endocrine system

Pharmacology

Sheet Slide

number	6
Done by	Somaya Alkiswani
Correction	AbdelMuez Siyam
Doctor	Malek

Diabetes Mellitus

The most important aspect of diabetes is **how to manipulate the drugs**, because the problem of diabetes is being a long term problem that starts in **14-35** year old patients (usually), and it will be with them their whole life. The problem with DM is that **it is something changeable** (not constant, likewise hypertension), and DM patients are not treated with the same drug for 20 years, for example. Growing and changing problem demands changing drugs for the same patient. Such diseases are chronic, and we have to know how to deal with them, so we don't say we're going to treat but we say we going to **manage** diabetes mellitus because it is all about management, you have to teach your DM patient how to eat not just how to live, because diabetes mellitus is a metabolic problem, and this metabolic problem needs a lot of modifications. Here in pharmacology we won't talk about food but we are interested in drugs; we have many drugs, we have 7 groups of antidiabetic drugs (for type 2), from that we must know: **Which one should I use? Which one shouldn't I use? Why are there so many of them?** And so on.

You are not a DOCTOR if you don't know how to "**manage**" (not how to treat) diabetes mellitus (or hypertension), because in our population we have 30-35% hypertension, most of them will have diabetes so it is a real common problem.

Middle East is one of the most growing areas regarding diabetes mellitus rates, in MENA area we have 22 million patients with diabetes and they'll become 50 million soon, so you must know how to face it. In **Jordan**, the percentage of diabetes in people over 50 years old is around 16-17%, in **Saudi Arabia** it is a bit more 18%, in **Bahrein** it equal 30%, in **UAE** it equal 18-19%. We are from the areas in the world that has a high incidence of diabetes Mellitus, Why? In the Arabian gulf ,it may be due to excess rice while in Jordan it's probably due to lack of movement (lazy peoples); add to the problem that 70% of Jordanians are overweight and this predisposes most of the Jordanians towards diabetes mellitus, so it is a metabolic problem.

We can prevent diabetes mellitus or protect cells from diabetes mellitus (prophylaxis)-which is very important. This is a new era, from 2012-2013 we have studies saying that we can prevent (or delay) the incidence of diabetes mellitus which is really interesting, The doctor said that he had done

experiments on mice and he found that diabetes mellitus can really be prevented.

We have many types of diabetes mellitus:

- type 1 diabetes
- type 2 diabetes
- gestational diabetes
- LADA (late-onset autoimmune diabetes of adulthood). Covered diabetics, which is very common in Jordanian community, or we call it prediabetic situation, or metabolic syndrome, or metabolic problems, these patients accumulative glucose is between 6-6.5,

All what we need is to manage diabetes. You may ask **Why do we need to manage diabetes?** Many of the patients are diagnosed with DM incidentally, most of the patients know by chance that they have DM. Polyuria, polydipsia and lethargy may appear in the patient but in reality, many of those patients don't know that they have it. **Leave the patient with DM as he is able to manage that… NO**, the most important problem is the complications of DM which may lead to death. If we talk about type 1 diabetes, due to ketoacidosis (we are so afraid of ketoacidosis, therefore, Insulin should be kept with type 1 diabetics, they cannot live without insulin. but in type 2 there is insulin in the body so we don't care about ketoacidosis (the idea is that if there is no insulin there will be a switch towards fat, and fat metabolism will make more fatty acids enter the liver and fatty acids will accelerate production of ketone bodies; which are toxic by nature) many people die because of that). In type 2 diabetes the problem is with these complications:

1. Retinopathy- Eye Complications (in eye complication we use a drug called Avastin (bevacizumab)), 2. Kidney Disease,
3. Neuropathy and Nerve Damage 4. Cardiovascular Disorders

So we need to understand that if we leave the patient without treatment, without management, without education, without real knowledge about DM, He/she will end up either:

1. Blind 2. with Nephrotic syndrome,
3. Having problems in the neurons 4. Stroke

You need to tell your patient that (diabetes, hypertension; silent killers), they're killing you without telling, and you have to tell him how to manage DM.

So DM is not treatable, no treatment, no cure, it is **manageable**. You cannot give the diabetic patient a drug and say: you don't have diabetes anymore.

You must understand 3 things:- **Insulin** (most important part of our life without insulin we cannot live, Until 1920 patients with type 1 DM died due to DM and its complications, then Canadians have discovered insulin), **Gluacagon**, **Amylin**. These three are the real balance of glucose (Homeostasis of glucose; glucose metabolism and glucose level in the blood of patient is built on them).

Glucose homeostasis:-

The body must control glucose levels because all cells use glucose to make ATP, the energy currency of cells. Some tissues like the brain almost never burn any other fuel molecule. But too much glucose damages cells by getting attached to certain proteins and changing their function. Key tissues in this balancing act are :-

- **Liver**
- **Fat**
- **Muscle**
- **Brain**
- **Pancreas(endocrine cells)**

Diabetes definition: Increase of blood glucose due to an imbalance between regulating factors. (**A1C level** ≥ 6.5% OR **FPG** ≥126 mg/dL (7.0 mmol/L)).

