑ peripheral glucose uptake and glycolysis
- Lowers postprandial and fasting blood glucose levels
- Reduces LDL, increases HDL

Indications: drug of choice in all patients with type 2 diabetes .

Clinical Characteristics:

Glycemic efficacy: lowers HbA1c by 1.2–2% over 3 months

Weight loss (often desired) or weight stabilization

No risk of hypoglycemia

Beneficial effect on dyslipidemia

Reduces the risk of macroangiopathic complications in patients with diabetes

Must be paused prior to surgery

Cost-effective

Important Side Effects:



Metformin-associated lactic acidosis Incidence: ~ 8 cases/100,000 patient years



High-risk groups

Elderly individuals
Patients with renal insufficiency or CHF



Clinical features:
frequently nonspecific

Gastrointestinal symptoms: nausea, vomiting, diarrhea, abdominal pain, flatulence
Severe symptoms: muscle cramps, hyperventilation, apathy, disorientation, coma

Diagnostics / Treatment:

↑ Serum lactate

Arterial blood gas: metabolic acidosis and anion gap

Treatment: Discontinue metformin and treat acidosis.

Vitamin B12 deficiency (Long-term metformin therapy impairs the enteral absorption of vitamin B12 in the terminal ileum by interfering with the calcium homeostasis).

Metallic taste in the mouth (dysgeusia).

Contraindications:

- Renal failure (if creatinine clearance < 30 mL/min)
- Intravenous iodinated contrast medium -(The elimination of metformin is reduced by the administration of iodinated contrast medium, even if overt renal failure does not develop (contrast-induced nephropathy).
- Heart failure (NYHA III and IV), respiratory failure, shock, sepsis
- Alcoholism
- Severe liver failure
- Chronic pancreatitis, starvation ketosis, ketoacidosis, sepsis
- Important interactions: sulfonylureas
- Side Note- Because of its favorable risk-benefit ratio, metformin is the drug of choice for monotherapy and combination therapy in all stages of type 2 DM.

Thiazolidinediones: (Glitazones- Insulin Sensitizers).

Active agents

Pioglitazone

Rosiglitazone.

Mechanism of action: activation of the transcription factor PPAR γ (peroxisome proliferator-activated receptor of gamma type in the nucleus) $\rightarrow$ $\uparrow$ transcription of genes involved in glucose and lipid metabolism $\rightarrow$ $\uparrow$ levels of adipokines such as adiponectin and insulin sensitivity $\rightarrow$ $\uparrow$ storage of fatty acids in adipocytes, $\downarrow$ products of lipid metabolism (e.g., free fatty acids) $\rightarrow$ $\downarrow$ free fatty acids in circulation $\rightarrow$ $\uparrow$ glucose utilization and $\downarrow$ hepatic glucose production

Indications: may be considered as monotherapy in patients with severe renal failure and/or contraindications for insulin therapy

Clinical Characteristics

- Glycemic efficacy: lowers HbA1c by 1% in 3 months
- Favorable effect on lipid metabolism: ↓ triglyceride, ↓ LDL, ↑ HDL
- No risk of hypoglycemia
- Onset of action is delayed by several weeks.

Side Effects:

↑ Risk of heart failure

↑ Risk of bone fractures (osteoporosis)

Fluid retention and edema

Weight gain

Rosiglitazone: ↑ risk of cardiovascular complications like cardiac infarction or death

- Note - TZDs can cause reduced bone formation and increased fracture risk, particularly with long-term use and especially in postmenopausal women.

Contraindications



Congestive heart failure (NYHA III or IV)



