הטיפול באינסולין לחולי DM-2

ד"ר רות פרצ'יק
המכון האנדוקרינולוגי, תל השומר

נושאים לדיון

למי להתחיל טיפול באינסולין ?

פיזיולוגיה של סכרת מסוג 2

קווי הנחיה

איך להתחיל טיפול באינסולין ?

סוגי אינסולין

בסיס פרמקולוגי

משלבים טיפוליים

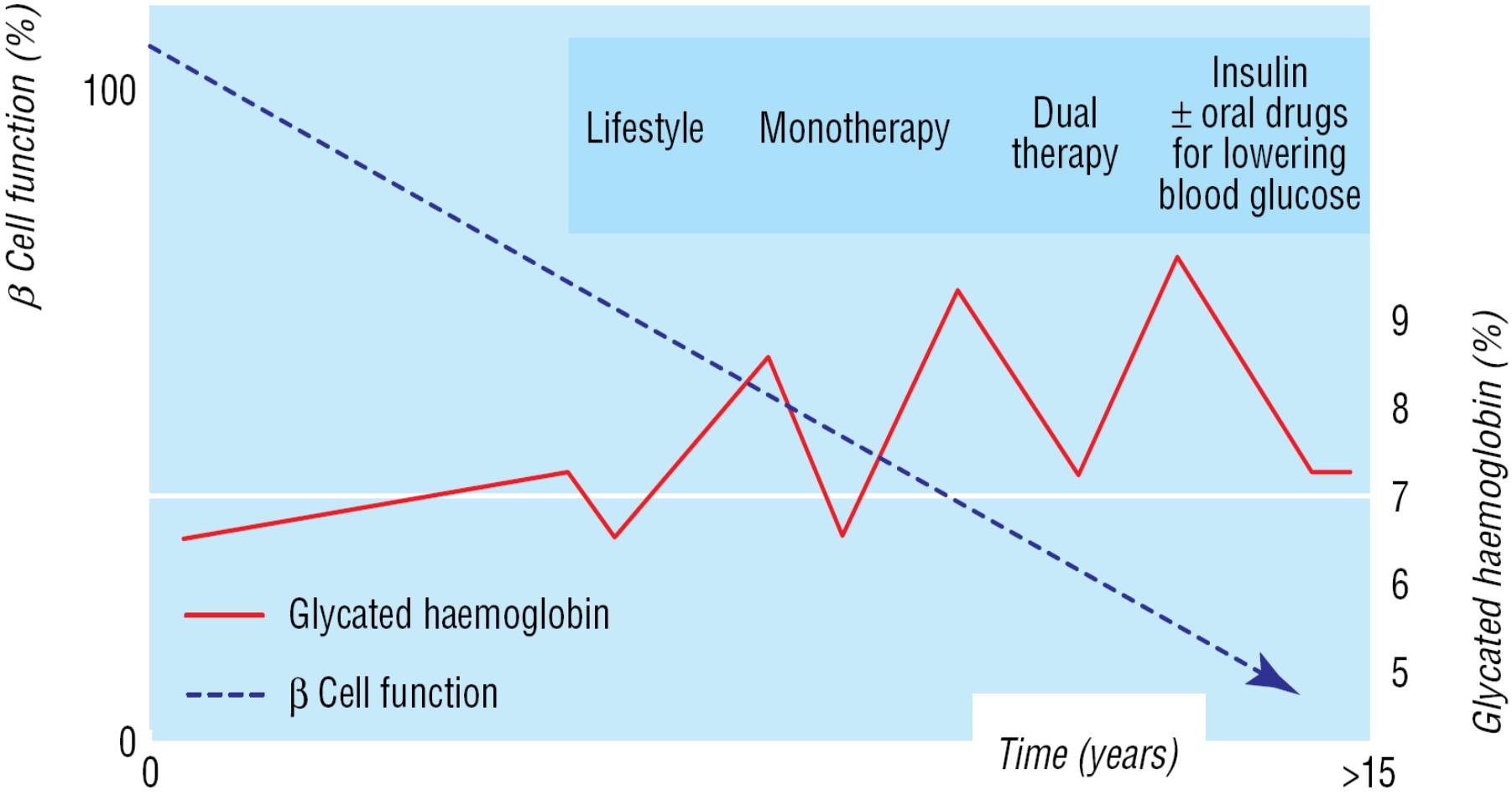
גליקמיה שלאחר ארוחה

קשיים ואתגרים

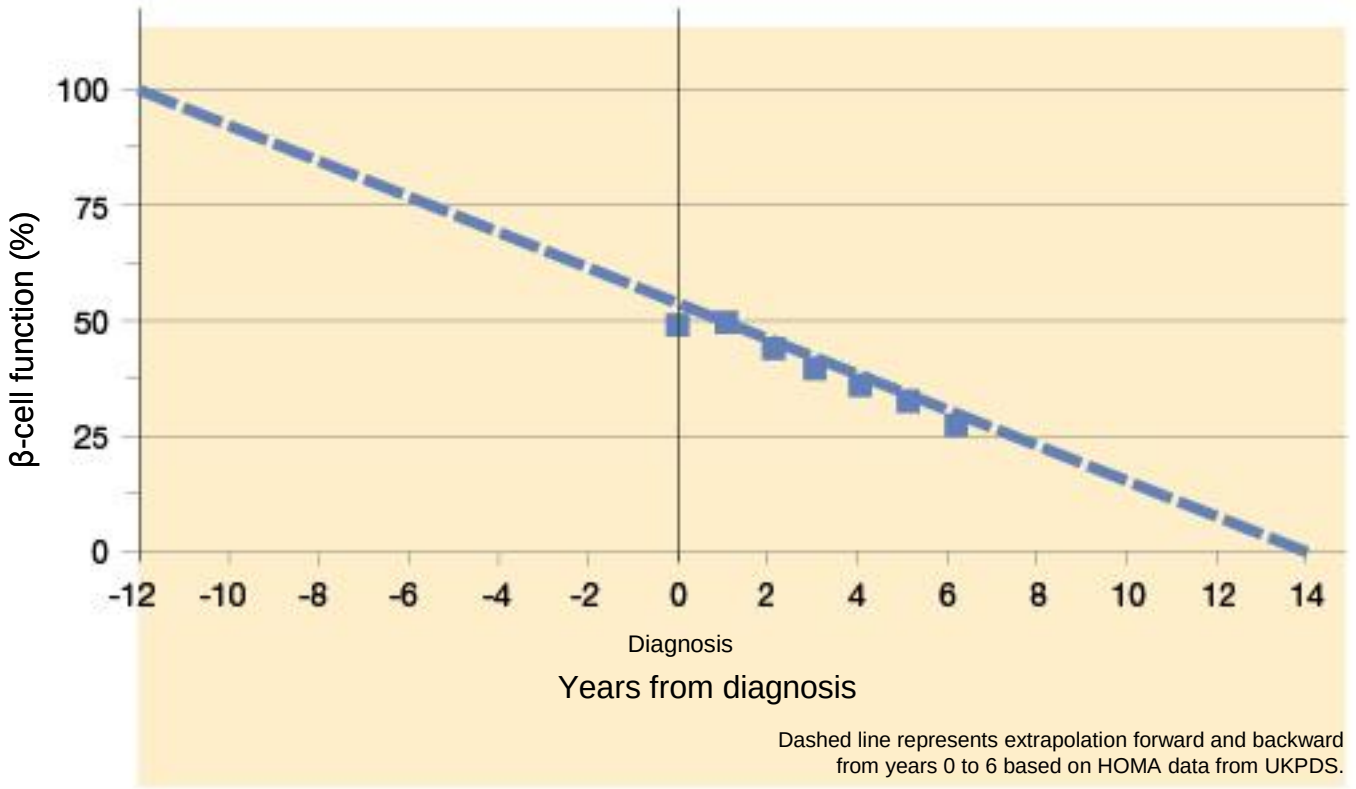
DM-2 Pathogenesis

- Insulin Resistance↑
- B-Cell failure, and insulin↓
- Hepatic Gluconeogenesis↑

DM-2 - Natural History

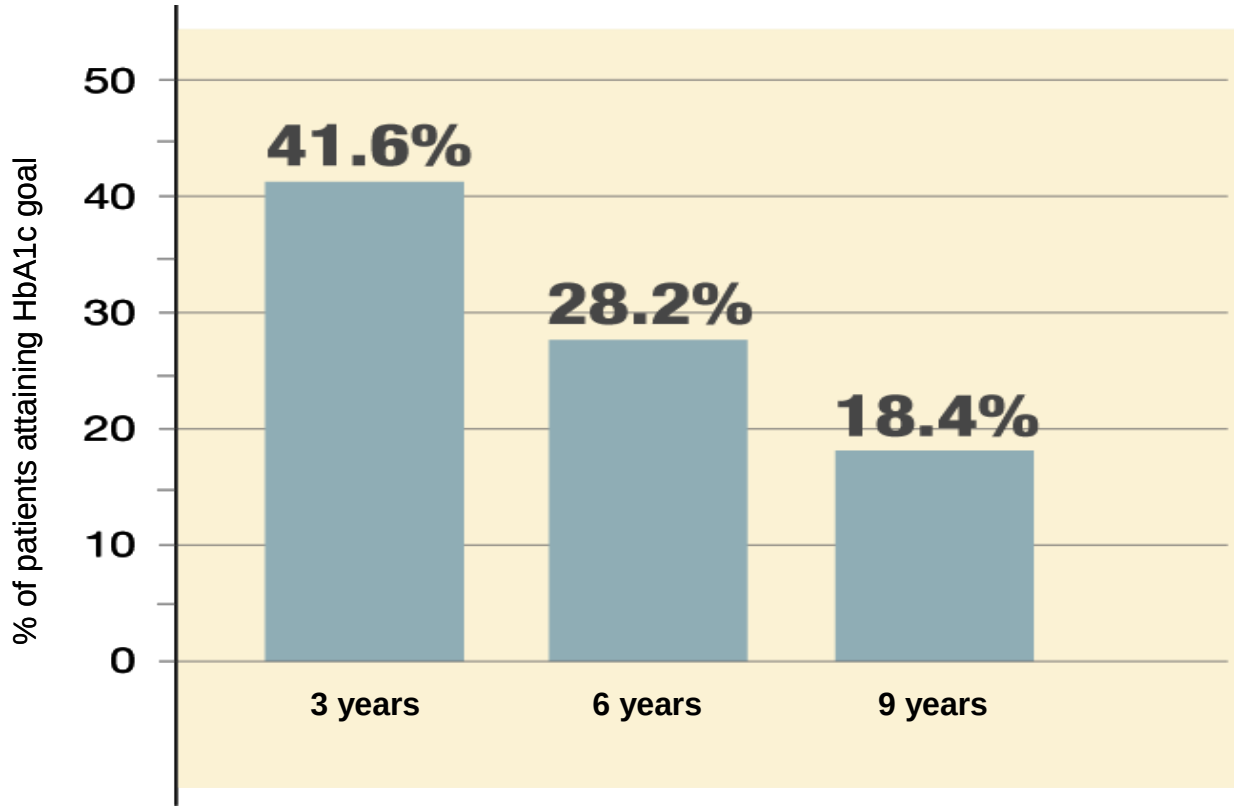


DM-2 - Natural History



Lebovitz H. *Diabetes Rev.* 1999;7:139–153.