A1C test: is a common blood test used to diagnose type 1 and type 2 diabetes and then to gauge how well you are managing your diabetes.

FPG: Fasting plasma glucose; (fasting is defined as no caloric intake for at least 8 h)

You have to know that you must measure it many times.

The only possible treatment is to keep the serum glucose level within normal. In reality, we're masking the symptoms of DM, and we need to fluctuate the glucose level within the normal range, before the disease progresses more and more towards the complications.

Prevalence of diabetes (2012)**:-**

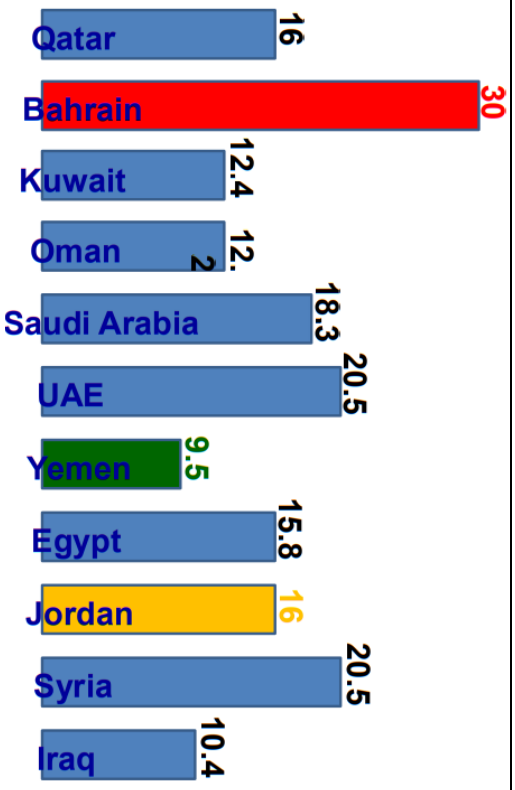
Iraqis (10.4%) Few: they do not eat too much rice.
Yemen (9.5%) Few: Yemenis are not fat, very thin, 18.6.

Smoking prevalence: it is high in Jordan, one of the highest numbers in the area.
Overweight: 69.8%, Jordanians are overweight.
Obese: 35%.

So we are at risk to have more and more diabetic patients, like all the Arab countries.

Kuwait: No sport.

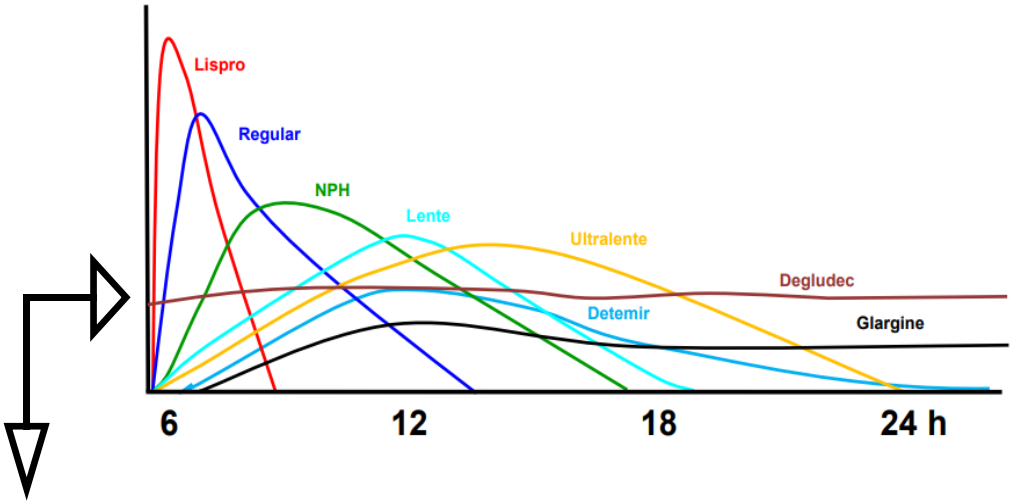
This is a view of the problem itself: we don't do sport, we are overweight, we smoke, we are obese, and we're that lazy (insufficient physical activities).



