The Endocrine System

PHARMACOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	10
Subject:	Anti-diabetic drugs part 2
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- **Note:** this sheet includes all the slides without exception from slides 68-127. I tried to put whatever the professor did not mention in italics but the professor said everything is important even if he did not mention it. The last five pages of this sheet contain the last part of slide 6 that Dr. Yaqoub said to read on our own. I left the colors that Dr. Yaqoub in the slides in case you want to read this sheet in color.

Oral antidiabetic agents:

A. Insulin secretagogues:

1. Sulfonylureas
2. Meglitinides

B. Biguanides

C.Thiazolidinediones

D. α-Glucosidase inhibitors

Oral Anti-diabetic Agents

Today we will talk about the oral anti diabetic or oral hypoglycemic agents. What is the difference between oral anti diabetic and oral hypoglycemic?

Anti-diabetic drugs treat diabetes. Some drugs aim to have euglycemia (normal glucose level), but all drugs can cause hypoglycemia if they are overused. Not all of the drugs are oral, but they are "other than insulin".

A. Insulin Secretagogues:

1. Sulfonylureas

There are two generations, the old and the recent:

1. **First-generation sulfonylureas: Tolbutamide, Chlorpropamide, Tolazamide.** It is the oldest group of sulfonylureas. It is no longer used today, so we will focus on the second generation.
2. **Second-generation sulfonylureas: Glyburide (glibenclamide), Glipizide, Glimepiride.**

The second generation has the same profile of activity and side effects as the first generation but **the frequency of side effects are lower**, thus, they are the drugs that are used today among the sulfonylureas. The second generation drugs all begin with the letter G. They stimulate insulin secretion in the same way as ATP. The differences between the drugs are the **half life** and the **frequency of administration** but they all have similar pharmacological administration. **Glipizide** has a short half life and is frequently administered but **Glimerpiride** on the other hand is given once daily and is long acting relatively speaking. The advantage of the short life is the low incidence of hypoglycemia. All these names are scientific names and they all stimulate insulin secretion.

In short second generation sulfonylureas are:

- Stimulants of insulin secretion (mechanism of action is explained below).
- Widely prescribed for type 2 DM.
- Differ in potency and adverse effects.

*Note: Hypoglycemia is very dangerous and is more dangerous than hyperglycemia. We cannot tolerate a blood sugar of 50, and that would lead to brain damage.

Mechanism of Action:

• They bind to their receptor which is associated with B cell ATP-sensitive K^+ channel.

• This inhibits the efflux of K^+ ions through the channel resulting in cell depolarization.

. opening of voltage-gated Ca^{2+} channel and calcium influx and the release of preformed insulin.

Glipizide:

• Have the shortest half-life of the potent agents (2-4 hours).

• Absorption is delayed when taken with food,therefore it should be ingested 30 min before breakfast to reduce postprandial hyperglycemia.

• 90% metabolized in the liver to inactive products, and 10% excreted unchanged in urine.

- *Contraindicated in patients with significant hepatic impairment and renal insufficiency.*
- *Less likely to produce serious hypoglycemia because of its short half-life.*

Glimepiride:

- *Most potent sulfonylurea.*
- *Given once daily, t1⁄2 of 5 hours.*
- *Completely metabolized in the liver to inactive metabolites.*

Glyburide (glibenclamide):

• Flushing has rarely been reported after ethanol ingestion.
• It slightly enhances free water clearance.
• It is contraindicated in the presence of hepatic impairment and in renal insufficiency.

Gliclazide

• It has a half-life of 10 hours. It is completely metabolized by the liver to inactive metabolites.

What is the problem with sulfonylureas?

Sulfonylureas all stimulate insulin secretion and this insulin secretion will take care of hyperglycemia, but these drugs commonly have **secondary failure.** Which means you give sulfonyluria and it improves glycemic control but after a while you find that it has failed. **This is not tolerance**.
Tolerance means it works initially and then the effectiveness decreases and then it stops working. The reason that there is secondary failure is that in diabetes when there is insufficiency in insulin secretion there is a problem in beta cells and this problem is progressive (تتفاقم) . The secondary failure of the sulfonylureas is due to the progression of the disease rather than the failure of the drug itself. So the beta cells will not produce adequate insulin, the insulin will decrease, and the glycemic control will not be adequate,

so the dose given to the patient will not be enough to correct the hypoglycemia. Sulfonylureas are readily used to treat type 2 diabetes **but they are not the first drug of choice.**

Secondary failure of sulfonylureas may be due to:

1. Progressive decrease in B cell mass (most IMP one)
2. Reduction in physical activity (if a person was walking for a certain period of time a day and then stops walking the person can develop secondary failure).
3. Decline in lean body mass or an increase in fat deposition (for example a person who becomes obese, there is a spectrum from mild to severe resistance).

