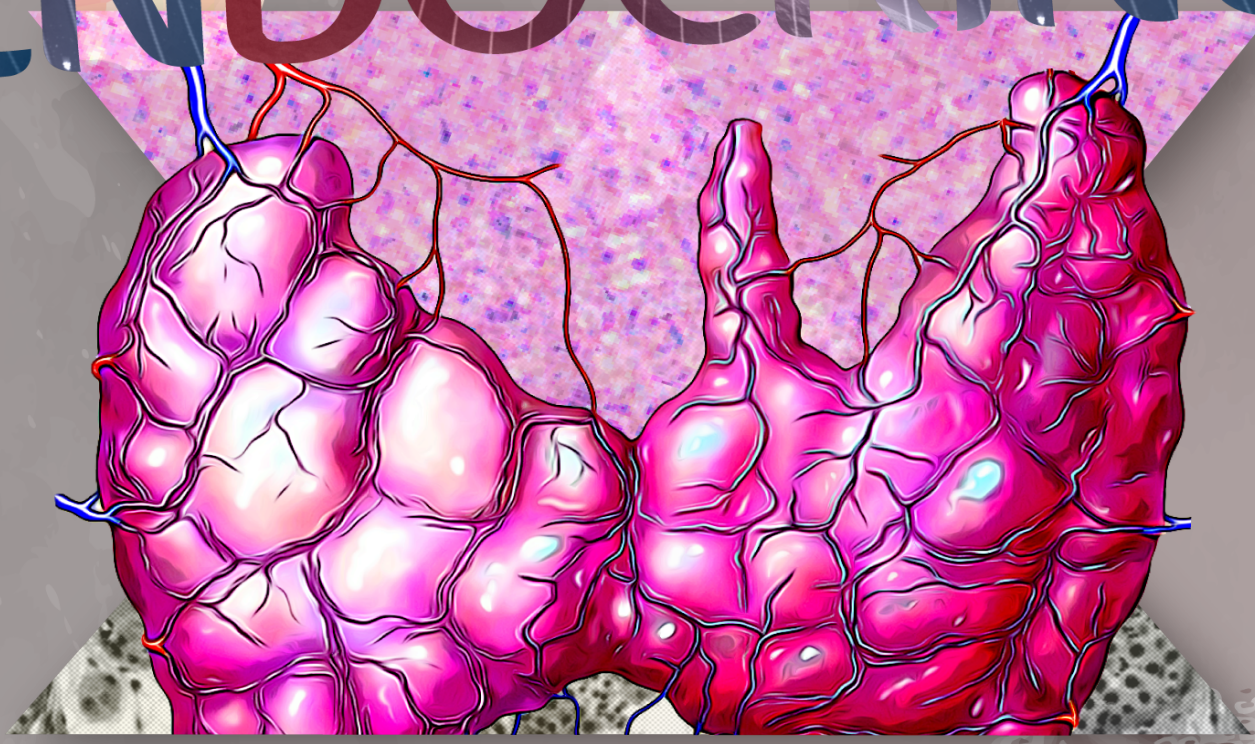
4

ENDOCRINE



SUBJECT: Pharmacology

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Checklist

1- Continuation on Strontium Ranelate
2- Secondary hormonal regulators of bone mineral homeostasis
   - Calcitonin
   - Estrogen
3- SERMs
   - Tamoxifene
   - Raloxifene
4- DM
5- DM Type 1 Drugs

Continuation on Strontium Ranelate

• This drug is approved in Europe but not US

• It's highly effective in increasing bone density (highest nonhormonal in effectiveness)

• Unlike bisphosphonates, denosumab, or teriparatide, this drug increases bone formation markers while inhibiting bone resorption markers.

• Large clinical trials have demonstrated its efficacy in increasing bone mineral density and decreasing fractures in the spine and hip.

Note: Remember that it's efficacy is high, similar to PTH.

Why isn't this drug approved in the United States?

Because the body recognizes strontium as calcium and this increases the risk of thrombosis by 3-4% approximately (there isn't enough documentation), it also increasing arrhythmias and the possibilities of tachycardia and tachypnea. So FDA thinks that the risk outweighs the benefits.

Secondary hormonal regulators of bone mineral homeostasis

• The physiologic impact of such secondary regulation on bone mineral homeostasis is minor.

• In pharmacologic amounts, they may have actions that are useful therapeutically.