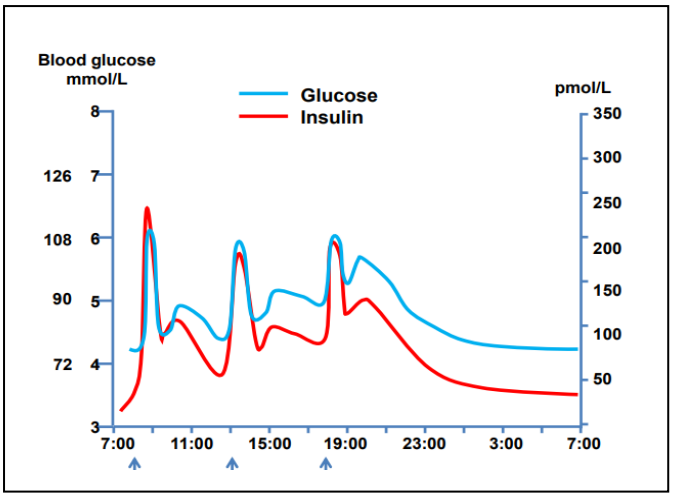
In DM patients, the probability of suffering from the **cardiovascular disease** is higher, The risk of a normal person todevelop CVD is around 1%. If the patient is newly diagnosed it equal 3.9%, and if he has been diabetic for a long time it's around 5%. so convince your patients to take their drugs. Remember that our patients don't take their drugs.

Insulin:-

It was manufactured by cow and pigs in the past. And now it is manufactured by human, so there are types of insulin, you will see in the pharmacy **:-** **(Lispro, NPH, Lente, Ultralente, Glargine, Detemir, Degludec)** and also there is regular insulin. What is the difference between them?

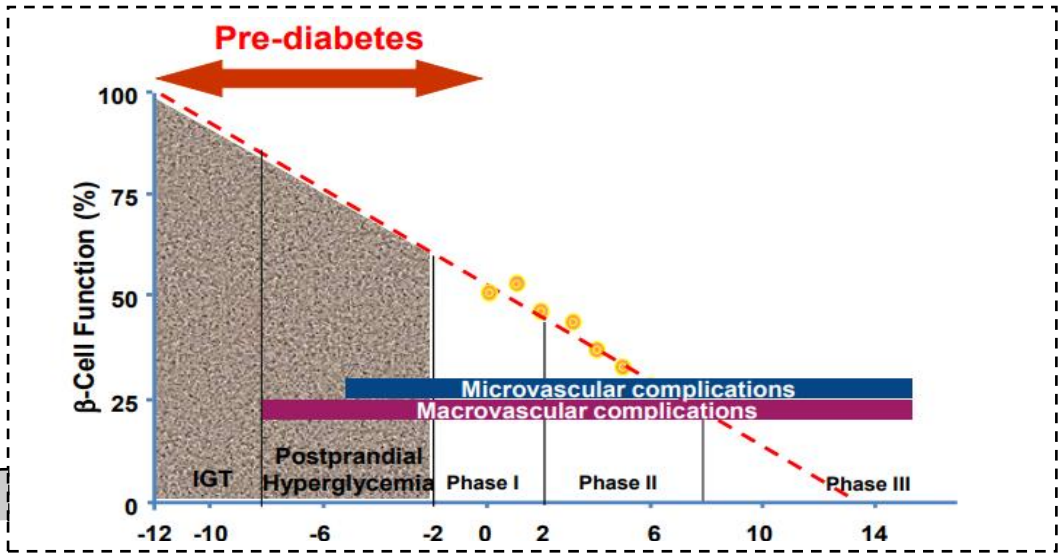


These types differ in their onset of action and duration of action. Some have sustained release, some are being released in for a long time and others for a short time, here we want to play on them, as we play a puzzle. Remember that every patient has different life style (different way of eating, different metabolism).



There is a basal level of insulin throughout the day and there are peaks: when glucose increases insulin increases. It is very important to understand that I'm here **because I want to mimic this situation**. In case that there is no insulin I give insulin to mimic the physiological level of insulin (during the baseline plus the peaks)

The release of insulin from beta cells (the same idea as alpha cells that secrete glucagon): You eat→ glucose go to the blood→ to the pancreas→ enter the beta cell →produce ATP→Close K+ channels + Open Ca++ channels →insulin release.



There is a decline in the function of beta cells, especially in **type 2 diabetes** (generally there will be a decline, but more progressive in diabetes).

12 years previous to the diagnosis of DM, You have 100% normal beta cells working properly. **With time,** a situation called postprandial hyperglycemia develops, because there is a decline in beta cells even before the patient is diagnosed with diabetes, and they may decline toward ZERO (long after). So this slide tells you that you may be able to protect or prevent diabetes if you protect the beta cells, and there are many drugs that are able to protect beta cells. In addition, type 2 DM patients will need insulin in their late stages. You must understand that if the doctor prescribes you a drug on **day 1** it will absolutely be different from the drug after **10 years** because the doctors assume that you (**NOW**) have insulin in your blood (because there is beta cells) but after **10 years** you will not have insulin in your blood so the doctor changes the drug from something depending on the presence of insulin towards supplying the patient with insulin, so things change.

Glucagon:-

The patient is either under hyperglycemia caused by glucagon or hypoglycemia caused by insulin. There is balance (for the glucose that lives in our blood).

