

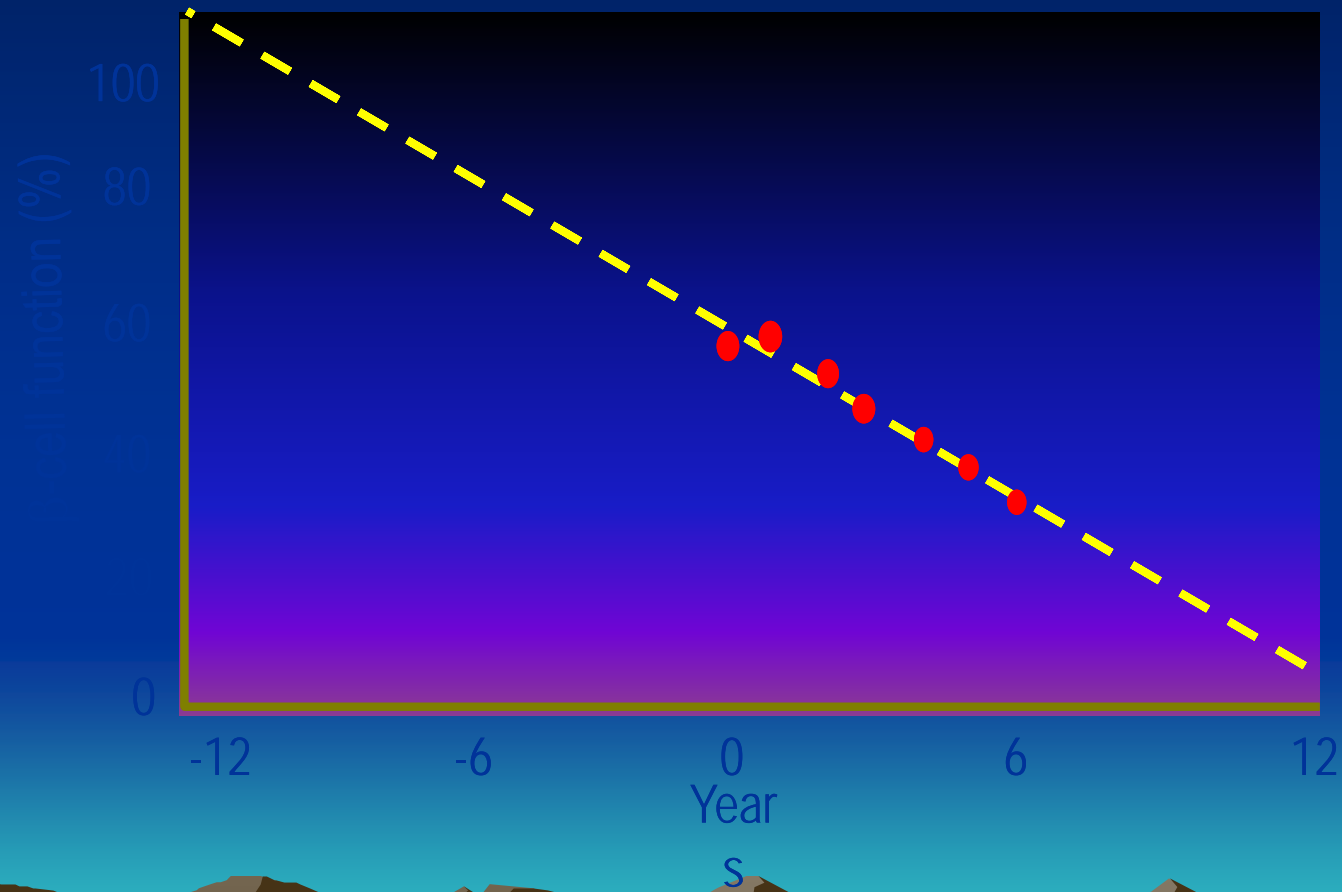
Insulin Therapy and GLP-1 analogues



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Progressive Beta Cell failure in Type II Diabetes Mellitus



What are the anabolic effects of Insulin?

- Stimulates entry of amino acids into cells, enhancing protein synthesis
- Enhances fat storage (lipogenesis) and prevents mobilization of fat for energy (Lipolysis and Ketogenesis)
- Stimulates entry of glucose into cells for utilization as energy source
- Promotes storage of glucose as glycogen in muscle and liver cells (glycogenesis)



When should Insulin be used in Type 2 diabetes mellitus?

“The Magnificent Seven”



When should Insulin be used in Type 2 diabetes mellitus?

1. Type 2 diabetes not controlled with maximal doses of Oral Hypoglycaemic agents

What do you mean by maximal doses of OHAs?

Metformin 2500/3000mg a day

+

Glipizide 20mg/glibenclamide 15-20mg/day

Gliclazide 320mg/ Glimepride 6-8mg/day

+

Rosiglitazone 8mg/ Pioglitazone 45mg/day

When should Insulin be used in Type 2 diabetes mellitus?

2. Type 2 diabetes during periods of physiological stress (surgery, infection)

Continue OHAs simultaneously.

Stop metformin in case of severe infections or impending reduction in renal perfusion



When should Insulin be used in Type 2 diabetes mellitus?

3. Pregestational diabetes

Metformin may be continued

Discontinue other medications



Indications of Insulin therapy?

4. Use of parenteral nutrition
or high-caloric supplements



Indications of Insulin therapy?