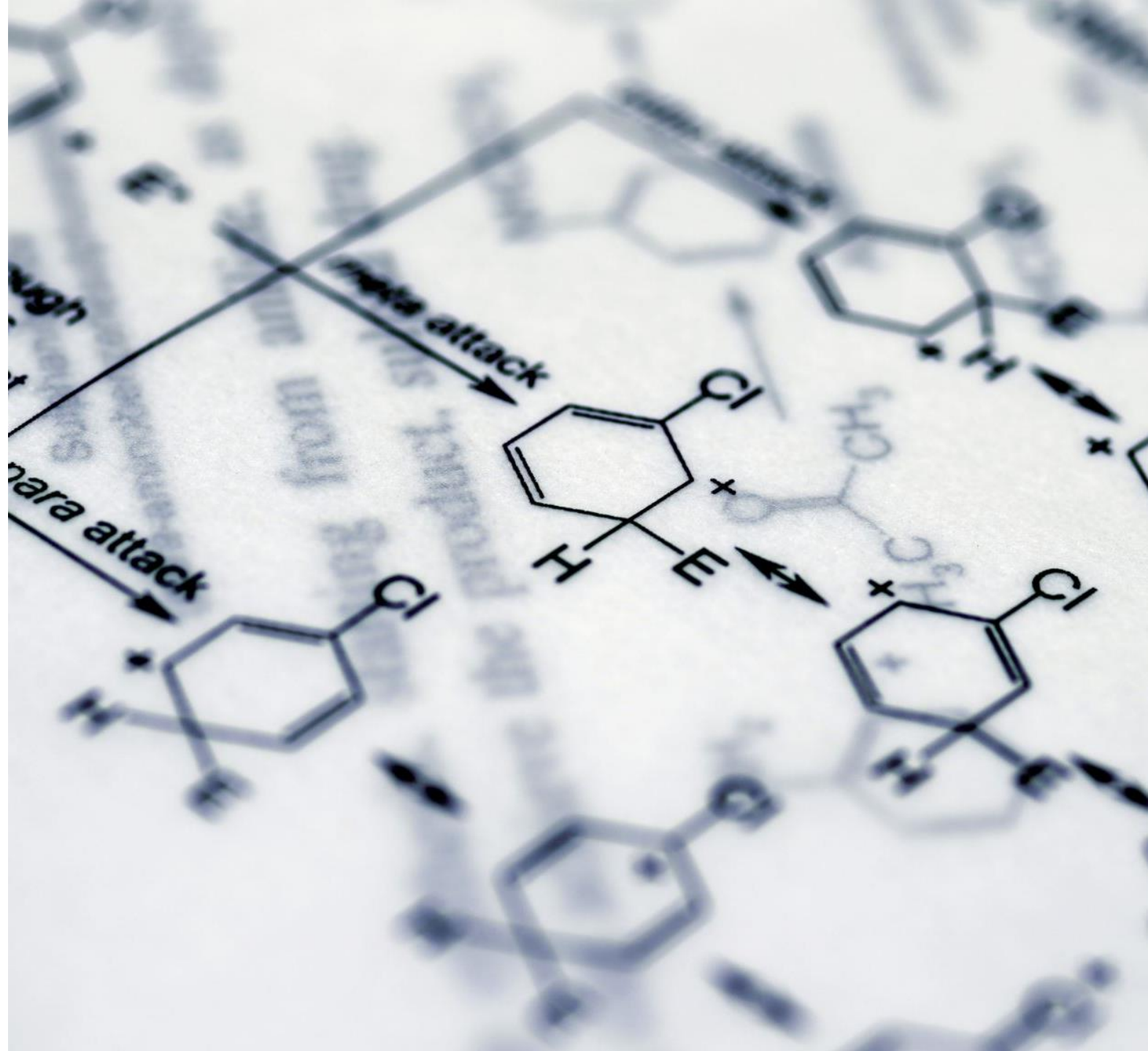
Liver failure



Pioglitazone: history of bladder cancer or active bladder cancer; macrohematuria of unknown origin.

SGLT-2 inhibitors : (Gliflozins).

- Active agents
- Dapagliflozin
- Empagliflozin
- Canagliflozin
- Mechanism of action: reversible inhibition of SGLT-2 in the proximal tubule of the kidney → ↓ glucose reabsorption in the proximal convoluted tubule of the kidney → glycosuria and polyuria
- Indications: especially in young patients with treatment-compliant type 2 DM without significant renal failure.



Clinical Characteristics.

- Glycemic efficacy: lowers HbA1c by 0.6% over 3 months
- Promotes weight loss
- ↓ Blood pressure
- ↓ Risk of cardiovascular mortality in patients with type 2 DM and cardiovascular disease.

Important Side Effects:

Genital infections (vulvovaginal candidiasis, balanitis) due to glucosuria

Dehydration → weight loss, orthostatic hypotension

Severe diabetic ketoacidosis

↑ Risk of lower limb amputation: Studies suggest a small increase in amputation rates under canagliflozin treatment.

Contraindications:

- Chronic kidney disease:
If GFR decreases, drug efficacy decreases and adverse effects increase.
- Recurrent or complicated genitourinary tract infections when the underlying etiology cannot be resolved (e.g., in patients with anatomical or functional anomalies of the urinary tract)



Alpha-Glucosidase Inhibitors.

Active agents

Acarbose

Miglitol

Mechanism of action

- Inhibit alpha-glucosidase (a brush border enzyme expressed by intestinal epithelial cells) → delayed and ↓ intestinal glucose absorption and ↓ carbohydrate breakdown, resulting in ↓ hyperglycemia after food ingestion
- Particularly effective in controlling postprandial blood glucose levels
- The undigested carbohydrates reach the colon, where they are degraded by intestinal bacteria, resulting in the production of intestinal gas.

Clinical Characteristics:

- Glycemic efficacy:
lowers HbA1c by 0.8% over
3 months
- No risk of hypoglycemia
- Important side
effects: gastrointestinal
symptoms
(flatulence, bloating,
abdominal
discomfort, diarrhea).



Contraindications:



Severe renal failure



Inflammatory bowel
disease



Conditions
associated
with malabsorption.

Links/Sources

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- Thank you