If you lose your insulin production; there is no pancreatic cells to produce insulin= **type 1 diabetes**, if you have something called insulin resistance (insulin cannot make tissues take up glucose)= **type 2 diabetes.**

Amylin:-

It is co-secreted with insulin from the pancreatic β-cells; when insulin is released, amylin is released with it, why? In order to decrease the absorption of glucose **(Amylin plays a role in glycemic regulation by slowing gastric emptying, decreasing glucagon secretion ,and promoting satiety, thereby preventing postprandial spikes in blood glucose levels)** , in order for the body to manage the peak of glucose.

Why do we care about it? Because many years have passed (100 years), and we believe that **type 1 diabetes** is only treated with insulin, but now there is an amylin analogous (2013) that can be used. We also can give it with **type 2 diabetes**, it is not popular but it will become popular.

There is a situation called **Hyperamylinemia**, (Very important):-
"a common pancreatic disorder in obese and insulin resistant patients, is known to cause amylin oligomerization and cytotoxicity in pancreatic islets leading to β-cell mass depletion and development of type-2 diabetes."

This is very interesting if we ask why will obese have DM? In fact amylin molecules are more produced, and these aggregate to give something like oligos; which are toxic for the Island and kills the pancreas' cells (This is just one reason not the whole story). There are many ideas regarding the use of analogs of Amylin for prevention of diabetes especially in obese patients.

Management of type 1 diabetes

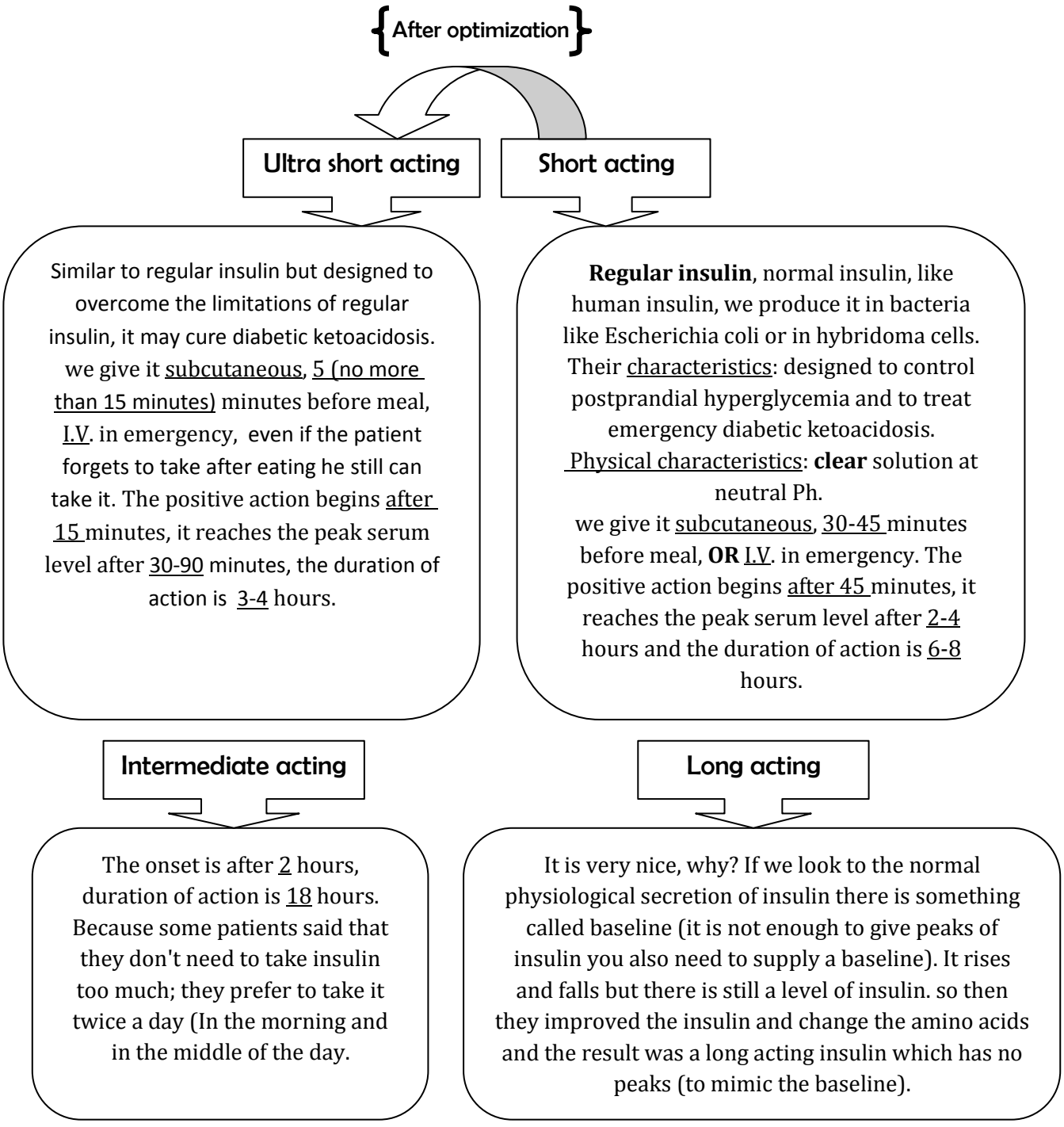
1. Insulin:

You must understand that insulin is a polypeptide, and there is something called modifications of polypeptides; (if you change one amino acid to another you will change the **kinetics** of the peptide or **the half life** of the peptide, the idea here is that how they a.acids are aggregated together, especially the two sites (28 and 29= proline and lysine), if I change them, the kinetics of the insulin change.

Examples:

1. Lispro: they change it by putting lysine in the proline place, by making a specific mutation in the DNA. When they change other things they produce **2. Aspart**, other changes give **3. Glargine**... more changes give other results.

So they made types of insulin and these types are divided into **4 groups** (modification of the amino acid sequence of human insulin have produced insulin with different pharmacokinetic properties):-

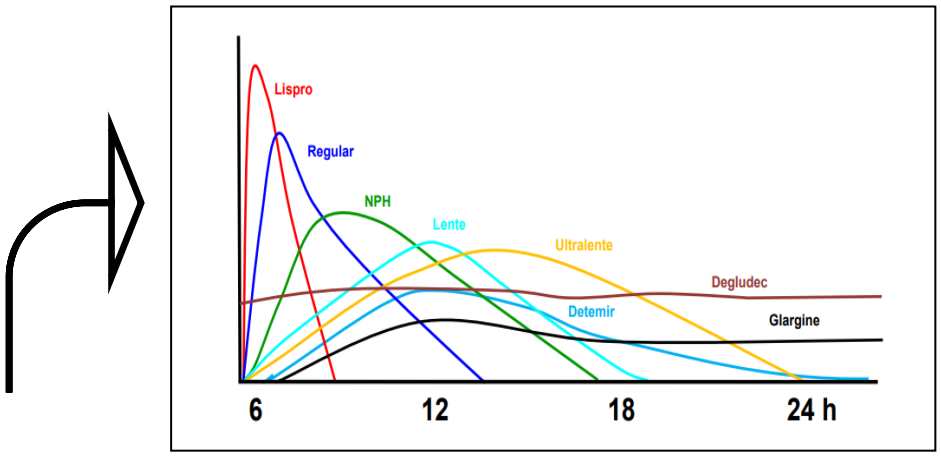


Lispro, Aspart, Glulisine = **Ultra-Short acting
Humulin R, Novolin R = **Short-acting (Regular)
NPH = **intermadiate acting
Glargine = **long acting

Because of the fact that insulin is a polypeptide, it is degraded in the GI tract if taken orally. It, therefore, is generally administered by subcutaneous injection.

If you remember, we have a physiological peak when glucose level is high ,so **in type 1 diabetes**, the patient takes insulin, and the idea of insulin is to mimic the physiological insulin secretion. If the insulin we gave peaks from 7 to 11am, that's good. But if it peaks for a long time, what may happen? **Hypoglycemia**, because there is insulin in the blood but no glucose.

The ultra short acting are much better, the chance for hypoglycemia to occur is much less, because the peak is sharp (this is ultra short like (Lispro+ Aspart), up and down exactly the same as normal insulin works in the body, for around 3 hours - insulin peak time-). What is the problem here? The problem is that it is more expensive than the regular(short). If you have to give your patient ultra short insulin you'll have to give him every single need of what he have to take (many times a day), some patients don't accept this and prefer to choose the intermediate acting insulin, it depends on the life style of the patient 34:00



As you see these are the different types of insulin, on the left there is the ultra short acting, also we see the regular insulin.