5. Diabetic ketoacidosis (DKA)/Hyperosmolar hyperglycemic nonketotic syndrome (HHNS)



Indications of Insulin therapy?

6. Progressive complications:

proliferative retinopathy/maculopathy,
progressive or painful neuropathy

For rapid control and tighter adjustment



Indications of Insulin therapy?

7. Chronic Renal Failure

For all above a creatinine of 4.0mg/dl

Cutoffs for other OHAs:-

Metformin: 1.5mg/dl

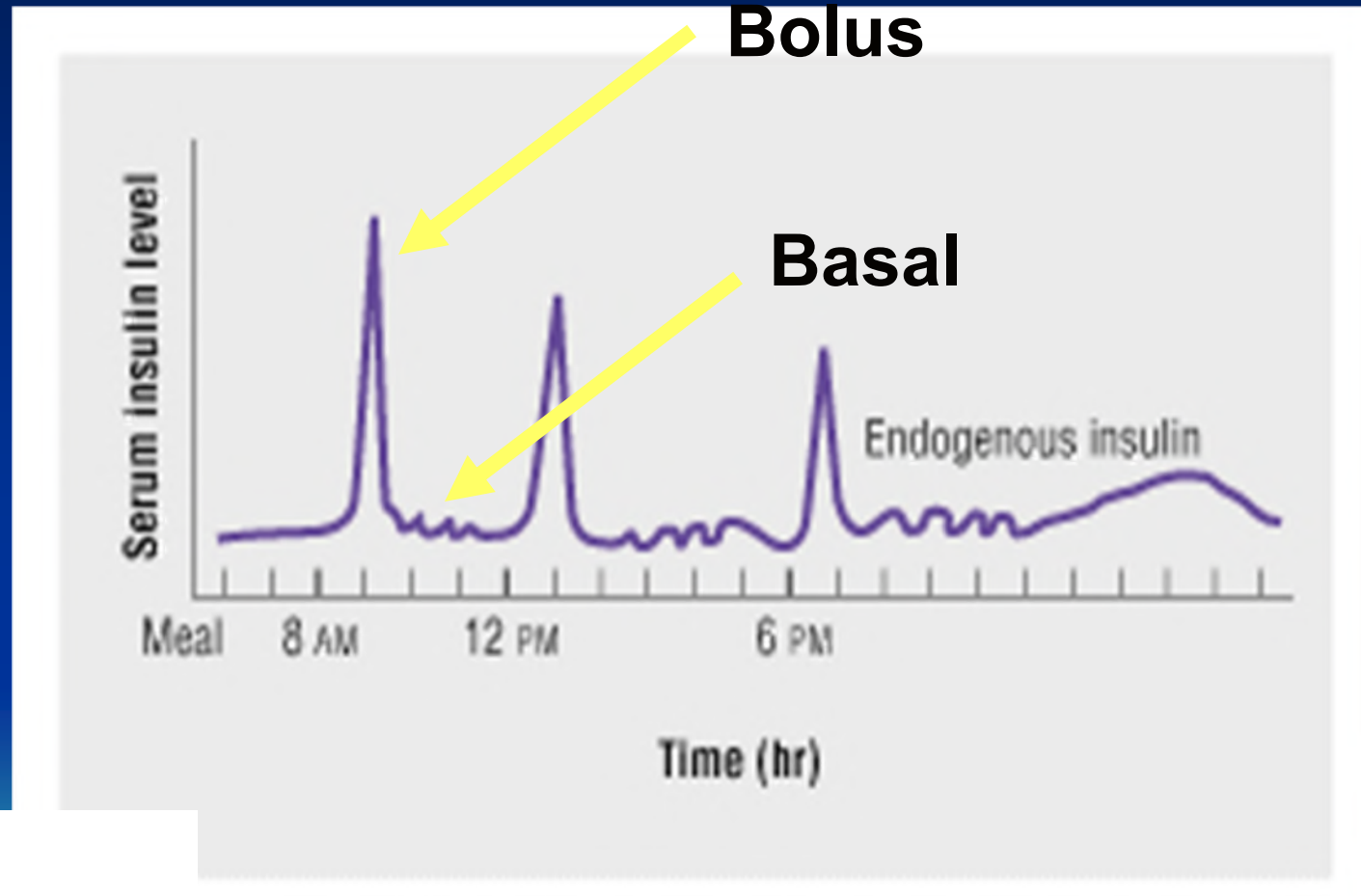
Glimeperide/Glibenclemide: 2.0mg/dl

Glipizide: 2.5mg/dl

Pioglitazone/Rosiglitazone: 4.0mg/dl



What is the normal insulin secretory pattern?



How does one classify the types of insulin?

- ◆ Generally classified according to peak effect and duration of action
- ◆ Short acting: regular/ Lispro /Aspart
- ◆ Intermediate acting: NPH/ Lente
- ◆ Premixed:(30/70), (50/50)



What are the types of Insulin ?