DM-2 - Natural History



Newly diagnosed patients with DM2 randomised to monotherapy: diet, metformin, sulphonylurea, insulin according to mean FBG concentration.

Data derived from Turner RC, et al. *JAMA.* 1999;281(21):2005-2012.

Case 1

- 60 years old patient
- DM-2 for 6 years
- S/P MI, not working
- eats 3 meals and
  3 inter-meal snacks
- 3 METFORMIN / day
  + 3 NOVONORM
  2mg / day

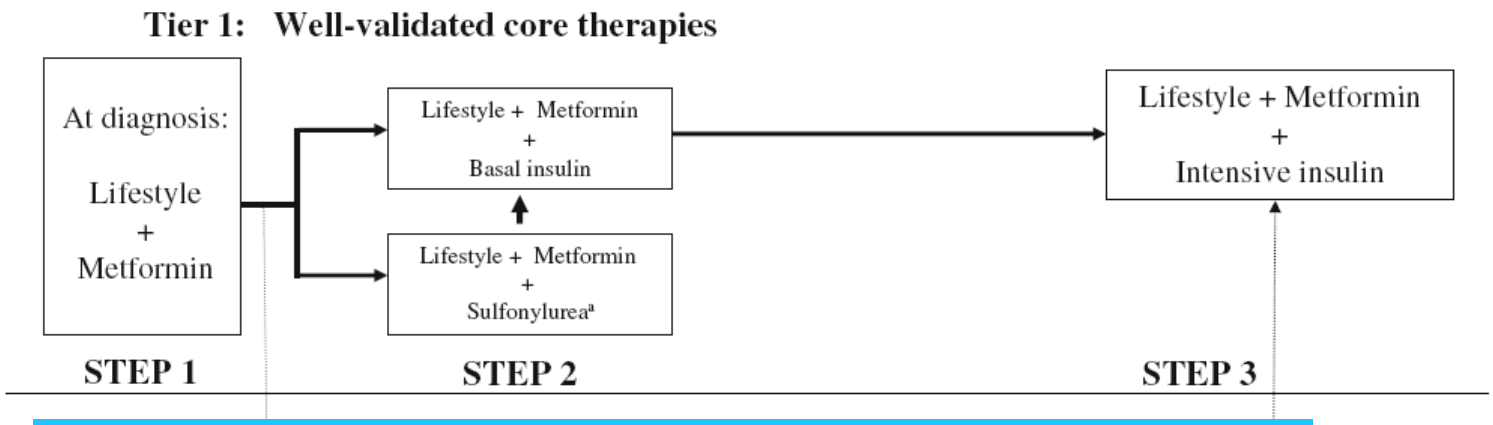
- HbA_1C=9.2

- Prefers to avoid Insulin injections if posible

	FBG	**PPG** breakfast	**Pre-dinner**	**PPG** Bedtime
	147	**176**	**156**	**164**
Target	<130	<180	<130	<180