Sulfonylureas increase body weight. That is why they are not the first line of treatment in obese diabetics, they will increase body weight and insulin requirement and derange glycemic control.

Adverse Effects:

1. Hypoglycemic: MOST IMPORTANT. Everything that was mentioned about hypoglycemia with insulin is applies here. Reactions to hypoglycemia include coma and convulsions.

- May mimic cerebrovascular accidents.
- The longer the half-life, the more likely is the hypoglycemia.
- More in elderly patients and those with hepatic or renal impairment. Why is this? Because the elderly usually have lower physical activity and might forget if they have taken the dose and take another dose. Sulfonylureas are excreted by the kidney, so if there is renal impairment the concentration in the blood might be higher.
- Sulfonylureas have high plasma protein binding so they will compete with all drugs that have plasma protein binding if given together. That will release free drug from binding site and the free drug will produce effect and cause hypoglycemia.

• *Potentiated by sulfonamides, clofibrate, dicumarol, salicylates and phenylbutazone(competition for protein binding) and alcohol (malnutrition).*

2. *Nausea and vomiting.*
3. *Cholestatic jaundice.*
4. *Agranulocytosis, aplastic anemia and hemolytic anemia.*
5. *Hypersensitivity reactions.*
6. **Disulfiram-like reaction: alcohol flush, chlorpropamide (first generation sulfonylurea)**

This reaction occurs with people who drink alcohol and take sulfonylureas. Alcohol is converted to acetaldehyde via alcohol dehydrogenase and this requires NAD which is converted to NADH. **Aldehyde dehydrogenase** which is inhibited by disulfiram is the enzyme that converts acetaldehyde to acetic acid. The inhibition of aldehyde dehydrogenase causes the accumulation of acetaldehyde which results in vasodilation, nausea, vomiting and headache which is caused by vasodilation. This happens only when alcohol drinkers take this drug. That is why in the past some people used to give alcoholics this drug in their food so they get these side effects when they drink alcohol which causes them to stop drinking, but that is unethical. The acetic acid also goes through the Kreb's cycle which gives you energy and that is why the alcohol drinkers eat less.

7. Hyponatremia by potentiating effects of ADH, chlorpropamide (first generation **sulfonylurea).**

We don't see this effect often with the new drugs but it happened with the old drugs. The ADH retains water in the body.
You get dilutional hyponatremia and electrolyte imbalance in the presence of these drugs. So it is not real hyponatremia it is dilutional.
We may see this effect with new drugs but it is very rare.

2. Meglitinides

A new class of insulin secretagogues. Same mechanism of action as sulfonylureas. The meglitinides' advantage is that they have a fast onset of action. The peak affect is after 1 hour and the absorption is within 15 minutes and the duration is of action is very short within 4-8 hours. These drugs are similar to the short acting insulin. So these drugs are suitable to correct post prandial hypoglycemia in type 2 diabetes and is not that associated with post prandial hyperglycemia. They have a much shorter side effect profile than sulfonylureas.

Rapaglinide*:*

• *Is similar to sulfonylureas in mode of action.*

• *Meglitinides have two binding sites in common with the sulfonylureas and one unique binding site*.

• Very fast onset of action with peak effect at 1 hour after ingestion, and a duration of action of 4-7 hours. It improves the post prandial hypoglycemia. This is oral so for type 2 diabetes.

• t1⁄2~1hour

Indications:

- Metabolized by CYP3A4.This is important for drug-drug interaction. Increase in elimination.
- Indicated for control of postprandial hyperglycemia, to be taken just before meals.
- Hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrates.
- It can be used in patients with renal impairment and in the elderly. You have to be cautious with elderly people, so here you can use it for elderly people. Remember, sulfonylureas on the other hand should not be used with patients with renal failure.

