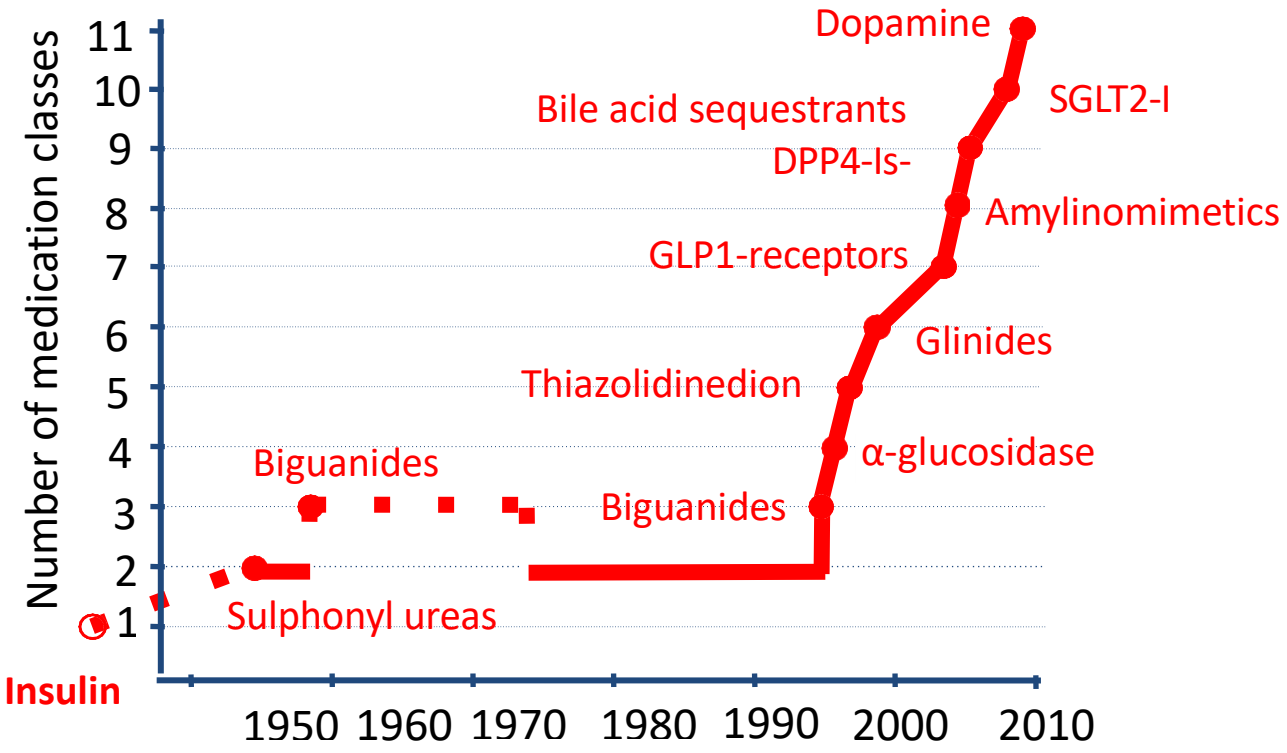
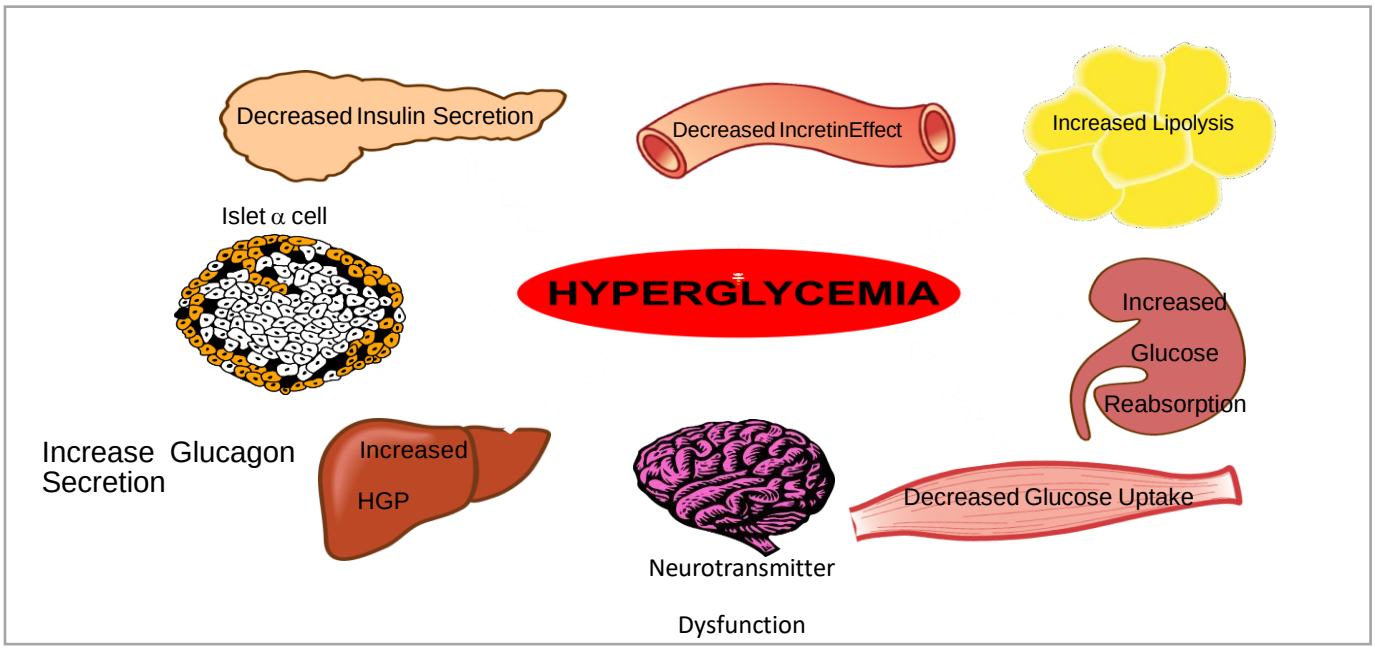
We'll be talking about the decision-making process for selected therapies in T2DM. That means how the physician will choose one treatment over all available options to treat diabetes. Remember that until the late 90s, only Sulfonylureas, biguanides and insulin were available. Starting 1998, several new classes came into the market.