Insulin in the Algorithm of DM-2 Therapy

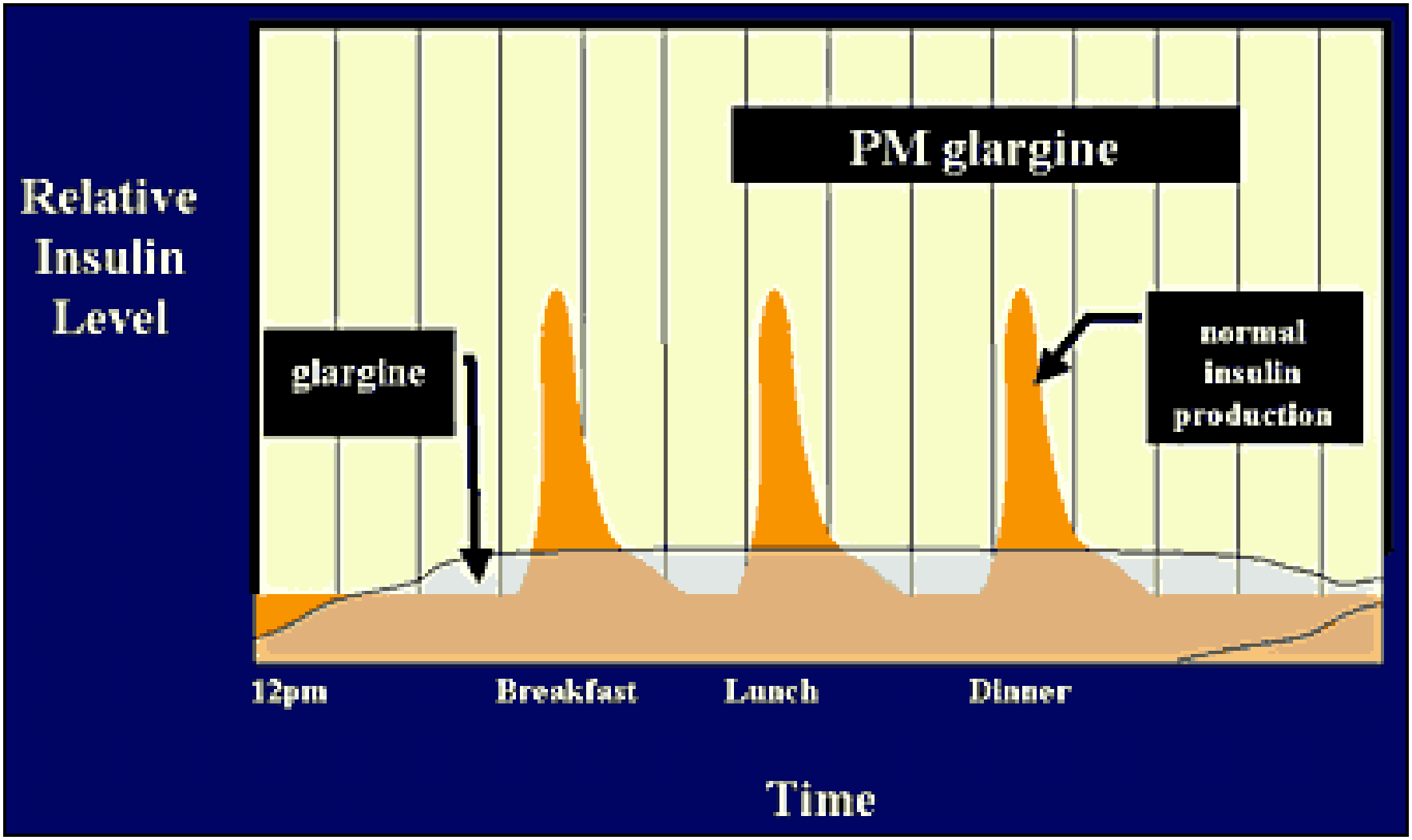
Diabetologia (2009) 52:17–30



Therapy Goals:

- $HbA1_C$=7.0-7.5
- FBG 90-130
- Post Prandial BG < 180

Basal Insulin



History & Basics

- 1889 Minkowski
- 1921

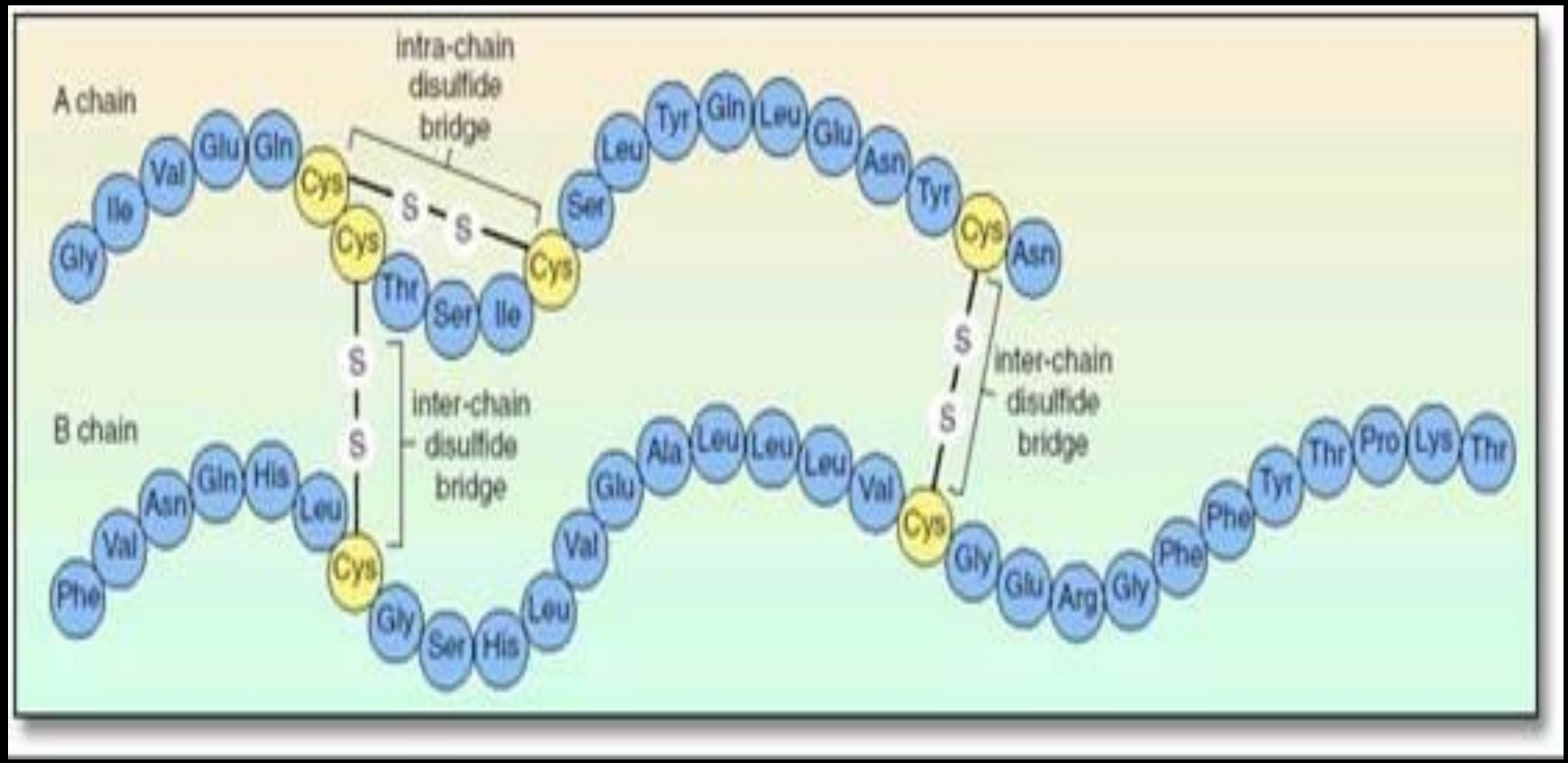
  Paulescu pancreatin
- 1922

  Banting & Macleud
- 1958 sequencing
- 1982 Human Insulin

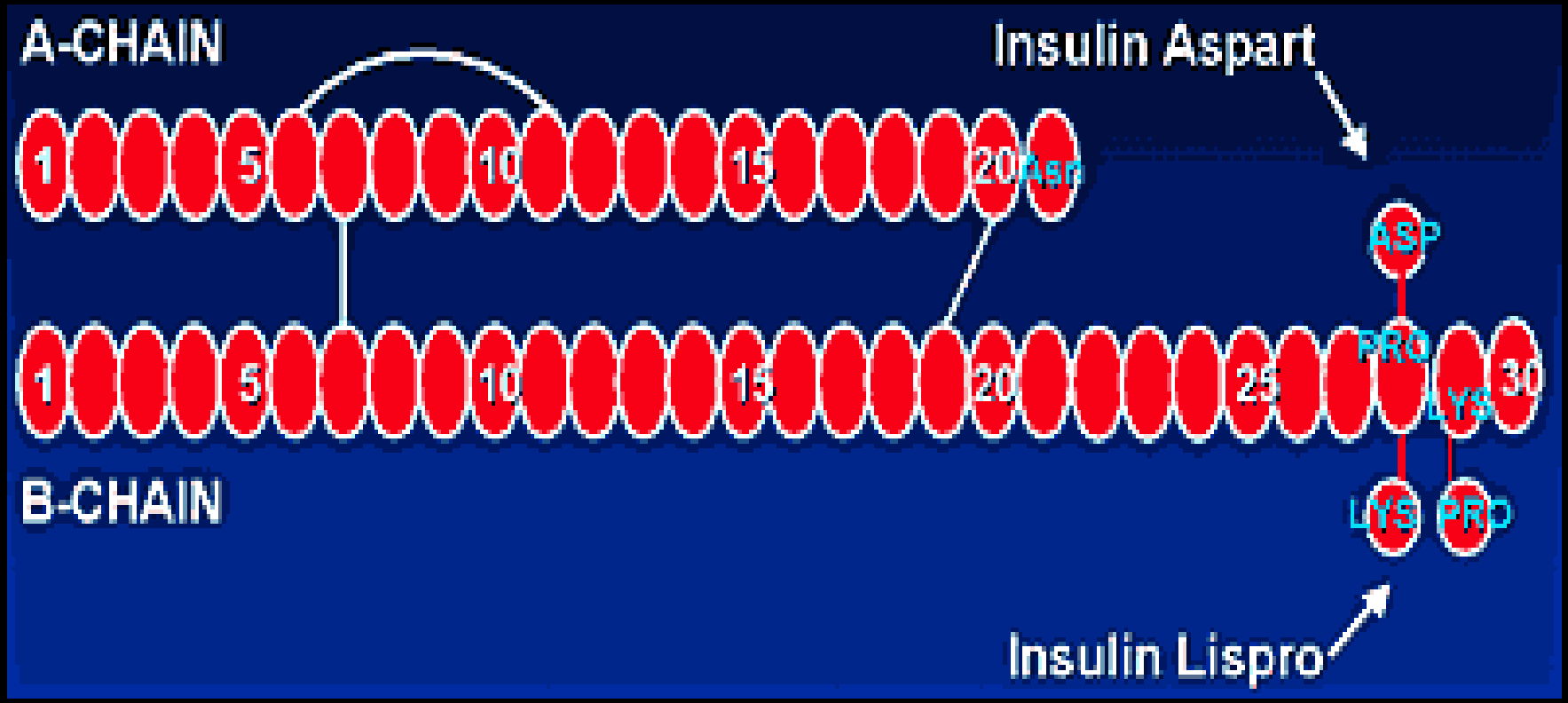
•Human Vs Analogues

•**Absorption** Distribution Elimination

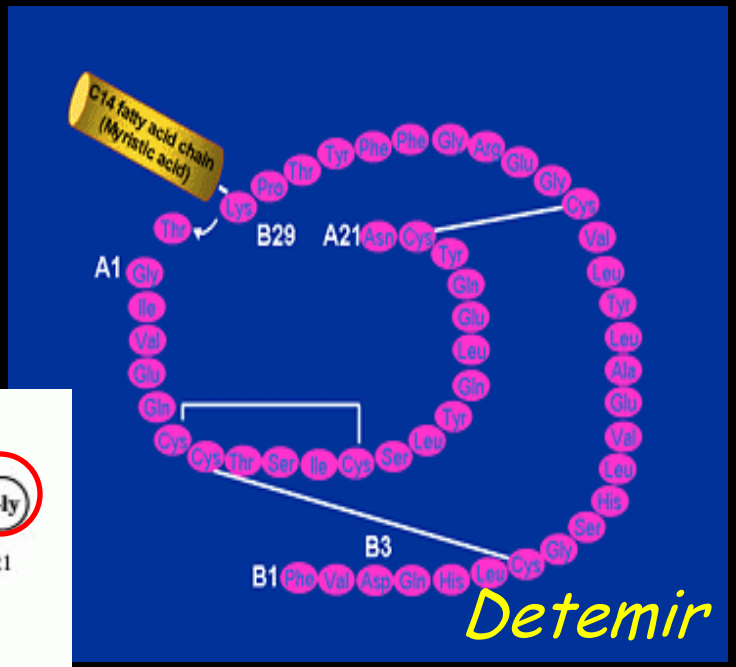
Human Insulin Structure

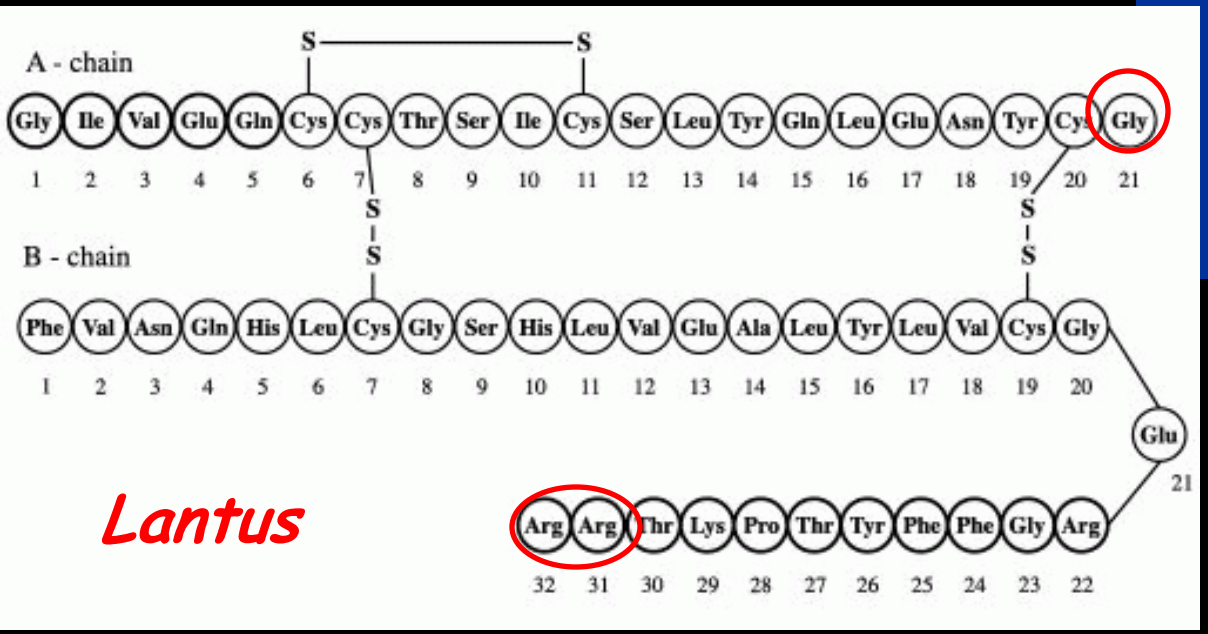


Insulin Modifications – Rapid Acting

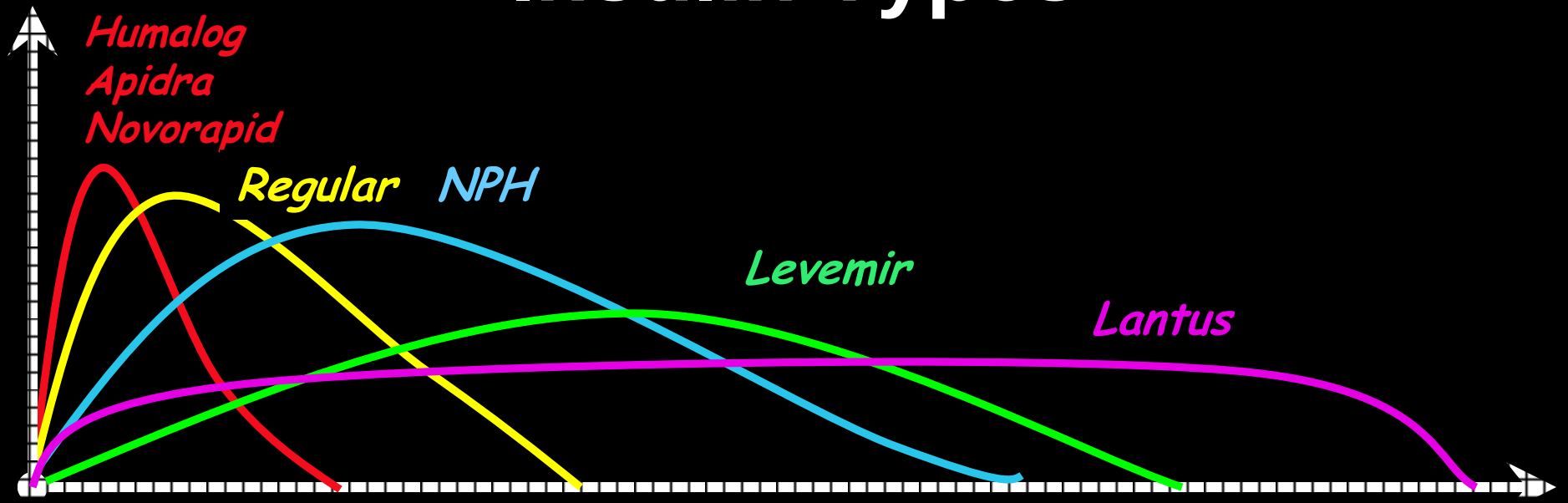