- Short acting : Regular insulin
- Intermediate acting : Lente insulin
NPH insulin
- Long acting : Ultralente

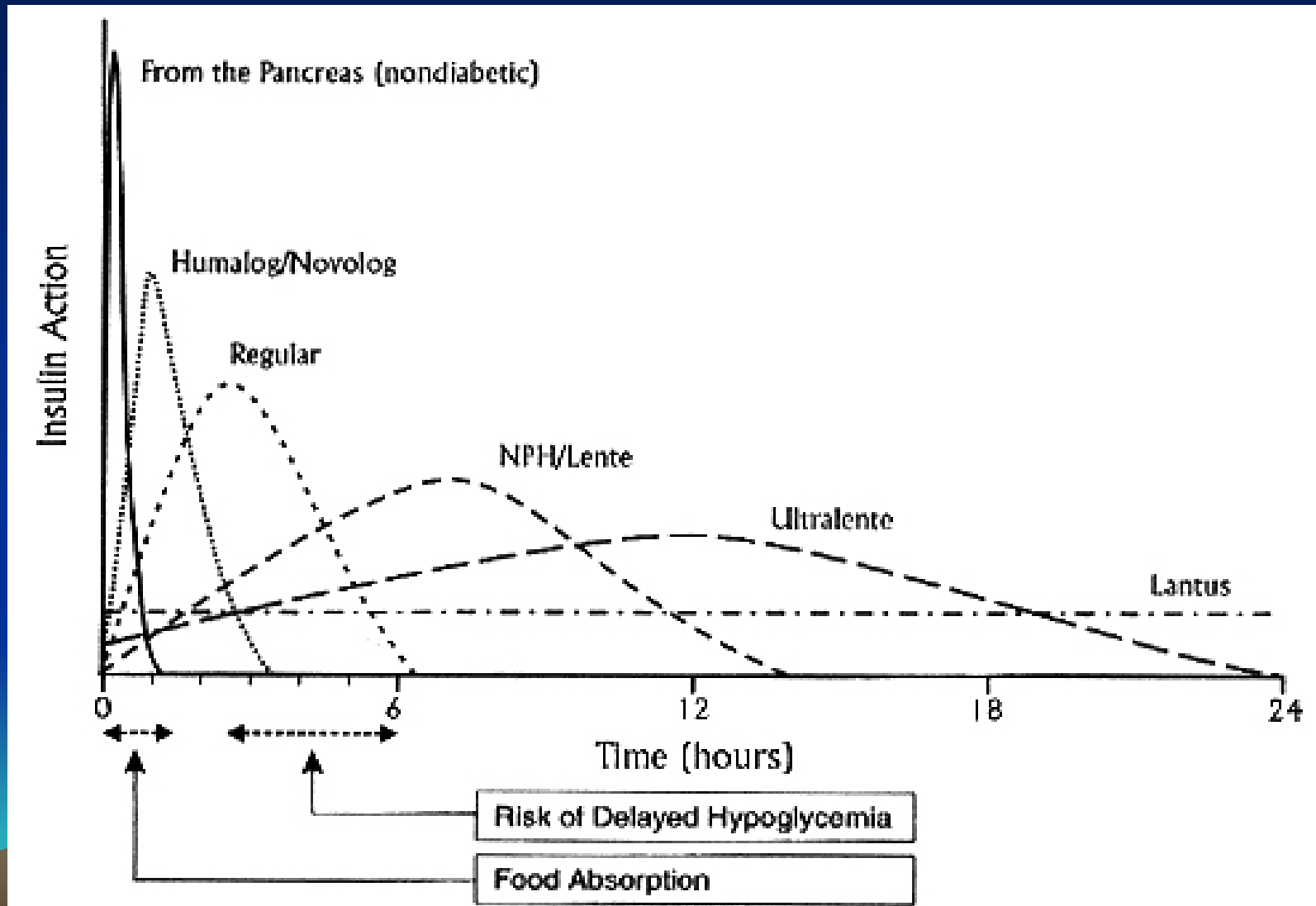
- **Analogs**

Short acting : Lispro, Aspart

Long acting : Glargine



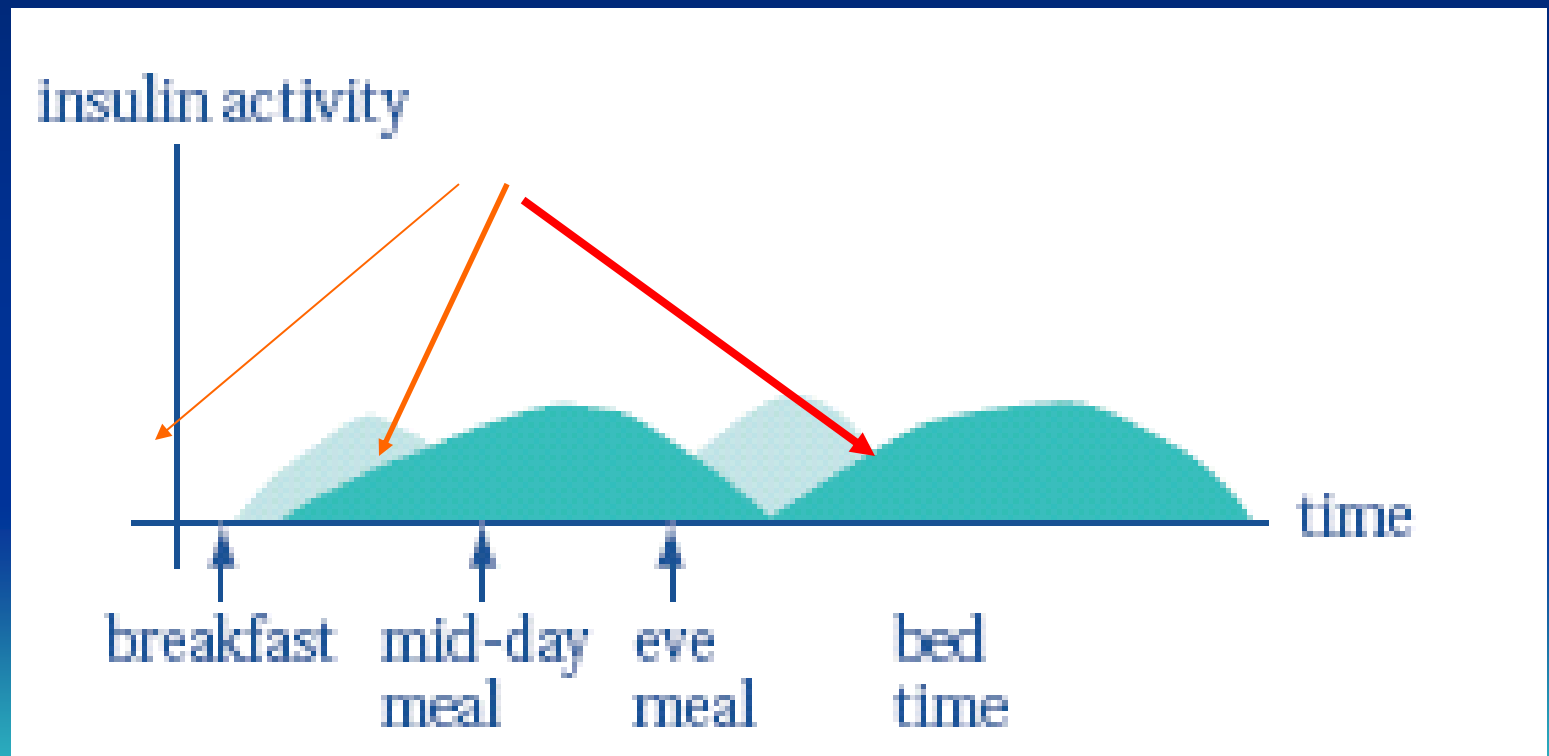
What is the time action profile of different types of insulins?



What are the types of insulin regimens?

- Premixed regimen
- Split mix regimen
- Basal bolus regime (multidose)
- Bedtime dosing alone (NPH/Lente/Glargine)
- Infusion

Premixed insulin:action



Premixed insulin

- Premixed(30/70): Regular: 30 % NPH : 70%
- Premixed (50/50): Regular 50% NPH 50%
- Premixed Analogs
 - Biphasic insulin aspart (30/70)
 - 30% : Aspart
 - 70% : protaminated aspart

Insulin Therapy Regimens

- ◆ Usual starting dose: 0.5-1.0 unit/kg/day



Premixed insulin

- Dose adjustment:
- The fasting sugar depends on the night dose of insulin
- The post breakfast sugar depends on the morning dose of insulin
- Rough calculation increase the insulin by one unit to reduce the sugars by 25mg/dl



Self Monitoring is crucial

Glucometers

At least 6-8 times a week ideally



Premixed insulin

Advantages

- more accurate dosing
- lesser injections
- Pen devices administer premixed forms

Disadvantages

- Fine tuning may not be possible
- Strict meal pattern
- Nocturnal hypoglycemia
- May need “diet changes for insulin” rather than “insulin changes for diet”