• *There is no sulfur in its structure, so it may be used in type 2 diabetics with sulfur or sulfonylurea allergy*

Mitiglinide is similar.

D-Phenylalanine Derivatives

Nateglinide: (new drug)

- Is the latest insulin secretagogue.
- *It stimulates very rapid and transient release of insulin from B cells through closure of the ATP- sensitive K^+ channels.*

- It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour and an overall duration of action is about 4 hours.
- *It is metabolized in the liver by CYP2C9 and CYP3A4 with a half-life of about 1 hour.*
- *Hypoglycemia is the main adverse effect.*
- It can be used in patients with renal impairment and in the elderly.

Things to consider before administering oral hypoglycemics:

1. Which drugs can be given to patients that are obese?
2. Which drugs increase body weight which is associated with resistance and which drugs decrease body weight?
3. Which drugs suppress the appetite and which drugs increase appetite?
4. Which drugs that cause hypoglycemia and which drugs cause hyperglycemia?

Example: The sulfonylureas cause hypoglycemia and they should not be used alone in obese individuals because they increase body weight.

B. Biguanides

Sulfonylureas are commonly used to treat type 2 diabetes but they are not the first drug of choice. **The drug of first choice is Metformin**. There used to be two drugs, two brothers, Phenformin and Metformin from the biguanides but one of the brothers (Phenfromin) is no longer used because it causes **lactic acidosis**, so only Metformin remains. Metformin can also

cause metabolic acidosis but only in hypoxic conditions such as congestive heart failure. Renal impairment also helps acidosis.

Metformin does not cause hypoglycemia, but can cause hypoglycemia when combined with other drugs. So we call Metformin as a euglycemic (normal glucose level) drug. It produces less fasting hyperglycemia as well as less postprandial hyperglycemia.

How do you know if someone is diabetic? You measure the fasting and post prandial blood sugar, so metformin decreases both.

For example if we measure fasting blood glucose at different times and it was 200-250, we also measure the post prandial blood glucose and it was at different levels. When we start Metformin the fasting hyperglycemia will drop and the postprandial hyperglycemia will drop.

Metformin:

• Is the only biguanide available for clinical use after withdrawal Of phenformin which was associated with fatal lactic acidosis.
• Its blood-glucose lowering action does NOT depend on functioning pancreatic B cells.
• It produces less fasting hyperglycemia as well as less postprandial hyperglycemia.
• Hypoglycemia during biguanide monotherapy is essentially unknown.
• More appropriately termed "euglycemic" agents.

Proposed Mechanisms of Action:

- Metformin is a very old drug, has been used for 50 years (since before Dr. Yaqoub started medical school) but until today the exact mechanism of action is not known but there have been some recent breakthroughs in understanding part of the mechanism.
- The primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic glucose production. AMPK triggers a shift from anabolic to catabolic activities.

- AMPK is activated in low energetic states. ATP is produced by catabolism and is needed for anabolism. Low energy you have low ATP so you need catabolism which gives you energy. Glycolysis is related to catabolism so some energy is released. How is this related to diabetes? Does this explain everything? No!

Metformin Actions:

Note: these are the actions and not the mechanisms of actions.

1. **Reduces gluconeogenesis**, which causes a decrease in glucose level, and it may impair hepatic metabolism of lactic acid. This explains the lactic acidosis, it stays as lactic acid and is not converted to other forms.
2. **Slows glucose absorption from the GIT**, with increased glucose to lactate conversion by enterocytes. Slowing the glucose absorption reduces the post prandial hyperglycemia. If you eat a meal you get hyperglycemia, the absorption of sugar is fast, so when you decrease the glucose absorption you decrease the post prandial hyperglycemia as a result of slow absorption. That is why metformin has to be taken immediately before or after or during because it reduces the glucose absorption from the carbohydrates.
3. **Directly stimulates glycolysis in tissues** ->increased glucose removal from blood. Glycolysis generates 2ATP. Glycolysis is degradation of glucose.
4. **Reduces plasma glucagon levels**. Glucagon has a positive effect on glucose, so glucagon increases the glucose, which means Metformin will reduce the glucose level.
5. **It decreases insulin levels** (which functions as a growth factor). This is Dr. Yaqoub's opinion that when you decrease the glucose, the insulin will decrease. **Metformin does not need beta cells or the action of insulin unlike sulfonylureas and meglitinides**.
6. ?? May reduce risk of some cancers according to epidemiologic studies. But this is premature to draw conclusions. There are clinical trials for breast, colon and prostate cancers which are the worst cancers. They are thought to reduce the risk (prevention) and also can