Calcitonin

Cells secreting it	Parafollicular cells of the thyroid gland (C Cells).
Structure	Single chain 32 AAs peptide
Metabolism	By the Kidney but still few intact calcitonin appears in Urine.
Principal effect	lower serum calcium and phosphate by actions on bone and kidney.
Half life	10 mins

Why isn't human calcitonin ever used? What's the alternative?

Because of its short half life, Salmon calcitonin has a longer half- life of 40–50 minutes and is used.

What are the effects of Calcitonin?

1- On Bone: It'll decrease bone resorption and eventually both resorption and formation will be inhibited as calcium levels fall due to renal excretion (no more Ca for bone deposition). (that's why it's not highly used in osteoporosis.)
2- On Kidney: reduces both calcium and phosphate reabsorption as well as reabsorption of sodium, potassium, and magnesium leading to many HYPOs and that's also a drawback for its usage.
3- On Gut: in pharmacologic amounts decreases gastrin secretion and reduces gastric acid output while increasing secretion of sodium, potassium, chloride, and water in the gut.

Note(Written in the slides but the Dr didn't explain): Pentagastrin is a potent stimulator of calcitonin secretion (as is hypercalcemia), suggesting a possible physiologic relationship between gastrin and calcitonin.

What's the overall effect on bone?

It increases bone mass and reduces spine fractures, but is less effective than bisphosphonates and teriparatide.

Is calcitonin deficiency as in thyrodictomy or calcitonin overproduction as in functional medullary carcinoma problematic?

In the adult human, no problem develops.

What are the therauptic uses?

Paget disease (second or third line.)

Hypercalcemia (not the first line.)

Osteoporosis (not the first line.)

Glucocorticoids are secondary hormonal regulators of bone but will be discussed on a lecture of their own

Estrogen

First, let's remind ourselves with postmenopausal osteoporosis which is osteoporosis that is caused by absence of estrogen in postemenopausal women.

Why to not give them all estrogen? First let's break the positive and negative sides of estrogen effects.

Positive Effects	Negative Effects
Bone: • Can prevent accelerated bone loss during the immediate postmenopausal period, and at least transiently increase bone in the postmenopausal woman. • Reduce the bone-resorping action of PTH. • Increase 1,25[OH]2D level in blood. Note: It's direct effect over bome as it'll have receptors there.	Estrogen therapy has been shown to be associated with endometrial and breast cancer in postmenopausal
Psychiatric: • Reduces depression, changes in personality and hot flushes.	

So because of its association with these cancers, we provide a consent form that includes the possible risks and the patient is free to sign and take the treatment or not.

Is it important for men?

Yes it's as we produce it from testosterone using Aromatase and this estrogen has receptors on bones. So, lacking estrogen receptors in some males, or those unable to produce estrogen because of aromatase deficiency, develop marked osteopenia and failure to close epiphysis (case reports).

SERMs

What are SERMs?

Selective estrogen receptor modulators, those are drugs that work as agonists and antagonists at different estrogen receptors.

Medication	Breast	Bone	Liver				Uterus	Vagina	Brain	
			Lipids	Coagulation	SHBG	IGF-1			Hot flashes	Antigonad
Estradiol	+	+	+	+	+	+	+	+	+	+
"Ideal SERM"	–	+	+	–	±	±	–	+	+	±
Bazedoxifene	–	+	+	+	+	?	–	±	–	?
Clomifene	–	?	?	?	+	+	?	?	–	±
Lasofoxifene	–	+	+	+	?	?	±	±	–	?
Ospemifene	–	+	+	+	+	+	±	±	–	±
Raloxifene	–	+	+	+	+	+	±	–	–	±
Tamoxifen	–	+	+	+	+	+	+	–	–	±
Toremifene	–	+	+	+	+	+	+	–	–	±

Effect: + = Estrogenic / agonistic. ± = Mixed or neutral. – = Antiestrogenic / antagonistic. **Source** template.

*** The Table isn't for memorization, it's just for illustration of the idea.

• We will care abour bone, endometrium and breast receptors.

Tamoxifen

• In Jordan, TAMOXIFEN has been used, this one is breast receptor antagonist and agoninst for bone and endometrium receptors.

It's used for 5 years after the treatment of breast cancer in a patient so we prevent the reoccurrence of breast cancer as it's an antagonist there, it also strengthens bones and increases their density.