Insulin Modifications – Long Acting



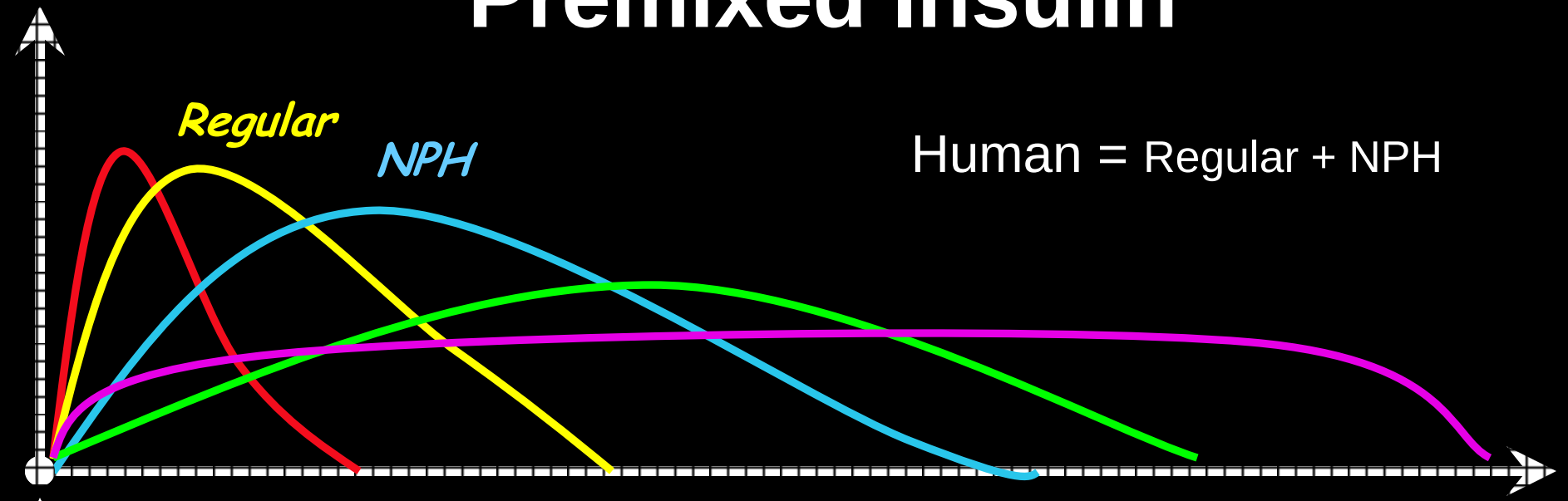


Insulin Types

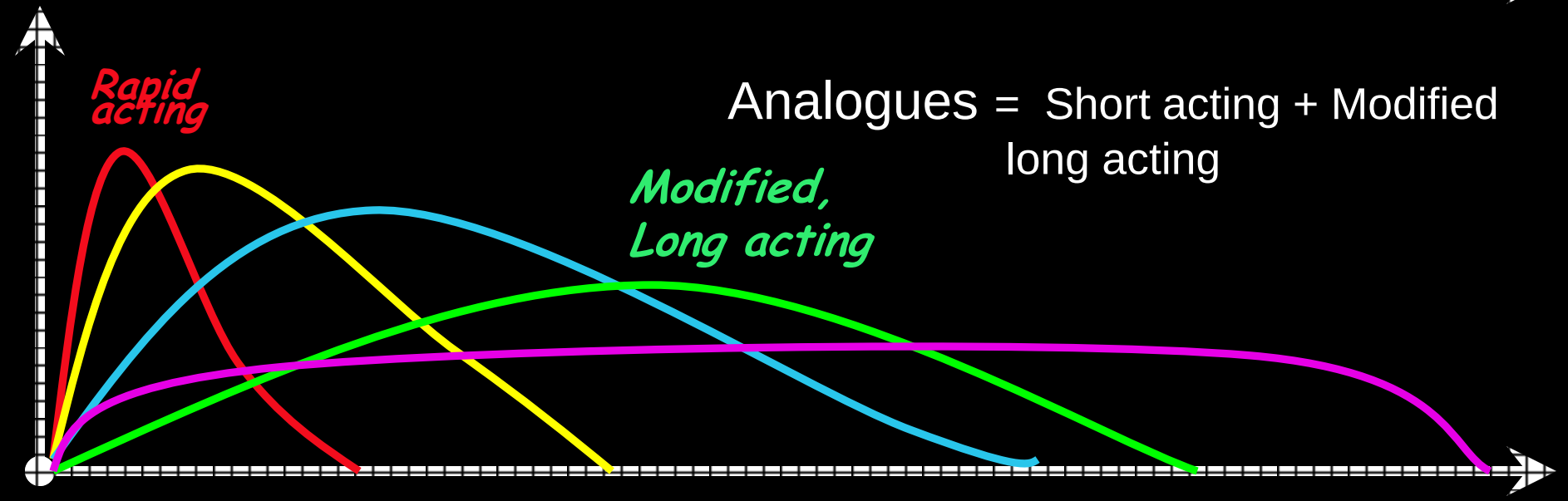


Category	Insulin Name	Brand Name	Manufacturer	Onset (Hr)	Peak (Hr)	Duration (Hr)
Rapid Acting	Lispro	Humalog	Lilly	1/4-1/2	1	3-5
	Aspart	NovoRapid	Novo-Nordisk	1/4-1/2	1	3-5
	Glulisine	Apidra	Sanofi-Aventis	1/4-1/2	1	3-5
Short Acting	Regular	Humulin R	Lilly	½-1	2-4	5-8
Intermediate	NPH	Humulin N	Lilly	1-2	4-10	14+
Long Acting	Glargine	Lantus	Sanofi-aventis	1.5	Ø	24
	Detemir	Levemir	Novo-Nordisk	3-4	6-8	~20