be used for treatments. Diabetes is associated with high incidence of cancer because it causes immortalization by decreasing the rate of apoptosis. So metformin would have the advantage of treating diabetes and also possibly cancer.

Pharmacokinetics:

- *t1⁄2 ~ 1.5-3 hours.*
- *Not bound to plasma proteins, not metabolized*.
- **Excreted unchanged in urine:**

So you should be careful for people with renal failure.

Clinical Pharmacology:

- It is the first-line therapy for type 2 diabetes.
- It is most often (second drug for treatment) prescribed for "insulin resistance" syndrome (ineffective insulin action). Any resistance to insulin you can add Metformin because it is an insulin sparing reagent and does not need insulin to decrease the glucose level. It can even be used in type 1 diabetes if you have resistance to insulin.

Metformin is most often prescribed for insulin resistance because:

1. It is an insulin-sparing agent
2. It does not increase body weight (some people use it for weight loss which is a non labeled use, this is not proven, when used for diabetes it either maintains the weight or it causes 3 kg weight loss).
3. It provokes hypoglycemia.

*Note: the good thing about this drug is that it does not need beta cells to function.

*Note: One of the complications of diabetes is vasculature complications which are two kinds: macrovascular which is for large vessels and microvascular which for small vessels. In the past diabetes was considered as a vascular complication but that is wrong, the vascular complications are a result of diabetes.

• It decreases the risk of BOTH macrovascular as well as microvascular disease, in contrast to other therapies which reduce only microvascular morbidity. This is an advantage because most other drugs only prevent one either the macro or the micro. Sulfonylureas only prevent the microvascular complications.
• It is useful in the prevention of type 2 diabetes in **middle-aged obese** patients with impaired glucose tolerance and fasting hyperglycemia, but **not in older, leaner pre-diabetics**.

What does it mean for prevention of diabetes? They have to be pre-diabetic. Pre-diabetic is a delay in the onset of diabetes.

How do you define a pre-diabetic?

Fasting blood glucose = 115 (between 100-125 mg/dL) is a person who is pre-diabetic. If you have someone who is obese with a history of diabetes, this person is pre-diabetic. History is very important. The prevention does not mean prevention, it means delay **in the onset in diabetes.** They delay is usually 5-10 years. A person with diabetes usually has cardiovascular complications (micro and macro) 5-10 years after onset. So Metformin could delay the cardiovascular complications by 15-20 years. This is more effective for the younger age group and for obese patients. So for young and obese and not for old and lean.

How do you know if someone is prediabetic?

You do a fasting blood sugar, today is normal, next time is normal and then normal and then once it is high. This person is ok with fasting but when there is stress on the pancreas you get hyperglycemia, the HDD>> gives you a good idea of the last couple months.

Metformin Adverse Effects:

1. **Gastrointestinal**: anorexia, nausea, vomiting, abdominal discomfort, and diarrhea. (this is transient, dose dependent and onset related)

- Most common, occurs in 20% of patients, especially at a dose > 1000 mg. Dose related. (The higher the dose the more the manifestation)
- Tend to occur at the onset of therapy and often transient.

Metformin needs to be administered as a full dose (2g per day) which is administered three times a day. So to avoid the side effects you do the following:

Week 1: 1 tablet, the first couple days there will be GI indications

Week 2: 2 tablets, one at breakfast and dinner during meal is best

Week 3: 1 tablet with each meal, if the patient skips a meal they skip a dose

*this is done to decrease the GI tract indications.

2. **Reduction of vitamin B_{12} levels during long- term therapy.**

- It interferes with the calcium-dependent absorption of vitamin B_{12}-intrinsic factor complex in the terminal ileum.

The endocytosis is calcium dependent.

Metformin has an effect on calcium but we don't know the mechanism.

