

5

ENDOCRINE

SUBJECT: Pharmacology

DONE BY: Riham

CORRECTED BY:

DOCTOR: Malik



Amylin “Islet Amyloid Polypeptide”

a peptide hormone that is co-secreted with insulin from the pancreatic β-cells in a ratio of approximately 100:1 (Insulin:Amylin). Amylin plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing post prandial spikes in blood glucose levels.

Amylin analog (Pramlintide)

- is a new adjuvant approved drug that can be used with Insulin to lower the dose of Insulin that is given to a patient.
- It is not used as a monotherapy.

So, Insulin is no longer the only drug used to treat type 1 DM.

Note: Metformin is expected to be approved as a treatment of type1 DM (discussed later).

Oral Hypoglycemic Agents

“Sulfonylureas: Glimepiride (Amaryl)”

1. Useful in treatment of type 2 diabetes patients.
2. Oral hypoglycemic agents should not be given to patients with type 1 diabetes.
3. Adjuncts to diet and exercise to lower blood glucose in patients w/ type II diabetes mellitus.
4. These agents bind to an ATP-dependent K⁺ channel on the cell membrane of pancreatic beta cells. This binding promotes insulin secretion from beta-cells of the pancreas, resulting in a reduction in the glucose serum level.
5. These agents lower **Glycated Hemoglobin A1c** by **1-1.5** when used for 3 months.

The normal range for the hemoglobin A1c level is between 4% and 5.6%

Prediabetes: between 5.6% and 6.4%

Levels of 6.5% or higher indicate diabetes.

6. A1c is an indicator for the effectiveness of the drug & is done every 3 months.
7. They're not the drug of choice, they cause destruction of the islets after 6-7 years of administration >> loss of activity and sensitivity to the drug.
8. They must be taken half an hour before meals.
9. Their adverse effects include **weight gain, hyperinsulinemia and hypoglycemia**.

Meglitinides

“Repaglinide & Nateglinide”

- Insulin secretagogues
- Mimic Ultra-Short Acting Insulin: short-lasting & fast working.
- Administered 10 mins prior to a meal.
- Same side effects & mechanism of action as Sulfonylureas.
- It restores initial insulin release in response to a meal. This restoration of more normal insulin release may suppress glucagon release early in the meal resulting in less hepatic release of glucose.
- It has minimal effect on overnight or fasting glucose level.

Biguanides “Metformin”

(Glucophage)

- ✓ Mechanism of action is unknown, but some suggestions are:
 - I. Stimulation of glycolysis in tissues.
 - II. Reduction of hepatic and renal gluconeogenesis.
 - III. Slowing glucose absorption from the intestine with increase glucose to lactate conversion by enterocytes.
 - IV. Reduction of plasma glucagon levels.
- ✓ The risk of hypoglycemia is far less than Sulfonylureas agents.
- ✓ Metformin **reduces hyperlipidemia** (LDL) and is the only hypoglycemic agent proven to **decrease cardiovascular mortality**.
- ✓ Metformin is the **drug of choice in newly diagnosed type 2 diabetes**.
- ✓ Metformin lowers A1c by 1.2%
- ✓ Does not result in weight gain (Ideal for obese patients).
- ✓ Metformin & CKD: On the basis of quantitative and qualitative syntheses involving 17 observational studies, metformin use is associated with reduced all-cause mortality in patients with CKD, CHF, or CLD with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.
- ✓ Metformin-associated lower risks were noted for cancers of the esophagus, stomach, colon, liver, pancreas, lung, breast, and prostate.

- ✓ It contributes to renal and cardiac protection.
- ✓ It increases anaerobic glycolysis resulting in Lactic acidosis (**rare** – 01/ 30,000-
exclusive in renal & hepatic failure patients).
- ✓ Contraindicated in pregnancy.
- ✓ Metformin has a diabetic protection activity; it decreases metabolic syndromes & Insulin Resistance.