Premixed Insulin



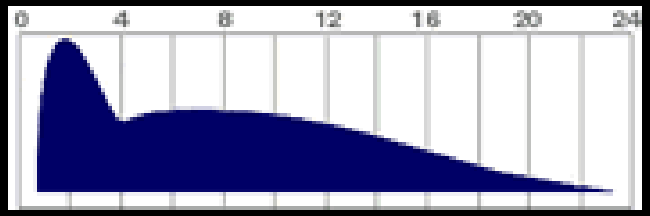
Human = Regular + NPH



Analogues = Short acting + Modified long acting

Premixed Insulin

ANALOGUES



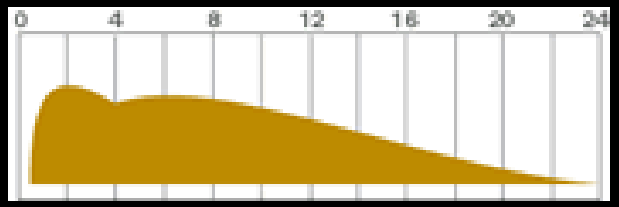
- HUMALOG MIX 25, 50

  Insulin lispro 25% & Insulin lispro protamine 75%, 50/50

- NOVOMIX 30, 50, 70

  Aspart 30% & aspart protamine 70%, 50/50, 70/30

RCB.DNA HUMAN



- HUMULIN 70/30

  Human Insulin 30% & NPH 70%

- INSULIN MIXTARD 30, 40, 50

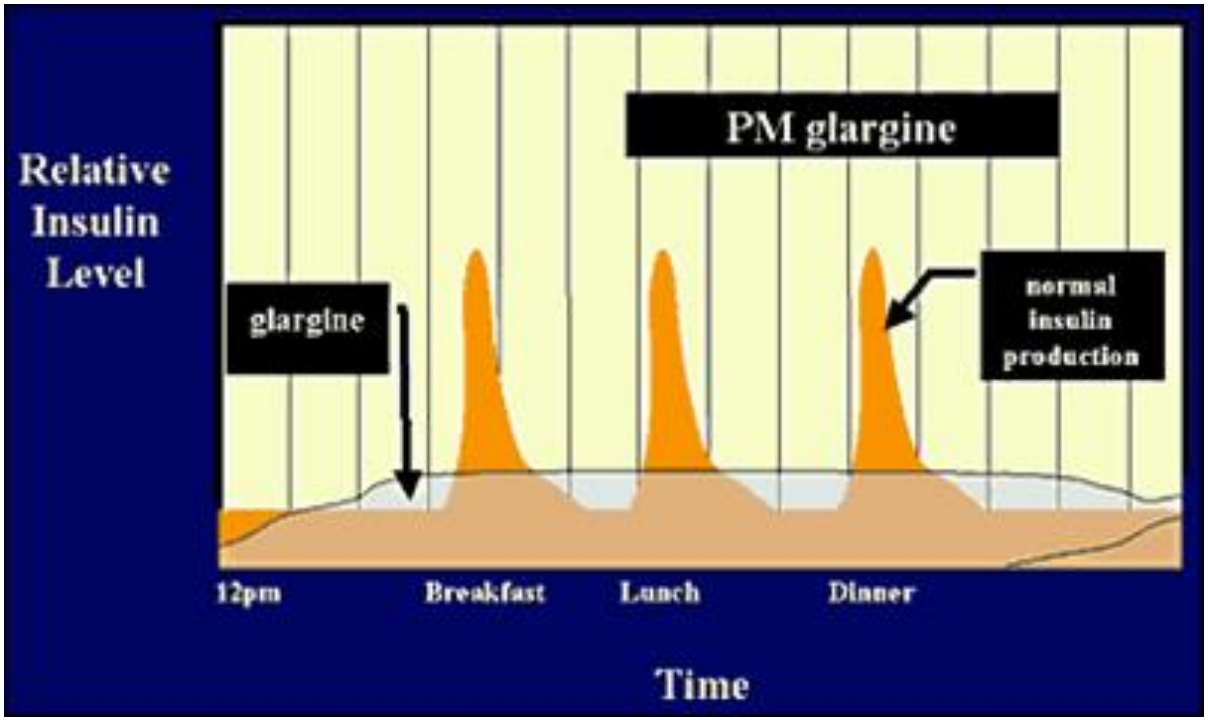
  Regular 30% & NPH 70%, 40/60, 50/50

Back to Case 1

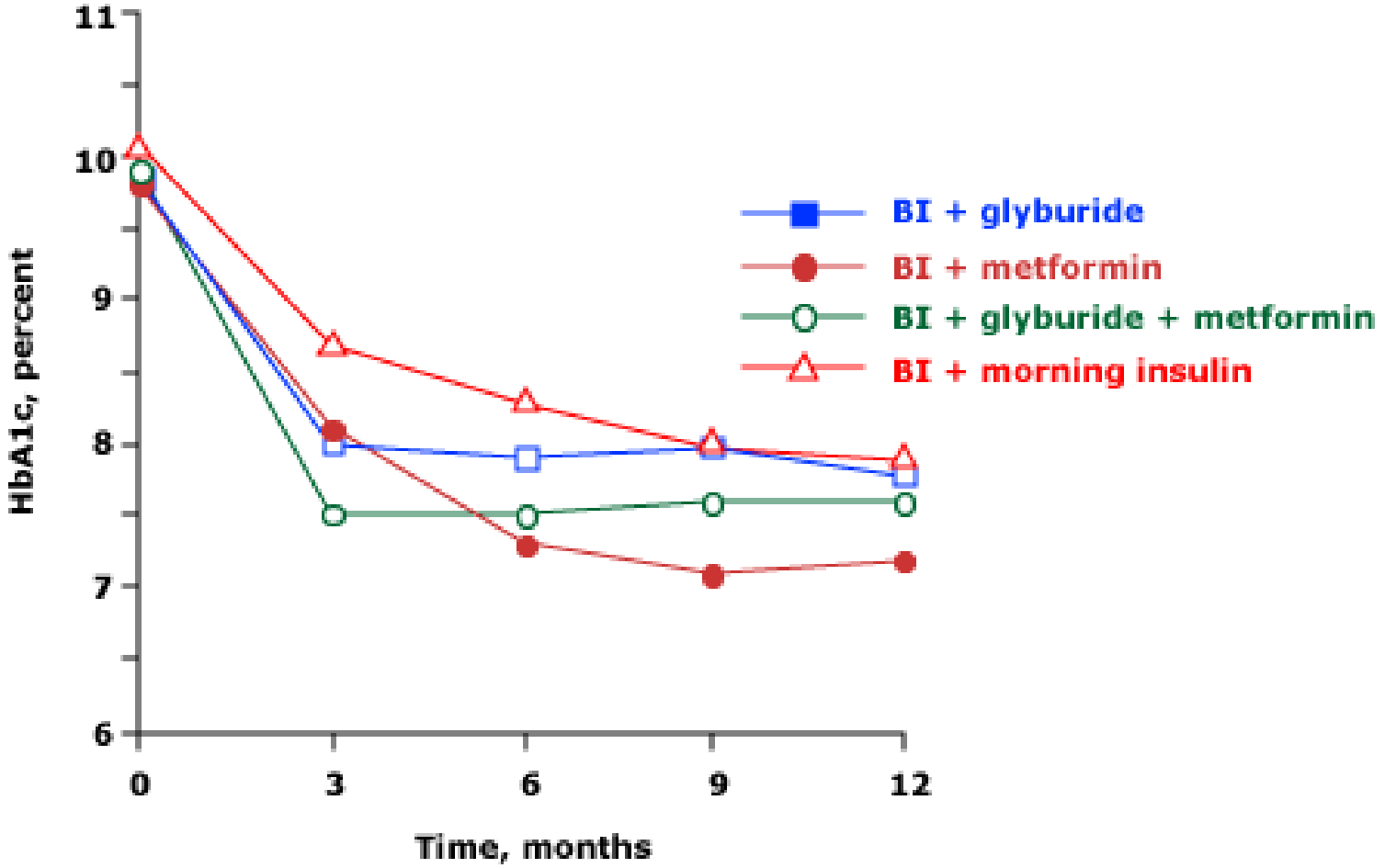
- 60 y o 6 years DM-2
- Max O.A.D.S/P MI
- FBG=150
- HbA_1C=9.2
- Reluctance to multiple injections

Basal Insulin

- Lantus, levemir OD / BID, NPH BID (careful when patient on NPO)
- Simple, convenient
- Post-prandial hyperglycemia not addressed