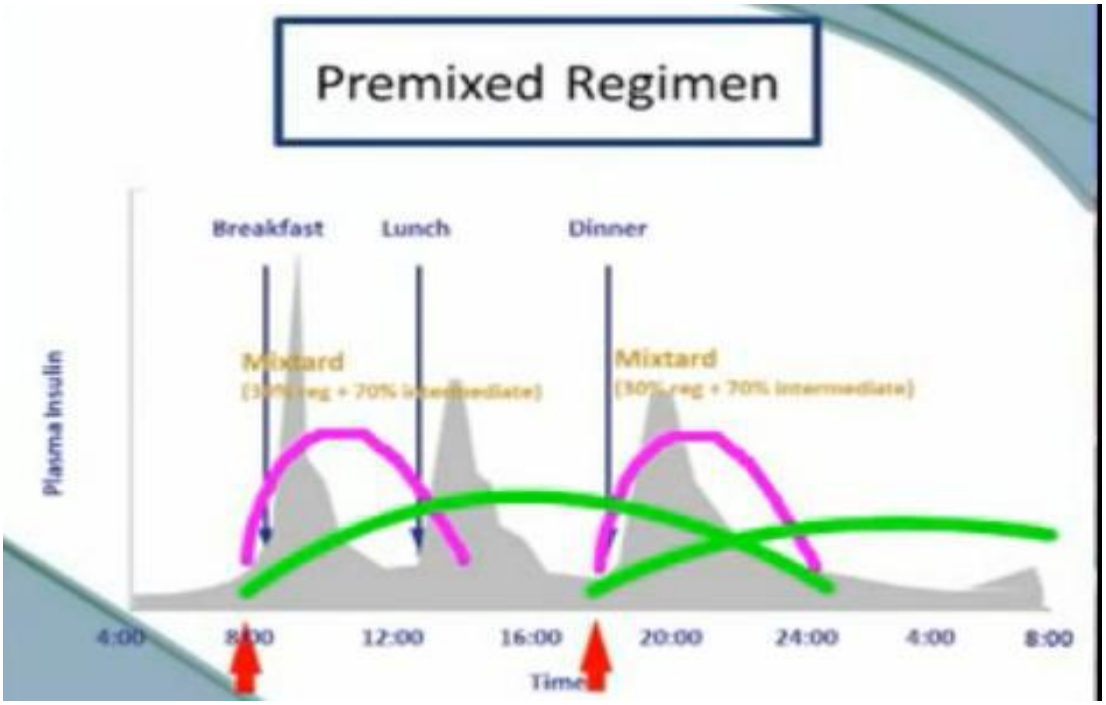
So, what I use as a baseline? Glargine (long-acting, peakless).

For every patient with DM, I'll have to keep a baseline of insulin in his body. I give **Glargine**, and when he eats I must give him **ultra short** acting insulin (Before eating each meal of the three meals for example), this is the best way to deal with DM type 1.

Glargine + Supplement of insulin (ultra short)

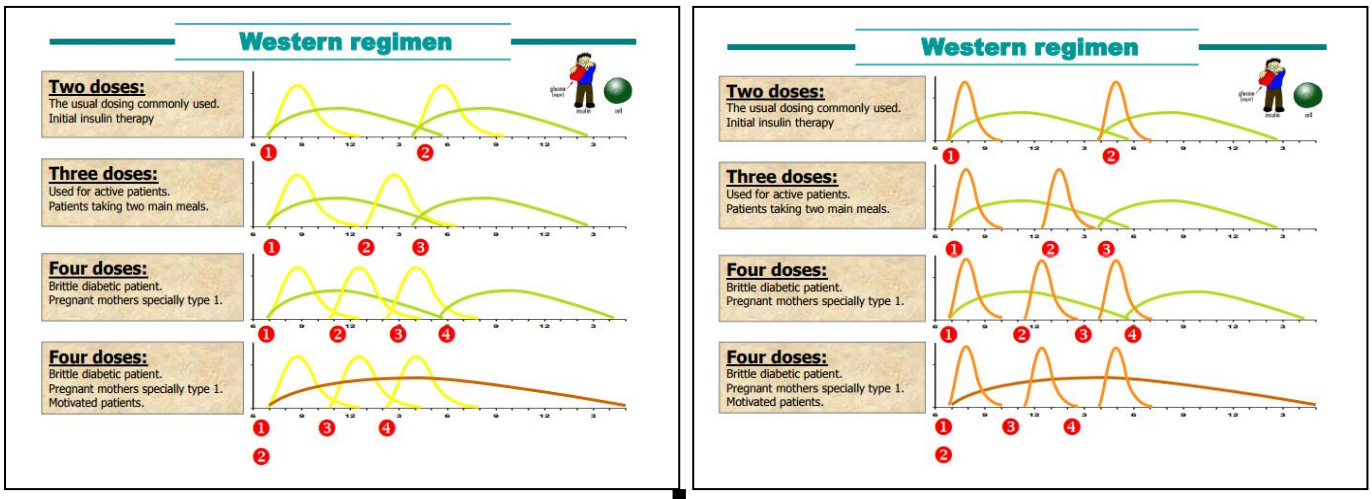
This is the best way but the most expensive way, many patients cannot afford this because it is really expensive + 4times a day is hard for many patients. This next method is more common.

The second choice: give 2 doses (needles) of **intermediate** acting insulin with **regular**, the shape of it is not a peak like the ultra short, it look like a hill, you can ***premix*** it (give mixture of NPH/regular as 75/25 or 50/50), so instead of taking 4 needles the patient will take only 2, here we cover all the need, and make a baseline. This situation has a chance to produce **Hypoglycemia**, where? Two times but the dangerous one is at night; when there is no food and there is insulin, there is a high incidence of hypoglycemia.
**Green= baseline, purple= regular (to consider peak times –meal times-).