- Increased intake of calcium may prevent the metformin-induced B_{12} malabsorption. Calcium tablets can be taken but the best option is to increase dairy intake.

3**. Lactic acidosis** in the presence of hypoxia and renal or hepatic insufficiency. Lactic acidosis is rare with metformin but common with phenformin. Lactic acidosis is indicated with renal failure.

It is contraindicated in patients with renal disease, alcoholism, hepatic disease or conditions predisposing to tissue hypoxia (chronic cardiopulmonary dysfunction).

- *It is dose-related adverse reaction.*
- It is not recommended at and above a serum creatinine level of 1.4 mg/dL in women and 1.5 mg/dL in men.
  A level higher than this will lead to lactic acidosis. Creatinine is produced from muscle mass, so men have more muscles than women so they will produce more creatinine.

Radiocontrast administration can cause acute kidney failure in patients with diabetes and incipient nephropathy.

Important note: the radiocontrast with metformin can cause kidney failure, so you have to stop the administration of metformin before performing the radiocontrast. So creatinine has to be constantly measured.

- Metformin therapy should therefore be temporarily halted on the day of radiocontrast use and restarted a day or two later after confirmation that renal function has not deteriorated.

C. Thiazolidinediones

- Act to reduce insulin resistance.
- Are considered "euglycemic". (they don't cause hypoglycemia)
- They act as ligands to (Peroxisome proliferator- activated receptor-gamma, PPAR-γ).
- *PPAR-γ is part of the steroid and thyroid superfamily of nuclear receptors.*
- *PPAR-γ are found in muscle, fat and liver.*
  They are last choice for treatment of diabetes.

They increase body weight and cause fluid retention that is excessive and common. So they are not the first choice, they are the last choice and specifically when someone is taking 3-4 drugs and not responding then you add a thizolidinedione.

Metformin	Thiozolidinedione
Maintain or decrease body weight	Increase body weight
	More toxic than the rest of anti diabetic agents
Euglycemic	Euglycemic
First line of therapy	Last line of therapy
Decreases insulin resistance	Decreases insulin resistance

• Mechanism of action to produce insulin sensitivity:
PPAR-γ receptors modulate the expression of the genes involved in 1. lipid and glucose metabolism 2. insulin signal transduction, and 3. adipocyte and other tissue differentiation.

Actions include:

1. **Increased glucose transporter expression (GLUT 1 and GLUT 4):**Glucose transporter transports the glucose into the cell, so it decreases in the blood.
2. **Decreased free fatty acid levels:** (it takes fatty acids to adipose tissue leaving the liver and decreasing fat content in the liver and consequently improving insulin sensitivity)
3. **Decreased hepatic glucose output**: (through decreasing gluconeogenesis and glycogenolysis).
4. **Increased adiponectin and decreased release of resistin from adipocytes**. Resistin produces resists insulin and adiponectin causes sensitization. This improves sensitivity to insulin.
5. **Increased differentiation of preadipocytes to adipocytes**.

Effects not related to diabetes:

6. Decreased levels of: (related to anti-inflammatory effect of the drug).
   - Plasminogen activator inhibitor type 1.
   - Matrix metalloproteinase-9.
   - C-reactive protein.
   - Interleukin-6.

*Note: They have ant-inflammatory reactions. You measure certain parameters of inflammation you find them reduced after the drug.

• In diabetes, the major site of action is adipose tissue: promote glucose uptake and utilization and modulate synthesis of lipid hormones or cytokines and proteins involved in energy regulation.
• Promote fatty-acid uptake and storage in adipose tissue rather than skeletal muscle or liver, which makes them more sensitive to insulin.

- May favor insulin sensitivity at the muscle and liver by stimulating AMPK. Similar to Metformin.
- Suppress glucose production in the liver.
- Restricted to patients who remain hyperglycemic despite taking other anti- diabetic medications.

Used when three or four anti diabetic drugs are being taken and there is still hyperglycemia, in this condition thiazolidinediones are administered. **Pioglitazone and Rosiglitazone** are the two drugs that are used in this class the rest were withdrawn from the market because of the adverse effects.