Adapted from Therapeutic Advances in Endocrinology and Metabolism

For that we must always remember that T2DM is a progressive disease. It starts with hyperinsulinemia to compensate insulin resistance. With time, B cell function will decline, and insulin secretion will decrease leading to Type 2 Diabetes Mellitus.

We should remember that multiple pathophysiological failures named the Ominous Octet by Defronzo contribute to hyperglycemia among the increased lipolysis, increased glucagon secretion, decreased incretin effect, increased glucose renal reabsorption. Fortunately, we have now drugs dealing with these pathophysiological failures and the treatment of T2DM is an approach based upon its pathophysiology.



R.de Fronzo. Diabetes 58:773-795, 2009

Our knowledge of the pathophysiology of T2D developed in parallel with the availability of drugs. recent guidelines shed light to patients at high risk of CV events and ask to start in these patients with drugs that have proved their efficacy in lowering CV risks (GLP1 agonists and SGLT2is). However, before 2000, the pathophysiology of diabetes was seen resulting in low insulin secretion, low glucose peripheral disposal, and high hepatic glucose production. And we had to treat this situation with metformin and Sulfonyl Urea.

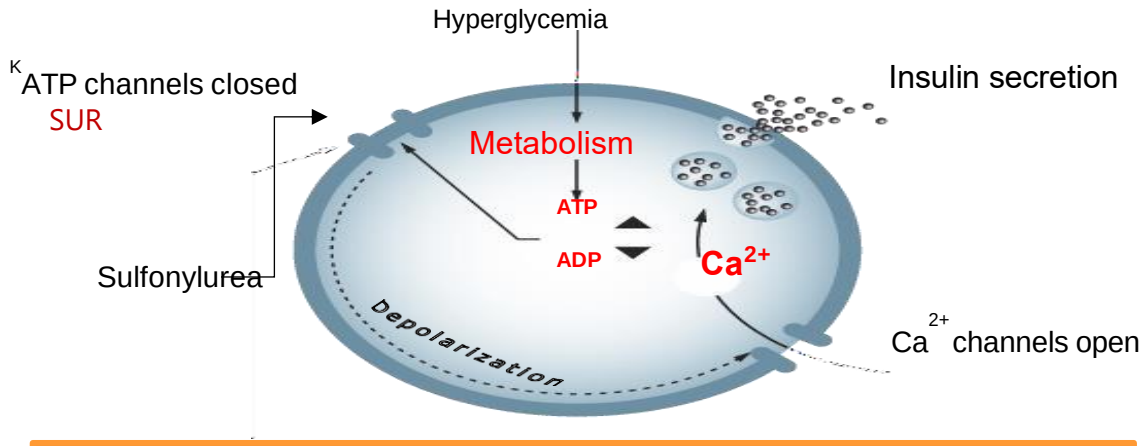
Metformin is a biguanide that reduces the increased hepatic glucose production. It works by helping to restore the body's proper response to the insulin naturally produced. It also decreases the amount of sugar that the liver makes and that the stomach/ intestine absorbs. It is now proposed by all guidelines as the first step of the treatment and used with a proper diet and exercise program and possibly with other medications to control high blood sugar. It has been proven in people with prediabetes to delay diabetes progression and it has the advantage to reduce body weight.