Intermediate acting insulin + regular insulin

So every method has advantages and disadvantages.



These slides till as that there are different ways to deal with insulin, and we manage according to the population, every patient has different way or different life style so I prescribe a different way of compensation. But remember that there is a baseline, insulin must always be present because I want to mimic the physiological condition and at the meal time there must be enough insulin level to reduce glucose level especially in **type 1 .**

There are side effects for insulin, such as **(1) Weight gain** because it will facilitate the entry of glucose into the tissues and keep the fatty acids in their places more and more , so you must protect your patient from being overweight (in two types of DM, but in **type 1** remember that the patient lives on insulin so there must be something that called nutritional control; to tell the patient that you are as any normal person and you need a specific amount of calories every day, also tell the patient what he must eat, in order to keep his weight normal). Also, you must always remember the **(2) Hypoglycemia**. Mothers must understand all these things when they have a child with DM, it is not a small proportion, In MENA area we have 22 million people with diabetes and 10% of them with **type 1** diabetes= 2 million. The mother must remember for example that **if your child forgot to eat the meal, don't give him insulin, so simple.**

Hypoglycemia (not hyper); emergency, the symptoms of hypoglycemia are the most serious and common to an overdose of insulin (when you give a large dose of insulin).

Other adverse effects include **(3) Lipodystrophy**; a lump or small dent in the skin that forms when a person keeps performing injections in the same spot (less common with human insulin), and allergic reaction. (Caused by insulin injection subcutaneous) "Very important".

(4) Diabetics with renal insufficiency must have their doses of insulin adjusted.

When we study some clinical pharmacology in the future we must know how to adjust the doses of insulin.

Amylin helps in the absorption of Glucose by:

Slowing gastric emptying
Promoting satiety
Inhibiting inappropriate secretion of glucagon

2. Amylin:-

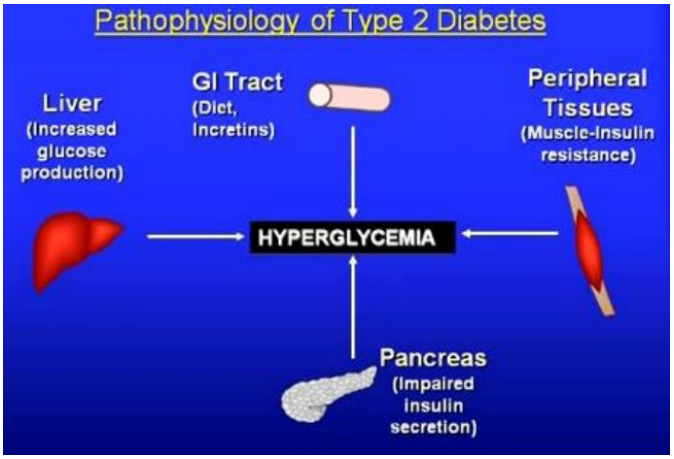
It is a hormone secreted by beta cells. It is a drug (new drug); **Amylin analogs**. For **type 1 & 2 DM**.

USMLE question: What is approved for treatment of **type 1,** is it only insulin? NO, there is a new drug called **Pramlintide,** How it works and why should I give it? It reduces the peak that may occur in the patient, decreases the absorption of glucose, makes the peak a pit straight, it decreases the need for insulin. So the new studies tell us that instead of giving a lot of insulin to the patient (1unit/kg in **type 1** for example, and 0.5 unit/kg for **type 2** patients), I may give this drug **Pramlintide** and lower the insulin dose. It is still under study.

2. Insulin pump:-

When they discovered it, it was very big. Now it is very small, they put it in the abdomen and there is a needle which enters subcutaneously, the patient must calculate how many calories he will eat on this day, and the pump will introduce insulin into his body, it is very expensive (5,500 JD). The idea of it is to put a tube in the patient body and the sustained release will continue, depending on the program. The problem is that it needs 1000 JD yearly.

Management of type 2 diabetes



1. Oral hypoglycemic agents:-

They use it in order to decrease body weight, **A BIG MISTAKE.**
They are useful in the treatment of type 2 diabetes patients that cannot manage their glucose level by diet only. Patients with the long-standing disease may require a combination of hypoglycemic drugs with or without insulin to control their hyperglycemia. The insulin is added because of the progressive decline in beta-cells that occur due to the disease or aging. Oral hypoglycemic agents should not be given to patients with **type 1** diabetes.

At the beginning, we must understand that we have different target tissues (Liver, Pancreas, GI, peripheral tissues). Remember that **type 2 DM**; is diabetes with insulin resistance rather than losing the ability to produce insulin; there is insulin in the blood of your patient, but this insulin also declines over time. (Retinopathy, Nephropathy, Pancreas: all of them are complications, so be careful of them when you make management on this patient)

The first and easiest way is to gives drugs that produce insulin, what we call them? **Insulin secretogogues**, the most important one of them is what we call **Sulfonylurea** (Amaryl): best drug used to reduce AUC!