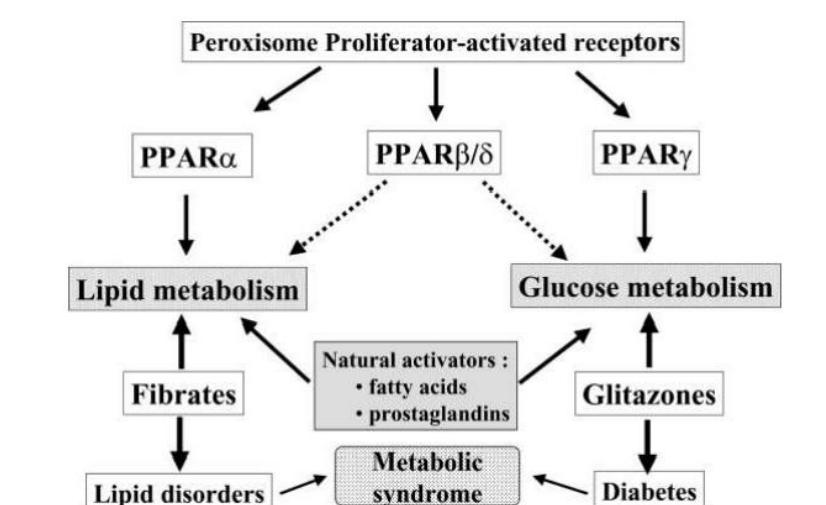
Glitazones

They act by binding to a group of receptor molecules inside the **cell nucleus**, resulting in a decrease in the insulin resistance.

PPAR

PPAR γ stimulation will increase Glucose Metabolism.

- ❖ The main side effect is fluid retention leading to edema, weight gain and potentially aggravating heart failure (Special Alert on February 2011).
- ❖ Contraindicated in patients with decreased ventricular function.



Troglitazone was withdrawn from the market due to an increased incidence of drug-induced hepatitis.

Resiglitazone is the most common one.

Alpha-Glucosidase inhibitors

- ❖ NOT the drug of choice.
- ❖ **Acarbose and Miglitol** are the members. They are taken in the beginning of the meals.
- ❖ Act by delaying the digestion of carbohydrates, thereby decreasing the glucose absorption.
- ❖ Both agents exert their effect by reversibly inhibiting membrane-bound alpha-Glucosidase in the intestine brush border.
- ❖ The major side effect is flatulence, diarrhea, and abdominal cramps.
- ❖ Patients with inflammation bowel disorder, colonic ulceration, and intestinal obstruction should not use them (contraindicated).

*Metformin is the only significant still-standing drug among previous old ones.

New drugs:

Dipeptidyl-peptidase (DPP) inhibitors

Sitagliptin/ Vildagliptin/ Saxagliptin

GLP-1 Modes of Action in Humans:

- I. Upon ingestion of food: GLP-1 is secreted from the L-cells in the intestine.
- II. GLP-1:
 - a. Stimulates glucose-dependent insulin secretion.
 - b. Suppresses glucagon secretion.
 - c. Slows gastric emptying.
 - d. Increases beta-cell mass.
 - e. Maintains beta-cell efficiency.
 - f. Reduces food intake.

- ✚ DPP is responsible for degradation of GLP-1.
- ✚ DPP Inhibitors: used as an adjuvant therapy with Metformin.
- ✚ Decrease A1c by 0.5% to 0.7%
- ✚ Almost no side effects; stuffy runny nose, headache & upper respiratory tract infections are very rare.

GLP-1 receptors agonist

- Exenatide - Liraglutide - Semaglutide - Albiglutide - Lexisena~~tide~~ – Dulaglutide.
- Effective in treating Obesity and Diabetes.
- Lower A1c by 1.5%
- Dulaglutide is an oral drug. Others are subQ.
- One of the best drugs that have introduced to markets.
- Side effects: severe/fatal pancreatitis & weight loss.

SGLT-2 Inhibitors

“Sodium Glucose Transport Inhibitors”

- Normally, 90% of glucose is reabsorbed in the kidney.
- Once inhibiting SGLT, high level of blood glucose will be excreted in the urine.
- Dapagliflozin - Canagliflozin - Remoglitiflozin - Sergliflozin - Empagliflozin – Tofogliflozin.
- Very effective drug; lowers A1c by 1.5%
- Approval to treat CHF is in prospect.
- Side effects: weight loss, Vaginal and male genital infections, Increased thirst, frequent Urination & UTIs especially in women.

To summarize management of Diabetes: start with **Metformin & Dipeptidyl-peptidase inhibitors** .. if A1c isn't significantly falling, **SGLT inhibitors** can be added in the case of a male patient, while **Sulfonylureas** in case of ladies, mainly.

- SGLT inhibitors & Sulfonylurea used to be replaced by insulin.

Gestational diabetes

- Peripheral insulin sensitivity during the third trimester decreases to 50% of that seen in the first trimester, and basal hepatic glucose output is 30% higher despite higher insulin levels.
- Insulin is the drug of choice.
- Glyburide and Metformin (Safe in pregnancy) are prescribed, but NOT approved. Glyburide does not cross the placenta. Metformin crosses the placenta in small doses.
- Glyburide does not cross the placenta, Metformin crosses the placenta in small doses.