BUT as we know you can't deny the possibility of breast cancer reoccurrence until 20 years pass, so why not to give all through this period????

Because it's an endometrail estrogen receptor agonist which means that it increses the risk of endometrial cancer so 5 years are optimal so risks don't jump high and breast reoccurrence possibility is reduced.

Raloxifene

t's a rising SERM that is replacing tamoxifen as it's only an agonist for bone estrogen receptors, an antagonist for breast and endometrium estrogen receptors. Additionally, it doesn't prevent hot flushes.

What are the drawbacks for it usage in osteoporosis as it doesn't induce cancers of any type?

- It is not as effective as estrogen in increasing bone density.
- Raloxifene may protect against spine fractures but not those of the hip (bisphosphonates and teriparatide protect against both).

Diabetes Mellitus

What are the type of Diabetes?

They will be discussed in pathology, they're type 1,2 and gestational diabetes(during pregnancy).

Remember type 1 vs type 2 table

Feature	Type 1	Type 2
Age	Commonly <20	Commonly >40
Body mass	Low to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High	High
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced

Type 1: autoimmune destruction of the beta cells in the islets of langerhans

Type 2: form of diabetes that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. (Dr said hyperinsulinemia. They suffer from it in the beginning due to decreased resistance then burnout happens to beta cells, it's a matter that will be covered in patho.)

Why is it important to control Diabetes?

Because of its many complications including neuropathy, nephropathy, cardiopathy and retinopathy and definitely ketoacidosis which emerges in absence of insulin.

How to measure for the complications?

By A1C test, whic measures your average blood glucose level over the past 3 months.

Type 1 DM

As we have said it's an autoimmune destruction of beta cells in the islets of langerhans establishing deficiencies in insulin, C peptide and Amylin.

What are the treatments?

• Amylin has been approved as a hormonal treatment but is rarely used, it'll slow down the movement of the gut and absorption of glucose.

• While Insulin is used for the treatment.

What are the sources of insulin?

• human insulin has largely replaced the insulin isolated from cows or pigs pancreas for therapeutic uses.

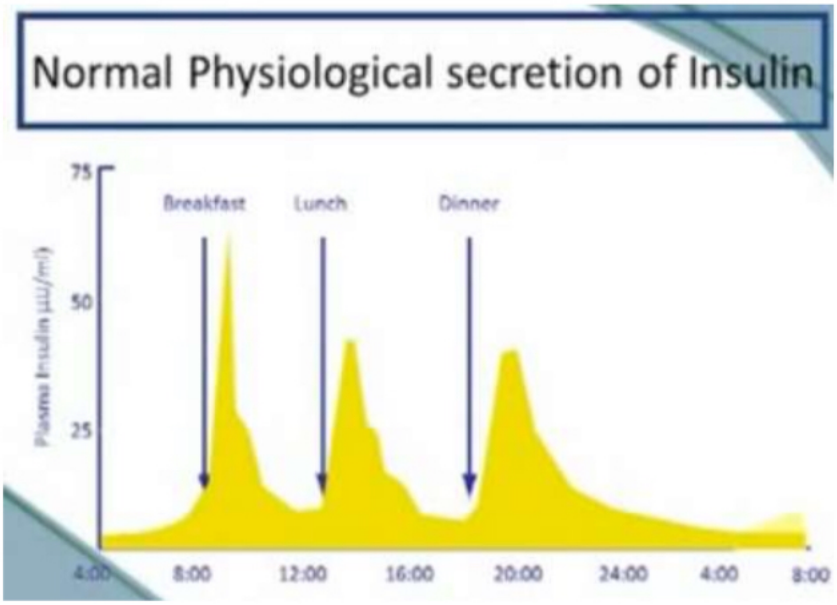
• Human insulin is produced by recombinant DNA technology using Escherichia coli or yeast that have been genetically alter to contain the gene for human insulin.

• Modification of the amino acid sequence of human insulin have produced insulins with different pharmacokinetic properties.

Note: The unmodified human, pigs or cows insulin is called regular Insulin.