Basal Insulin + OAG



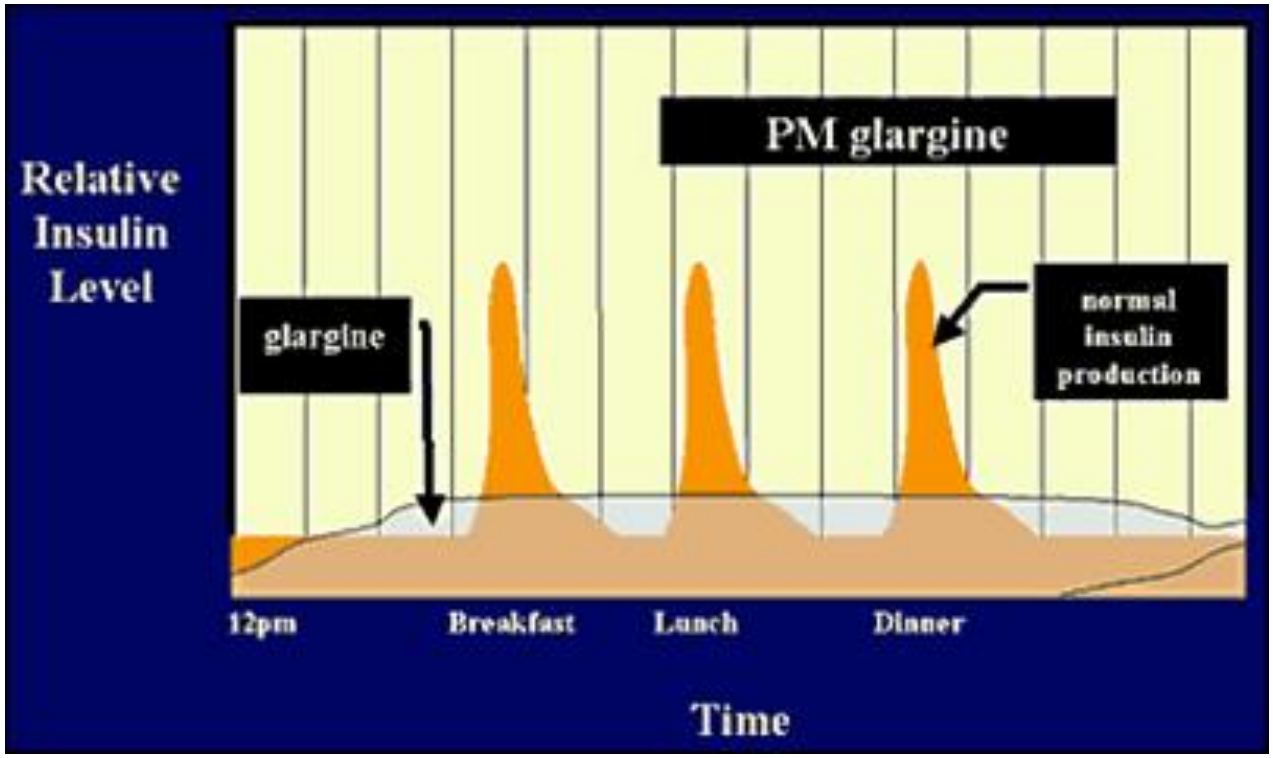
Adjustments of Basal Insulin

- Continue oral agent (s), eventually reduce
- Add single evening basal Insulin dose (~10 IU)
- Adjust dose every 3-7 days according to average FBG
  - FBG > 130 ↑ 2 units
  - FBG > 180 ↑ 4 units
  - FBG < 70 ↓ 2 units

Case Summery

- HbA1c > 9.0 on max O.A.D.>> consider insulin Tx
- Glucose measurements give info about
  - β-cell reserve
  - basal insulin secretion
  - gluconeogenesis pattern
- Start low and adjust dose
- Basal insulin works well with O.A.D. !
- Basal insulin regimen – pro’s and con’s

	FBG	PPG breakfast	Pre-dinner	PPG Bedtime
	147	176	156	164
Target	<130	<180	<130	<180



Case 2

- 38 YO male
- Smoker, obese (BMI=34)
- LOOOOVES Coke, snacks, nightly binge eating, beer
- Blurred vision, dry mouth, 3P for the last 6 weeks
- BG=340
- → HbA1c=13.1

Considerations

- Naïve patient
- Young, DM-2 diagnosis
- Obesity
- Diet
- HBA1C extremely high

Intervention	HbA1C decrease	Advantages	Disadvantages
Lifestyle	1-2	Low cost, many benefits	Fails for most in first year
Metformin	1-2	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Sulfonylureas	1-2	Inexpensive	Weight gain, hypoglycemia
Glinides	1-1.5	Short duration	Three times/day, expensive, hypoglycemia
- Glucosidase inhibitors	0.5-0.8	Weight neutral	GI side effects, three times/day, expensive
Glitazones	0.5-1.4	Improved lipid profile	Fluid retention, worsens CHF, potential MI, weight gain, expensive
GLP-1 analogues	0.5-1.0	Weight loss	Injections, nausea, expensive, little experience
DPP-4 inhibitors	0.5-0.8	Weight neutral	Expensive, little experience
Insulin	1.5-3.5	No dose limit, inexpensive, efficient	Injections, monitoring, hypoglycemia, weight gain

Considerations

- Assertive approach to lifestyle and diet
- Baseline HbA1C, δ to target
- Glucose toxicity
- B-cell reserve
- Basal = long acting insulin + Metformin
- Close monitoring!

Case Summery

- Long acting Insulin – Lantus, Levemir
- + Metformin
- No permanent dependence, possible withdrawal of insulin therapy (BMI, sweet consumption, main element is I.R.)
- Glucose toxicity a major consideration

Case 3

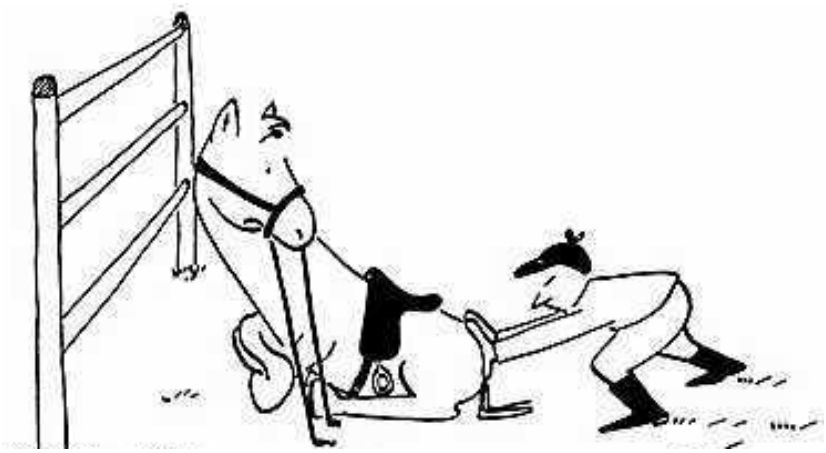
- 48 yo
- 5 years DM-2
- BMI=28
- Light breakfast and lunch main meal = dinner
- On max dose of Metformin and Novonorm
- HBA1C=9.5

	FBG	**PPG** breakfast	**Pre-dinner**	**PPG** Bedtime
	135	**163**	**140**	**306**
Target	<130	<180	<130	<180

- Afraid of injecting insulin
- Concerned about routine disruption
- Should insulin be started ?
- What regimen ?
- What should be done with O.A.D. ?

Reluctance to Insulin Therapy

- Weight gain
- Hypoglycemia
- Fear of injection
- Failure
- Complicated
- Dependence



Reluctance to Insulin Therapy

- Pain
  - Thinner needles, insulin pens
- Worsening diabetes
  - Progressive disease, delays complications β-cell failure
- Patient's failure to follow treatment regimen
  - Progressive decline in β-cell activity not related

Reluctance to Insulin Therapy

- Θ Fear of hypoglycemia
- ☼ Severe hypoglycemia rare, avoid &treat

- Θ Interference with daily routine
- ☼ Specify concerns, less intrusive than complicated regimens

- Θ Decreased quality of life
- ☼ Benefits of glucose control: energy, sleep, well-being