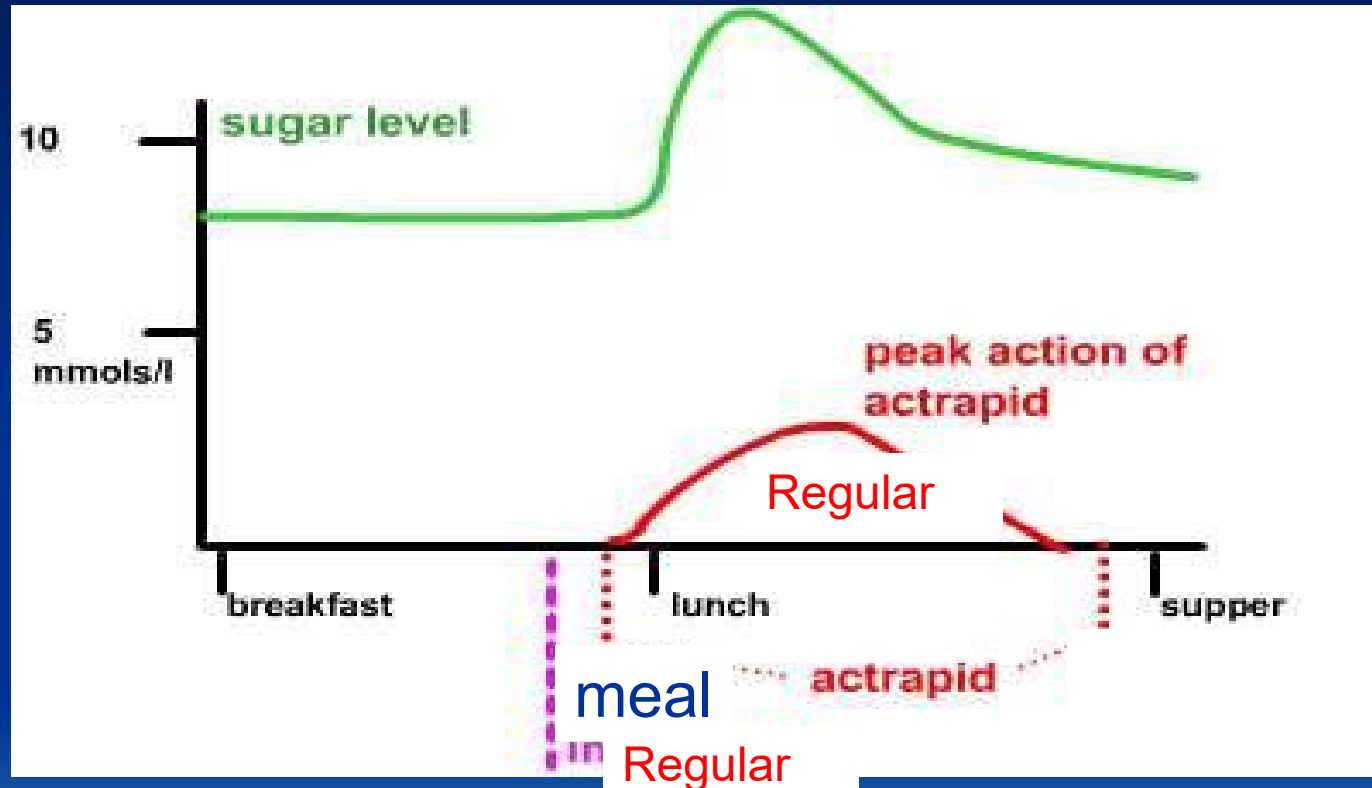
Split-mixed insulin

- **Common combinations:**
Short acting plus intermediate acting
in a syringe:-

Regular + NPH



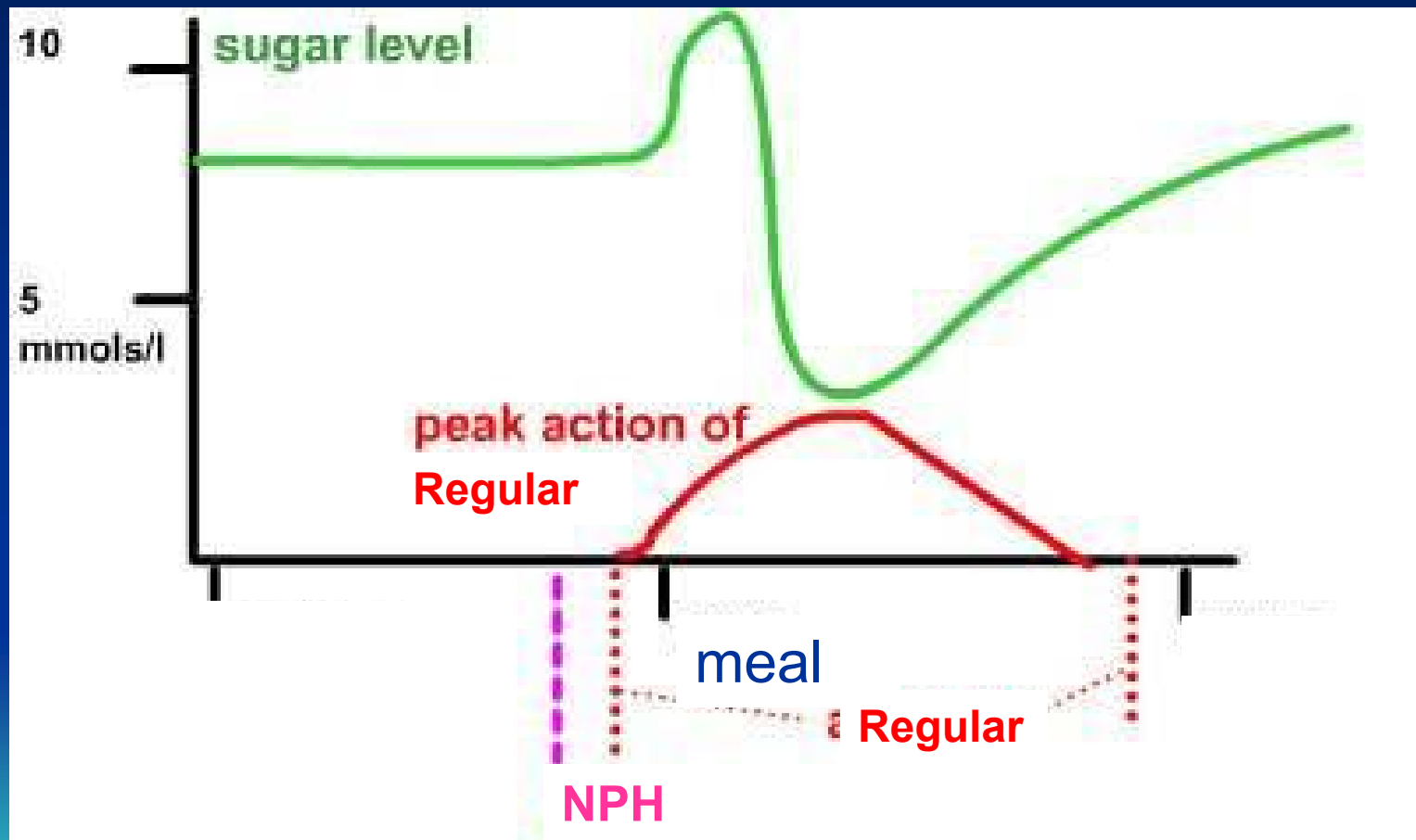
How to adjust insulin doses in a split mix