In normal condition (non-diabetic), after 10 minutes of ingesting a meal the β-cells of the Islets of Langerhans start to secrete Insulin into the blood-stream. The Insulin then goes to the portal vein into the liver, where half of the total secreted Insulin undergoes what is known as first- pass metabolism and then the other half is secreted to the blood as active Insulin. After its peak concentration the concentration starts to decrease until the concentration of Insulin reaches it base-line concentration 1-2 hours later. What is meant by the base-line concentration is that there is a certain concentration of Insulin present in the blood stream at all times for the regulation of certain biochemical processes such as Gluconeogenesis. It is very important to be aware that the base-line is a certain concentration and not zero. In non-diabetics there is never zero Insulin in the blood.

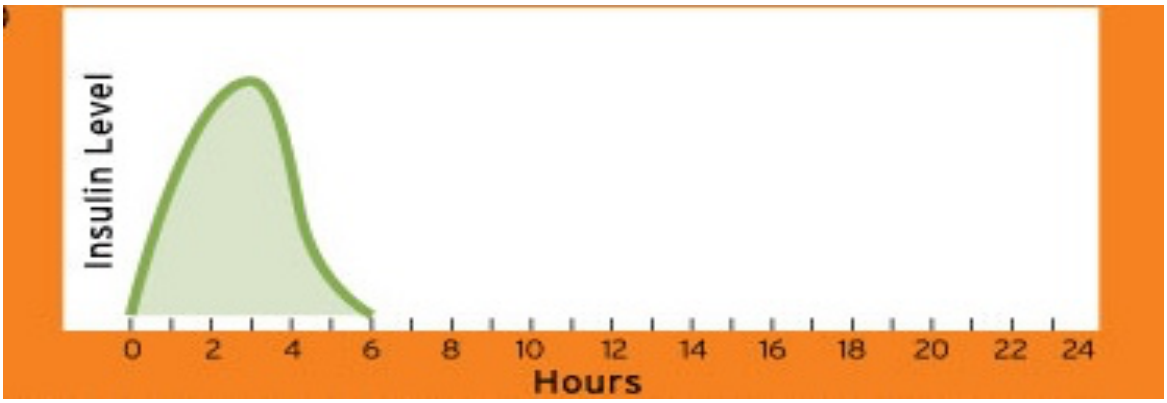
In type 1 Diabetes there is no secretion of Insulin, therefore you neither have that peak that occurs after ingesting a meal nor a baseline concentration of Insulin in the blood. That being known, in the maintenance of Type 1 Diabetes we need to administer Insulin after a meal and also maintain a base-line concentration of Insulin in the blood. This is where the different preparations of Insulin come into play.



Notice the peaks after meals and the baseline.

Short Acting (Regular Insulin Preparation)

Structure: animal insulin, human insulin
Examples: Humulin R, Novolin R (those are recombinant human)
Pharmacokinetics: Onset: 30-45 mins. Reaches Peak in: 2-4 hours. Effect last for: 6-8 hours.
Chemical structur: Hexameric analog.
Physical characteristics: Clear solutions at neutral pH.
Usual administration: 2-3 times /day or more.
Negative point: It doesn't have a baseline as it falls rapidly until you take it before the next meal in 30-45 mins.
****Was used in the past alone and in some as 4 injections****



This graph represents the short acting.

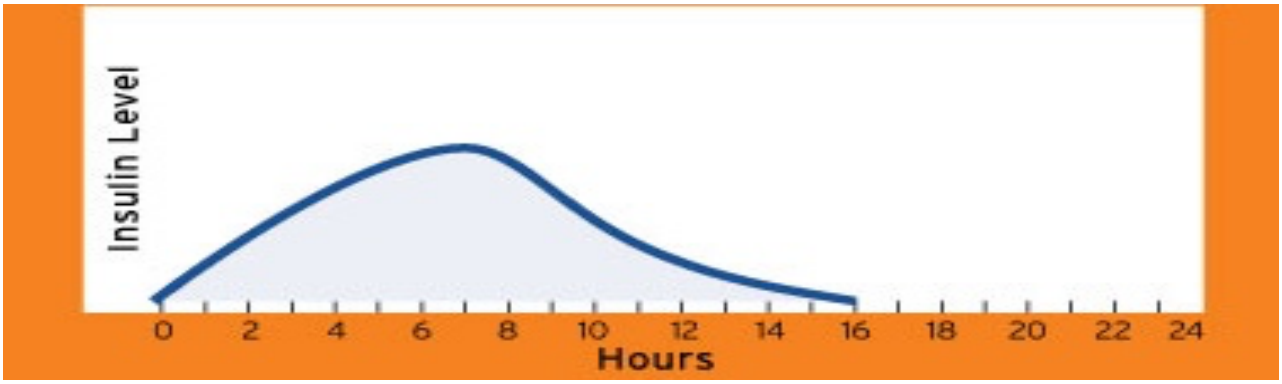
Intermediate acting Insulin/ NPH:

Structure: insulin hexamer bound to zinc and mixed with colloidal material known as protamine which leads for the release into the blood after the subcutaneous administration to be slower yielding a baseline

Examples: Isophane

Pharmacokinetics: Onset: 1-2 hours. Reaches Peak in: 5-7 hours. Effect last for: 13-18 hours.