You must know -**Glimepiride, Glipizide, Glyburide**- (there are older generations(not required)), Why we give them to the patient? We give those adjuncts to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus, by stimulating insulin release from beta-cells of pancreatic islets. How? By closing the potassium channel, thus depolarizing the cell and

causing Ca entry in order to release the insulin. These agents bind to an ATP-dependent K+ channel on the cell membrane of pancreatic beta cell, this binding promotes insulin secretion from beta-cells of the pancreas, resulting in a reduction in the glucose serum level. They are very nice because they mimic the insulin in the body of the patient. However, they are the strongest accumulative drugs in reducing the accumulated diabetes (they reduce the glucose by 2, if the patient started with diabetes=9 within 6 months of use or maybe 3 months, they will reduce it to 7), except **if you use insulin** because it reduces it regardless of how much you want ,depending on the DOSE, but as a drug we don't begin with insulin with the patients if it was 8 or 9 but if it was 10 or 11 we do, and then (after lowering AUC a little bit) we convert to others. But as a beginning we begin with **Sulfonylureas**, it is the same as insulin so it has the same side effects (weight gain+ hypoglycemia).

Their adverse effects include weight gain, hyperinsulinemea, and hypoglycemia.

They are contraindicated in patient with hepatic and renal insufficiency.

(If you don't have time, don't read this) Other insulin secretogues include **Meglitinides (Repaglinide, Nateglinide)** . What we really want to know about them is that if the patient undergoes renal failure and I'm forced to use insulin secretogogues I must use **Nateglinide**, because of that the **Sulfonylurea** and ------ and -----...!!!, are contraindicated in renal problems. Remember that your patient has a decline in his vision and nephrons. So on day one you use **Sulfonylurea** but with time you have to change them to **Nateglinide** (we don't use them too much except if the patient has renal failure.

Metformin (from Biguanides):-

Now let's come to the best drug: **Metformin** (glucophage), it has a very nice antioxidant activity, it decreases the chance of cancer, reduces plasma glucagon levels, modestly reduce hyperlipidemia, the only hypoglycemic agent proved to decrease cardiovascular mortality, very little side effects, it has a different MOA from insulin secretogogues drugs (it is not the same of **Sulfonylurea** nor **Nateglinide**). The adventage of it is that it does not depend on insulin production so it don't make hypoglycemia. "Like Sulfonylureas, **Metformin** requires insulin for its action, but differs from Sulfonylureas that it does not promote insulin secretion. (The risk of hypoglycemia is far less than Sulfonylureas agents)."

They also keep the beta cells alive,

So the international guideline: If your patient has a **DM type 2,** he has to take **metformin**. As we said it doesn't depend on insulin secretion so there is no hypoglycemia, it protects the beta cells, has nice mechanisms of action, it works on different areas.

In some books, you may found that this drug may decrease the insulin resistance, **YES**, that's true but not real, it doesn't make desensitization of tissues toward glucose.

It doesn't increase the weight because it doesn't increase insulin production (It keeps the weight normal, but it decreases the weight 3 kilos "ONLY" when the patient starts taking it), Ideal for obese patients.

Compared with sulfonylurea users, **metformine** users had a 10% lower incidence of cancer. This 10% reduction was highly statistically significant, **Metformine**-associated lower risks were noted for cancers of the: **esophagus, stomach, colon, liver, pancreas, lung, breast, and prostate.**

Side effects :-

1. Diarrhea, flatulence, a condition similar to irritable bowel syndrome (GI problems, in 20% of the population in the first 2 weeks, then this percent becomes 6-7%) so what is the solution? I begin with **metformin** 500mg in the first week, then I increase the dose, my target is 1000 to 2000mg daily but we shouldn't start with it because the chance for GI side effects will be very high, so we control the dose to reduce the incidence of the GI problems.
**The remaining 6% shouldn't take metformin, they can't tolerate it.
2. Metallic taste in the mouth
3. Contraindicated in a patient with hepatic and renal diseases, cardiac or respiratory insufficiency, severe infections, and pregnancy
4. Long term use may interfere with vitamin B12 absorption
5. Lactic acidosis (rare – 01/ 30,000-exclusive in renal and hepatic failure)

Medicine really matured me as a person because, as a physician, you're obviously dealing with life and death issues, issues much more serious than what we're talking about in entertainment. You can't get more serious than life and death. And if you can handle that, you can handle anything.

Ken Jeong

"اللَّهُمَّ انْفَعْنَا بِمَا عَلَّمْتَنَا, وَعَلِّمْنَا مَا يَنْفَعُنَا, وَزِدْنَا عِلْمًا إِلَى عِلْمِنَا"