The most common side effects associated with its use are GI related, like nausea, vomiting, stomach upset and metallic taste. Stomach symptoms that occur after the first days of your treatment may be signs of lactic acidosis. Metformin does not usually cause hypoglycemia. Alcohol intake, while using this medication, should be limited because it can increase the risk of lactic acidosis and developing low sugar level.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5552828/

Howlett HCS, Bailey CJ. Discovery of metformin. In: Bailey CJ, Campbell IW, Chan JCN, Davidson JA, Howlett HCS, Ritz P, editors. *Metformin—the gold standard.* Chichester: Wiley; 2007. pp. 11–16.

Sulfonylureas are widely used to treat non-insulin dependent diabetes mellitus. These drugs exert their hypoglycemic effects by stimulating insulin secretion from the pancreatic beta-cell. Their primary mechanism of action is to close ATP-sensitive K-channels in the beta-cell plasma membrane, and so initiate a chain of events which results in insulin release the role of high level of free fatty acids resulting from insulin resistance at the level of visceral adipose tissue was outlines since free FA will provoke insulin resistance at the level of the liver.



MECHANISM OF INSULIN RELEASE IN RESPONSE TO HYPERGLYCEMIA OR SULFONYLUREA ADMINISTRATION

The primary benefit of **Sulfonylureas** is their effect on increasing insulin secretion and therefore helping to reduce blood glucose levels. however, is limited with time because they are not able to stop the progressive decline in B cells function and they have the disadvantage with high doses (for a better Hba1c reduction) associated with increased risk of hypoglycemia and weight gain.

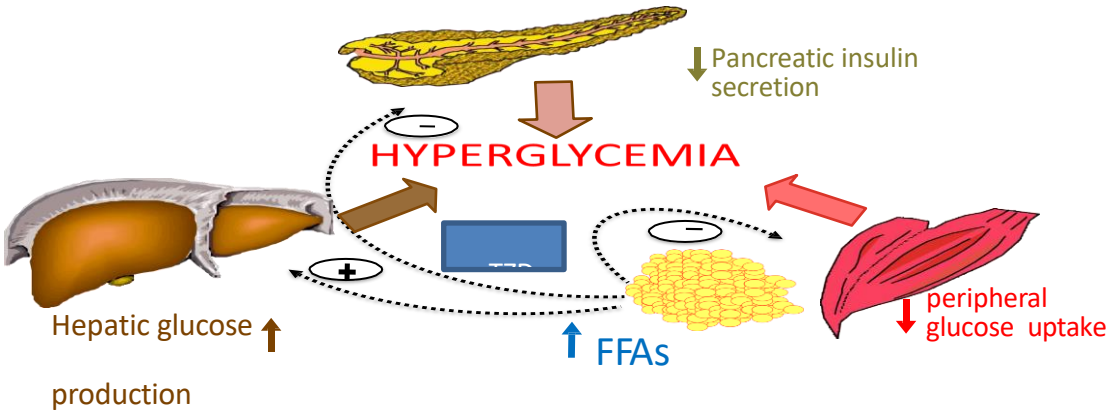
Their effect on insulin levels also means users are at increased risk of hypoglycemia (low blood sugar), although this risk is reduced with newer **Sulfonylureas** ,However SUs are not recommended for people who are overweight or obese, as their mode of action (increase in insulin production and secretion) means that weight gain can be a relatively common side effect:

- Signs of low blood sugar, such as sweating, dizziness, confusion, or nervousness
- Hunger

- Weight gain
- Skin reactions
- Upset stomach
- Dark-colored urine

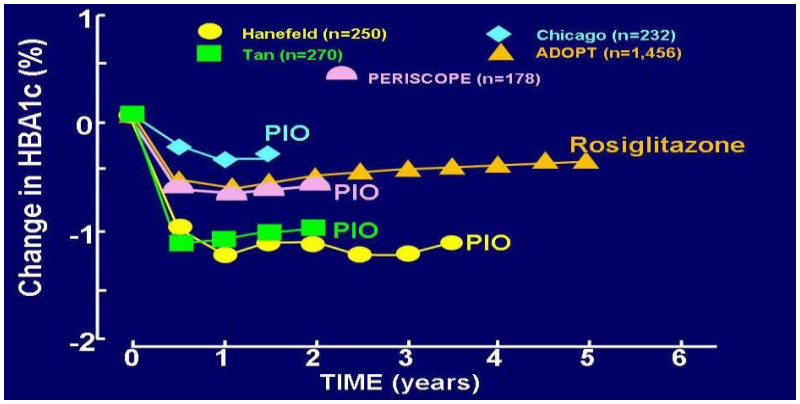
https://www.everydayhealth.com/sulfonylureas/guide/

Thiazolidinediones (TZDs) were released in the market in 1998 and these drugs are treatment for insulin resistance at the level of adiposities, the role of free fatty acids was outlined .. Thiazolidinedione do not tell the pancreas to make more insulin, but rather increases the sensitivity to insulin at the cellular level. Glucose uptake by muscles is improved when taking TZDs. This is through a mechanism in the cellular DNA, whereby TZDs interact with molecules inside the cells, and another substance that is normally present in fat tissue. These three factors working together can affect cellular function by regulating metabolism of lipids, or the fat that is found in the bloodstream. In addition, the combination regulates a hormone called, "adiponectin." This hormone works to improve insulin uptake by the cell receptors, thus improving insulin sensitivity. Muscles can utilize glucose easier. All these effects tend to reduce HDL, or "good" cholesterol in the bloodstream, but cause a mild elevation in LDL, or "bad" cholesterol. Thereby, insulin secretion based on insulin needs is reduced.



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

TZDs can slow the decline in B cell function and Hba1c remains stable for many years.



R.DeFronzo ADA 2008

Side effects that can occur following starting a TZD

- **Swelling (edema) –** feeling fatigued and gaining weight due to water retention from TZDs is common at onset of drug therapy; TZDs upset the salt balance that normally exists in your body, causing the kidneys to hold onto excess salt. The salt then leaks out through blood vessels and starts to build up in the body. This is what causes the edema or swelling.

R.DeFronzo ADA 2008

- **Heart Failure –** increased blood pressure places undue pressure on the heart, which could lead to congestive heart failure. Many studies have been done to look at TZDs relationship to heart failure. Long term use of TZDs can lead to increased swelling from the retention of fluid. The pressure in the heart increases, which increases the risk for heart failure.
- **Increased LDL, or "bad" cholesterol levels –** a mild elevation in LDL or "bad" cholesterol has been noted, along with an increase in HDL, or "good" cholesterol. TZDs may increase bad cholesterol in the blood steam. This occurs more often with rosiglitazone than with pioglitazone. LDL "bad" Cholesterol is a contributor to Plaque build-up in the arteries, or atherosclerosis. This can be combated with diet and exercise.