Usage: It's used with the regular short acting in a regimen called the mixture or the premixed..



*this graph above represents intermediate acting alone.

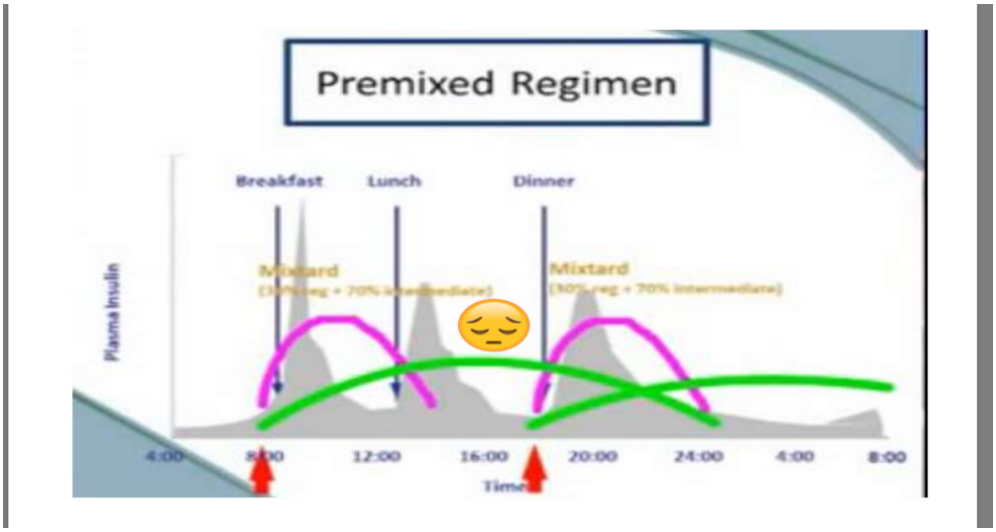
The mixture:

Providing two injections with regular and intermediate insulin one at 8 am and one at 6 pm

Positive points: it's inexpensive and only with two injections and we have postpandiary peaks and a baseline.

Negative point: as we see in the graph, the area where the sad emoji is, we have insulin with no

meal and this is an area of risk for hypoglycemia so we advise them to eat in between meals.



Ultra-Short Acting Insulin:

Structure: hexamers of insulin where the AA connected to zinc (proline) is replaced by aspartic acid and this leads for the structure to become loose and for fast disassociation of the hexamer into monomers that are biologically active.

Examples: Lispro, aspart, glulisine

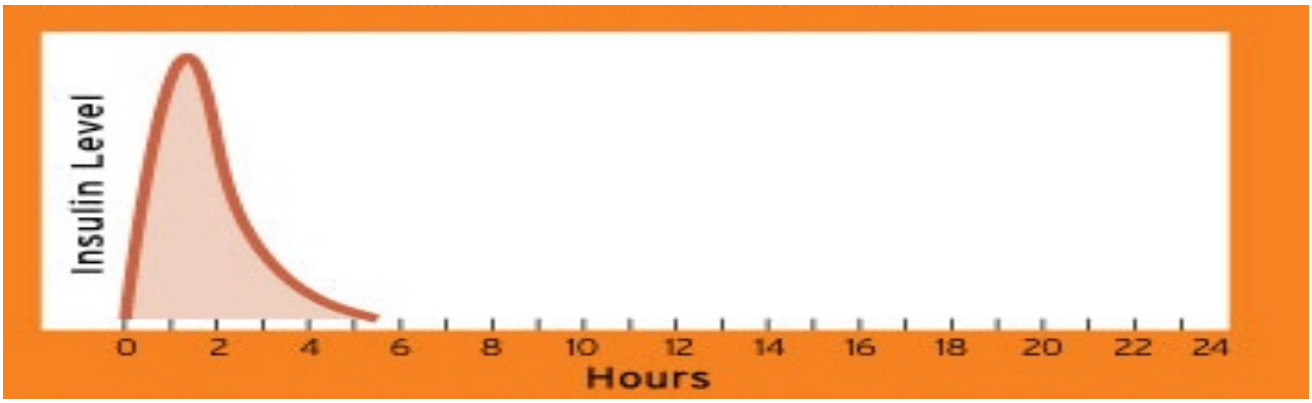
Pharmacokinetics: Onset: 0-15 mins. Reaches Peak in: 30-90 mins. Effect last for: 3-4 hours.