NPH

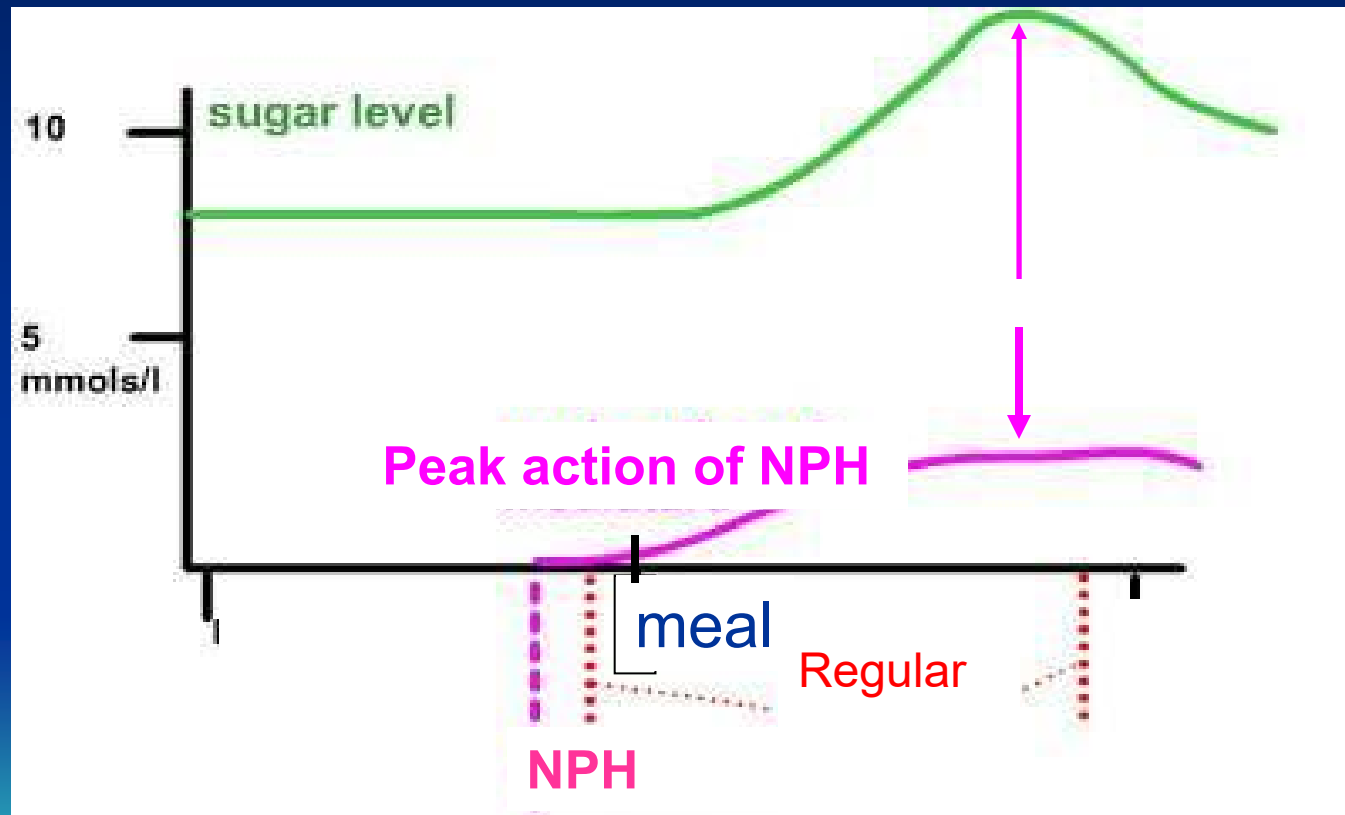
Increase regular insulin

How to adjust insulin doses in a split mix



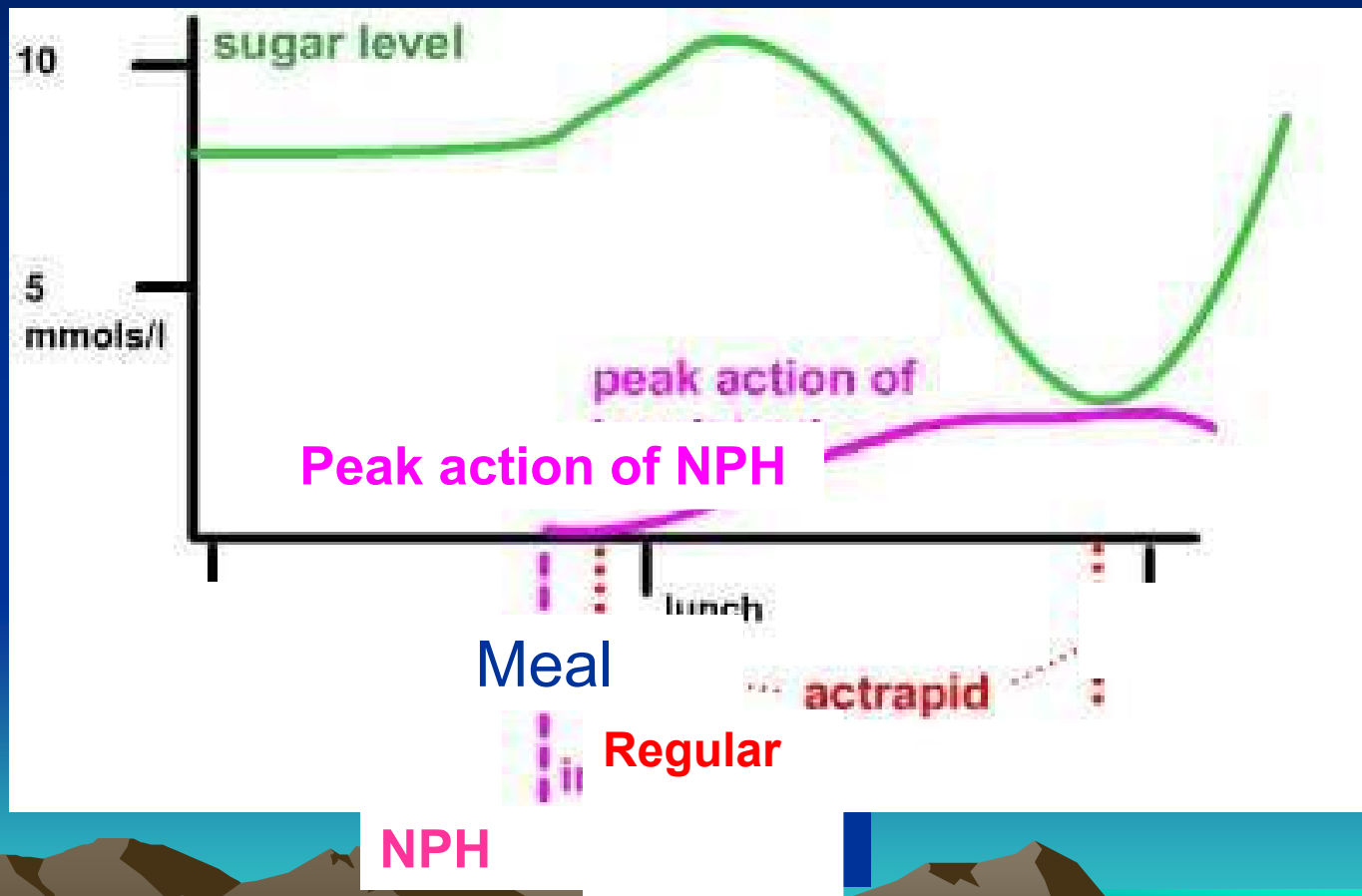
Reduce regular insulin

How to adjust insulin doses in a split mix ?



Increase NPH insulin

How to adjust insulin doses in a split mix ?



Reduce NPH insulin

Split-mixed insulin

Advantages

- Less hypoglycaemia, with fine tuning