Pioglitazone:

• Food may delay absorption, extent not affected.
• Metabolized by CYP2C8 & CYP3A4 to active metabolites. (drug interactions with estrogen- containing contraceptives for example).
• It lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol.
• Pioglitazone is approved as a monotherapy and in combination with metformin, sulfonylureas, and insulin for the treatment of type 2 diabetes.

Rosiglitazone:

• Rapidly absorbed and highly protein bound. • Metabolized mainly by CYP2C8 to minimally active metabolites.
. • Have anti-inflammatory activity.
• It is approved for use in type 2 diabetes as monotherapy, in double combination therapy with a biguanide or sulfonylurea, or in quadruple combination with a biguanide, sulfonylurea, and insulin.
• It increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides.

Thiazolidinediones

• These drugs have been shown to improve the biochemical and histologic features of nonalcoholic fatty liver disease.
• *They seem to have a positive effect on endothelial function: pioglitazone reduces neointimal proliferation after coronary stent placement.*
• *Rosiglitazone has been shown to reduce microalbuminuria.*
• *Individuals experiencing secondary failure to other antidiabetic drugs benefit from the addition of thiazolidinediones.*

• *Have a slow onset and offset of activity over weeks or months, because their mechanism of action involves gene regulation.*
• *Have the benefit of preventing type 2 diabetes.*

Adverse Effects: (which caused the withdrawal from the market)

1. Fluid retention: occurs in about 3–4 % patients on thiazolidinedione monotherapy and occurs more frequently (10–15%) in patients on concomitant insulin therapy. Heart failure can occur, as well as dilutional anemia. It is so severe it causes hypertension, heart failure, excessive weight increase. The mortality rate is increased by using these drugs.
2. New or worsening macular edema with rosiglitazone. Improves when drug is discontinued.
3. Dose-related weight gain, especially when used in combination with a sulfonylurea or insulin. Some of it may be fluid related.
4. Loss of bone mineral density and extremity bone fractures in women, which is postulated to be due to decreased osteoblast formation. Increased incidence of osteoporosis and bladder cancer.
5. Increased risk of bladder cancer with increased dosage and duration of pioglitazone use.

Precautions and Contraindications:

1. Should not be used during pregnancy, in the presence of liver disease, in the presence of heart failure. We don't know about their safety and pregnancy. Should not be used in hypertension.
2. Anovulatory women may resume ovulation pregnancy. This occurs even in women with menopause. Menopause is called انقطاع الحيض in arabic. There is no ovulation so there is no hormones. These drugs might resume ovulation so might be a side effect for elderly but a therapeutic effect for younger individuals. Common adverse effect with metformin.
3. Hepatotoxic, monitor for liver function. (troglitazone was withdrawn because of this).

The classes that follow are important.

Amylin Analogues

Pramlintide:

- Slow gastric emptying – vagally mediated. Which means there is slow absorption of glucose, which decreases post prandial hyperglycemia.
- Reduce glucagon secretion.
- Promote satiety or reduce appetite - centrally. Which means less intake of carbohydrates and food.
- Produces moderate weight loss.
- Given by subcutaneous injection before meals.
- Used in type 1 DM, and type 2 DM unable to achieve their target postprandial blood glucose levels.

This is where the professor stopped in section 1 and said to read the rest on our own. I tried to put some of the points he mentioned in section 2 in bold.

Pramlintide

• *It is rapidly absorbed after subcutaneous administration; levels peak within*

20 minutes, and the duration of action is not more than 150 minutes.
• Shouldbe injected immediately before eating, always by itself using a separate syringe; it cannot be mixed with insulin.

Pramlintide
1. Hypoglycemia: concurrent rapid- or short-acting mealtime insulin dosages should be decreased by 50% or more.
2. GIT:nausea,vomiting,anorexia.
Adverse effects:

GLP-1 – Based "incretin" Therapies A. GLP-1 analogues (exenatide, liraglutide,
albiglutide, and dulaglutide): Exenatide:

- *It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.*
- *Used as adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control.*

Exenatide

- It increases insulin secretion in a glucose- dependent manner. The increased insulin secretion is speculated to be due in part to an increase in beta-cell mass, from decreased beta- cell apoptosis, increased beta-cell formation, or both. (Noticed in culture)
- Suppresses postprandial glucagon release.
- Delays gastric emptying.