Chemical structur: monomeric analog (according to the table in the slides but it's a hexamer that rapidly breaks into monomers.)

Physical characteristics: Clear solutions at neutral pH.

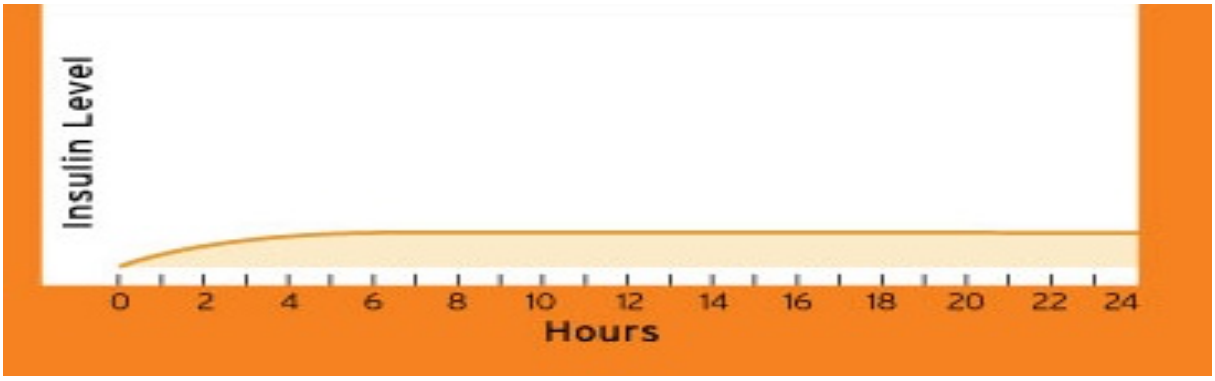
Usual administration: 2-3 times /day or more.

Negative point: It doesn't have a baseline as it falls rapidly until you take it before the next meal 5 mins.

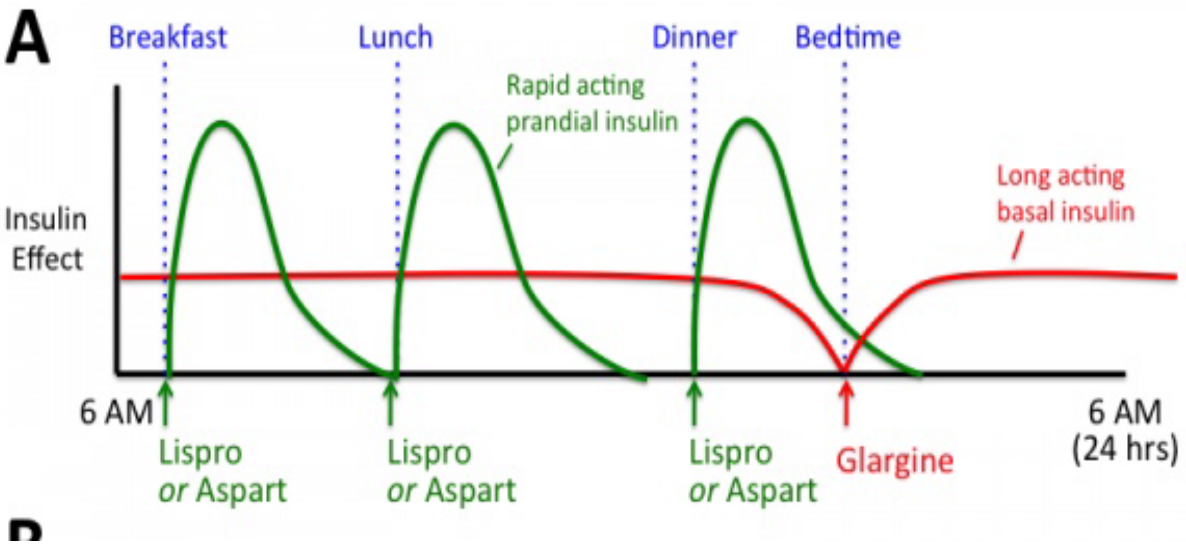


Long acting Insulin:

Structure: insulin hexamer bound to chemicals rather the zinc like glutamic acid and others that hold them tight and prevent their reales leading to a long sustained release, flattened peakness and a sustained baseline.
Examples: insulin glargine
Pharmacokinetics: Onset: 2 hours.. Effect last for: 24 hours.
Usage: It's used with the ultra short acting in a regimen.



Ultra short acting + Long acting regimen:



It's better than the premixed regimen in mimicking normal pancreatic function but requires 4 injections, 3 with the ultra short acting at meals and one long acting daily, add to that an advantage that there's no need to eat between meals or have risk of hypoglycemia and that the ultra short acting is taken 5 mins before meal which means you're definitely going to eat unlike the short acting where it's 30-45 mins as something could emerge like a need to go somewhere or you may fall asleep or even forget yielding severe hypoglycemia as insulin takes action.

Side effects of Insulin:

1. Hypoglycemia(especially with NPH)
2. Hyperglycemia when doses are missed
3. Weight gain.
4. Lipodystrophy: caused by administering the injection in the same spot every time and this is why the patient is informed to change the site of injection
5. Allergic Reactions

Note: short and ultra short acting insulin preparations can be used in the treatment of ketoacidosis crisis as they act fast!

Finally: The Dr didn't explain many physiology slides and didn't even mention them, this sheet is enough for what he said in this lecture and for our learning purposes. You can check the slides if you are interested in more or think he would ask about physiological and insignificant stuff from a pharmacological aspect and don't forget to memorize the drugs of each preparation.

- Useful table in the slides:

	Short-acting (regular) insulins e.g. Humulin R, Novolin R	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	Designed to control postprandial hyperglycemia & to treat emergency diabetic ketoacidosis	Similar to regular insulin but designed to overcome the limitations of regular insulin
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
Chemical structure	Hexameric analogue	Monomeric analogue
Route & time of administration	S.C. 30 – 45 min before meal I.V. in emergency (e.g. diabetic ketoacidosis)	S.C. 5 min (no more than 15 min) before meal I.V. in emergency (e.g. diabetic ketoacidosis)
Onset of action	30 – 45 min (S.C)	0 – 15 min (S.C)
Peak serum levels	2 – 4 hr	30 – 90 min
Duration of action	6 – 8 hr	3 – 4 hr
Usual[3] administration	2 – 3 times/day or more	2 – 3 times / day or more

END, nexttt page is aa quizzzz.

QUIZ IN THE SHEETS 2-4:

1- A patient suffering from acromegaly, this patient also suffers from pernicious anemia and billary issues, what's the treatment you would suggest?
   A- Octreotide B- Pegvisomant C- Cabergoline D- Bromcriptine

2- A patient suffers from hyperprolactinemia, he is an old man that takes many drugs he wants a drug that is given with least doses per time. What would you suggest?
   A- Cabergoline B- Bromocriptine C- Quinagolide D- Reserpine

3- Which of the following is contraindicated with hyperparathyrodism induced osteoporosis?
   A- Bisphophosnate B- Calcimemitics C- Denosumab D-Teriperatide

4- Which of the following anticancer drugs has been used in treatment of osteoporosis?
   A- Taxol B- Plicamycin C- Anthracylins D- Nonanthracylins

5- One of the following can be used in rare hypoparathyrodism induced osteoporosis?
   A- Cinacalcet B- Estrogen C- Paracetamol D- CaSR antagonist.

6- One of the following isn't an ultra short acting insulin preparation
   A- Aspart B- Lispro C-Glusiline D- Isophane

7- How many injections are given in the ultra short/long regimen?
   A- 1 B- 2 C- 3 D- 4

8- Insulin preparation with replacement of zinc is:
   A- Ultra Short B-Short C- Long D- Intermediate

Solutions: B,A,D,B,D,D,D,C

"There's no talent here, this is hard work. This is an obsession. Talent does not exist, we are all human beings. You could be anyone if you put in the time. You will reach the top, and that's that. I am not talented, I am obsessed."

- Conor McGregor, the plumber that ended up in Forbes.