- More physiologic
- Adjustable meal pattern

Disadvantages

- More patient education required
- Cumbersome mixing
- Pen device not feasible if two injections are planned for.



Bedtime NPH/Glargine

Continue daytime oral hypoglycaemic agents:
especially sulphonylureas
(The BIDS regimen)

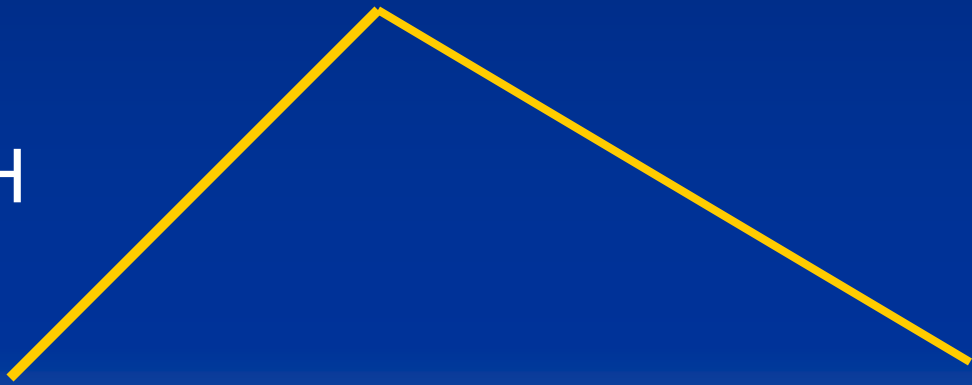
Advantage: Once daily dosing
Easy dose titration