The effect is to decrease apoptosis and increase beta cell mass. There is low beta cell mass in diabetes.

Exenatide
• It is injected subcutaneously within 60 minutes before breakfast and dinner.
• It peaks in ~ 2 hours with a duration of action of up to 10 hours.
• The oral hypoglycemics dosage may need to be decreased to prevent

hypoglycemia.

Exenatide

- *Suppresses appetite. (Type 2 diabetes patients on GLP-1 therapy are less hungry). May be related to the deceleration of gastric emptying or suppression of appetite).*
- *Associated with weight loss.*

Exenatide

1. Nausea,vomiting,diarrhea:majoradverse effect is nausea (45%), which is dose dependent and declines with time.

2. Acutepancreatitis.

3. Renalimpairmentandacuterenalinjury.

4. Not associated with hypoglycemia unless used in combination.

Adverse effects:

GLP-1 – Based "incretin" Therapies

B. Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin):

Sitagliptin:

• Inhibit DPP-4, the enzyme that degrades incretin hormones.

• Prolong the half-life of endogenous GLP-1. • Decrease postprandial glucose levels. • Decrease glucagon concentration.

Sitagliptin

• Increase circulating GLP-1 and glucose- dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose- dependent manner.

• Most commonly used in combination with a TZD or metformin, or sulfonylureas.

• May be used as monotherapy.

GLP-1 – Based "incretin" Therapies

• Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of

approximately 12 hours.

- *Dosage should be reduced in patients with impaired renal function*
- *Weight neutral.*

GLP-1 – Based "incretin" Therapies

Adverse effects:

1. *Nasopharyngitis, upper respiratory infections, headaches*
2. *Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.*

3. Acutepancreatitiswhichmaybefatal. 4. Allergicreactions.

D. α-Glucosidase Inhibitors

- *Complex starches, oligosaccarides, and disaccharides must be broken to monosaccharides to be absorbed in duodenum and upper jejunum.*
- *This is facilitated by enteric enzymes attached to the brush border of intestinal cells such as pancreatic α-amylase and α-glucosidase.*

Acarbose and Miglitol

- *Are competitive inhibitors of intestinal α- glucosidases: sucrase, maltase, glycoamylase, dextranase.*
- *Miglitol is 6 times more potent than acarbose.*
- *Miglitol alone inhibits isomaltase and β-glucosidases.*
- *Acarbose alone inhibits α-amylase.*
- *Administered just before each meal.*

α-Glucosidase Inhibitors

- *Reduce the postprandial digestion and absorption of starch and disaccharides reducing postprandial hyperglycemia and delaying absorption of sugars to distal segments of the intestine, thus having insulin sparing action.*
- *Used for type 2 diabetes.*
- *Can prevent type 2 diabetes development in prediabetics.*

α-Glucosidase Inhibitors

- *Reduce cardiovascular disease and hypertension.*

Adverse Effects:

1.Flatulence, diarrhea and abdominal pain. Due to undigested carbohydrates in the colon which is fermented by bacteria gases. These effects are transient because of induction of α- glucosidase in jejunum and ileum.

α-Glucosidase Inhibitors

2. Hypoglycemia with combination therapy whichshould be treated with glucose and NOT sucrose (why?).

Precautions and Contraindications:

1. *Inflammatory bowel disease or GI diseases that could be worsened by gas and distension.*
2. *Should not be administered to patients with renal insufficiency (excreted by the kidney).*

α-Glucosidase Inhibitors

3. Acarbose should be used with caution in hepatic disease because it has been shown to elevate hepatic enzymes (reversible).

Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- *SGLT2 is the main transporter for glucose re- absorption in the proximal tubules (90%).*
- *Inhibitors include canagliflozin, dapagliflozin, and empagliflozin.increase urinary glucose loss.*
- *Not very effective in chronic renal dysfunction and even contraindicated.*

(SGLT2) Inhibitors

Adverse effects:

1. *Increased incidence of genital and urinary tract infections.*
2. *Intravascularvolumecontractionandhypotensionosmotic diuresis.*
3. *Increase LDL cholesterol*
4. Higher rates of breast cancer and bladder cancer.

* Prof. Yacoub is against this idea. There is no logical reason to increase the blood sugar. Bacteria can enter and cause infection. So this is dangerous.