Disadvantage: May need premeal bolus



NPH

NPH



Glargine

Glargine



Bedtime Long- acting

Advantages

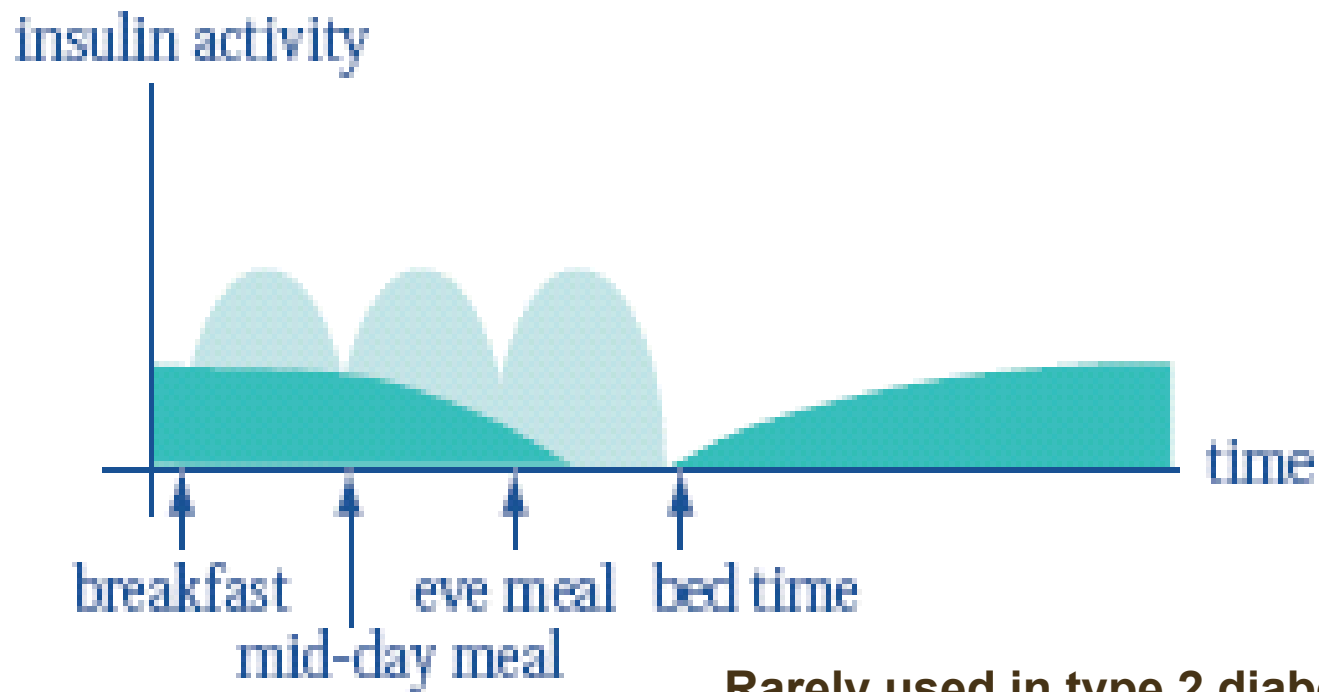
- Single Daily dosing

Disadvantages

- Suitable for only <15% of
Type 2 Diabetes



Basal bolus regime(multidose)



Starting insulin in type 2 diabetes - patient on full dose OHA

- Continue the OHA
- Start on insulin (approx 0.2 U/kg/day, morning 2/3, evening 1/3)
- Reassess control with SMBG & titrate dosage
- Consider adding short acting premeal bolus if uncontrolled PPBG
- Consider withdrawing sulphonylurea



Can Oral hypoglycaemic agents be continued at the same time with insulin?

- **Metformin**

- **Best continued if renal function is normal. May reduce insulin requirements by 15-30%.**

- **Adjunctive weight reducing effect**

- **Thiazolidinediones**

- **May be continued with insulin.**

- **Can reduce insulin requirements from 15-60%**

- **Major issue of weight gain, accentuated by insulin: 7.5%. 15% > 5kg.**

Can Oral hypoglycaemic agents be continued at the same time with insulin?

- **Sulphonylureas**
- **Glimeperide: doses of 2-4mg a day have a peripheral GLUT-4 activity reducing insulin requirement by 10-20%.**
- **Glipizide and Glibenclemide can reduce insulin requirements by 5-15%.**
- **Unpredictable- recommended previously in those with high C-peptide levels**



Infusion

**Used in situations like
DKA, immediate control of sugars**

**monitor sugars more frequently
monitor potassium
over lap with long acting insulin**

GLP-1 Analogues

- **accounted for by following effects:**
 - – **stimulation of insulin secretion**
 - – **inhibition of glucagon release**
 - – **delay of gastric emptying**
 - – **increase of insulin sensitivity**



- **Stimulates insulin gene expression**
- **Stimulates insulin biosynthesis**
- **Stimulates β -cell proliferation and survival**
- **Stimulates differentiation of exocrine cells or islet precursors toward β -cell phenotype**



When do you start?

- As mono or combination therapy
- Obese type 2 Diabetics
- Along with oral drugs.



Development of Exenatide: An Incretin Mimetic

- **Exenatide (Exendin-4)**
- – **Synthetic version of salivary protein**
- **found in the Gila monster**
- – **Approximately 50% identity with**
- **human GLP-1**
- • **Binds to known human GLP-1**
- **receptors on cells *in vitro***
- • **Resistant to DPP-IV inactivation**



DOSAGE AND ADMINISTRATION

- Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart).
- Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response .
- Initiation with 5 mcg reduces the incidence and severity of gastrointestinal side effects.



- BYETTA is supplied as 250 mcg/mL exenatide in:
 - • 5 mcg per dose, 60 doses, 1.2 mL prefilled pen
 - • 10 mcg per dose, 60 doses, 2.4 mL prefilled pen



Contraindicated--

- Type 1 DM
- History of pancreatic disease
- Should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min).
- Severe GI problems
- Hypersensitivity to drug



Summarizing.....

Insulin administration is suitably as premixed fashion for most type 2 diabetes. Split-mix may be required in a subset.

The necessity of self blood glucose monitoring as an accessory is emphasized.