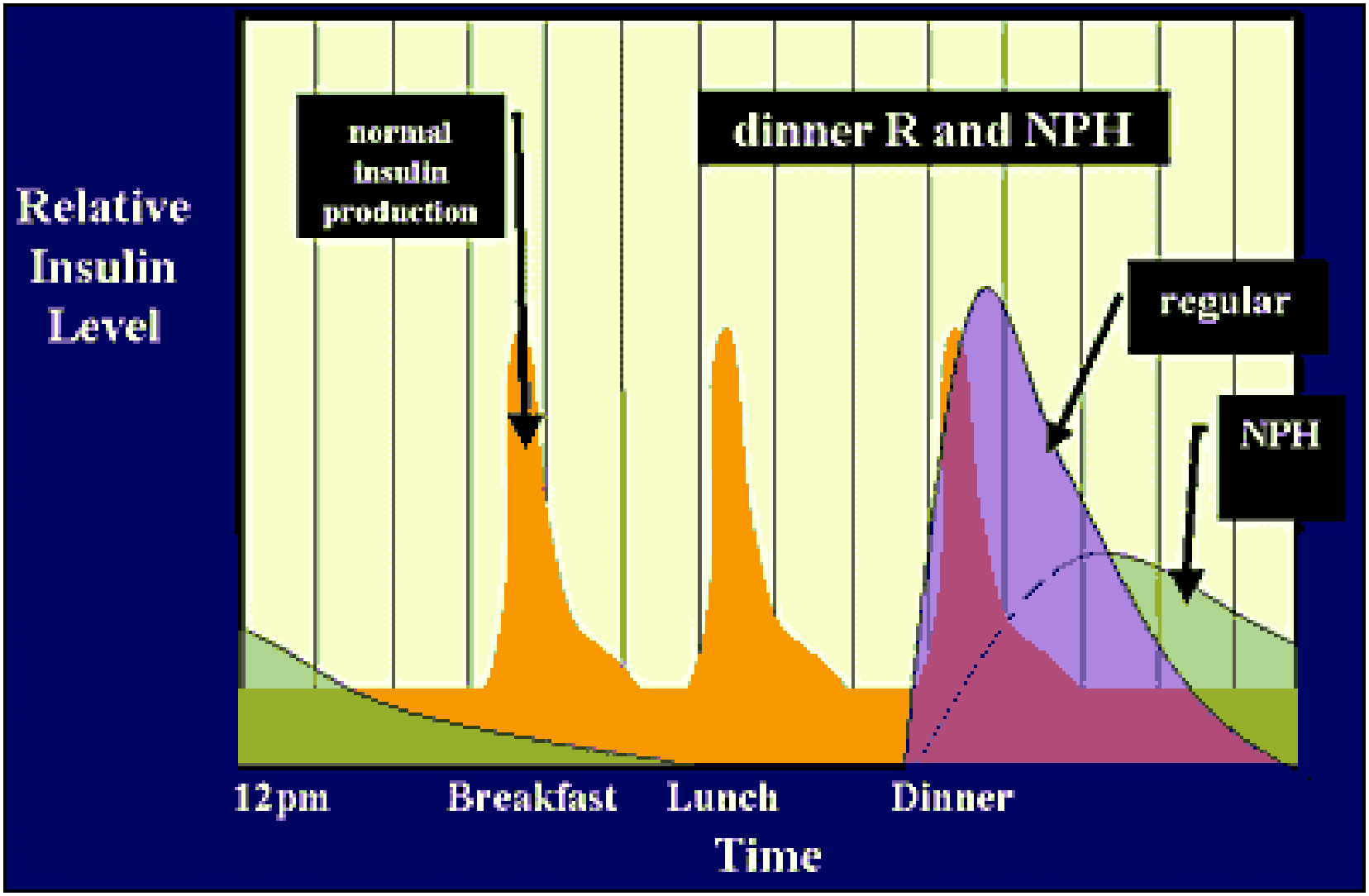
Reluctance to Insulin Therapy

- Insulin leads to diabetic complications

- Weight gain
  - Role of diet and exercise

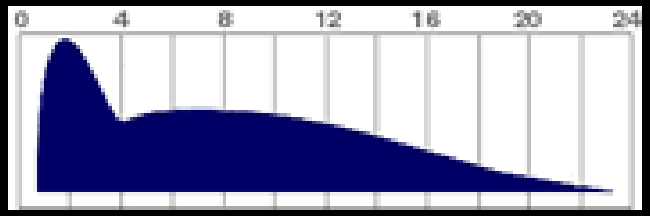
- A more natural alternative therapy preferred
  - The most natural therapy, replacing the hormone the patient does not make enough of

Premixed Regular and NPH at Dinner



Premixed Insulin

ANALOGUES



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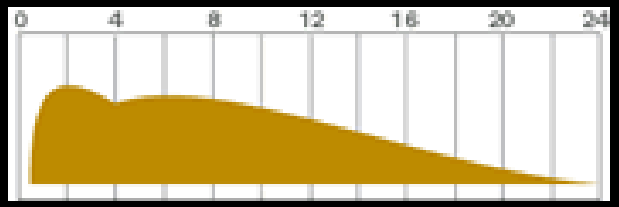

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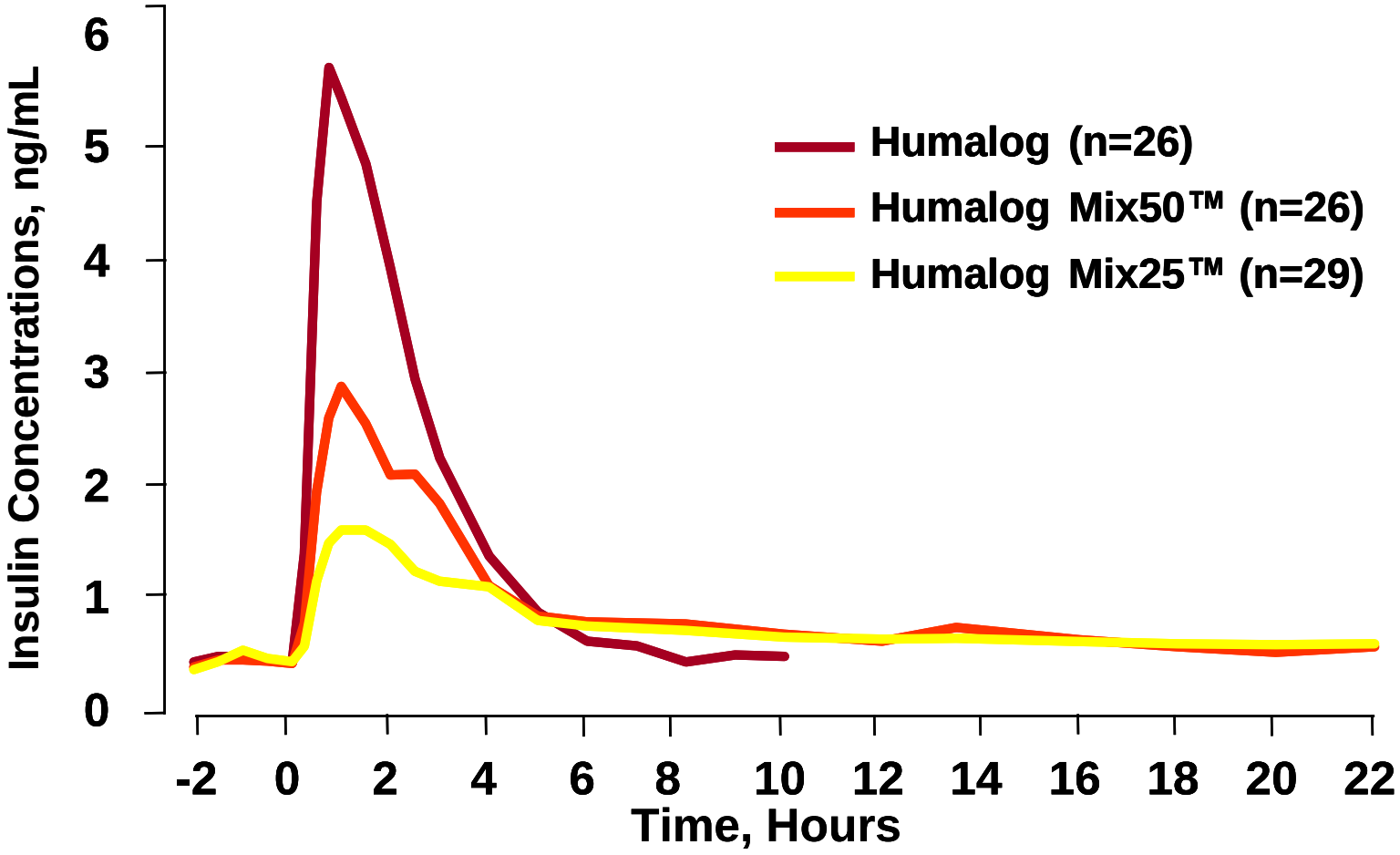

Insulin Concentrations, ng/mL
0
1
2
3
4
5
6
-2
0
2
4
6
8
10
12
14
16
18
20
22
Time, Hours
Humalog (n=26)
Humalog Mix50™ (n=26)
Humalog Mix25™ (n=29)

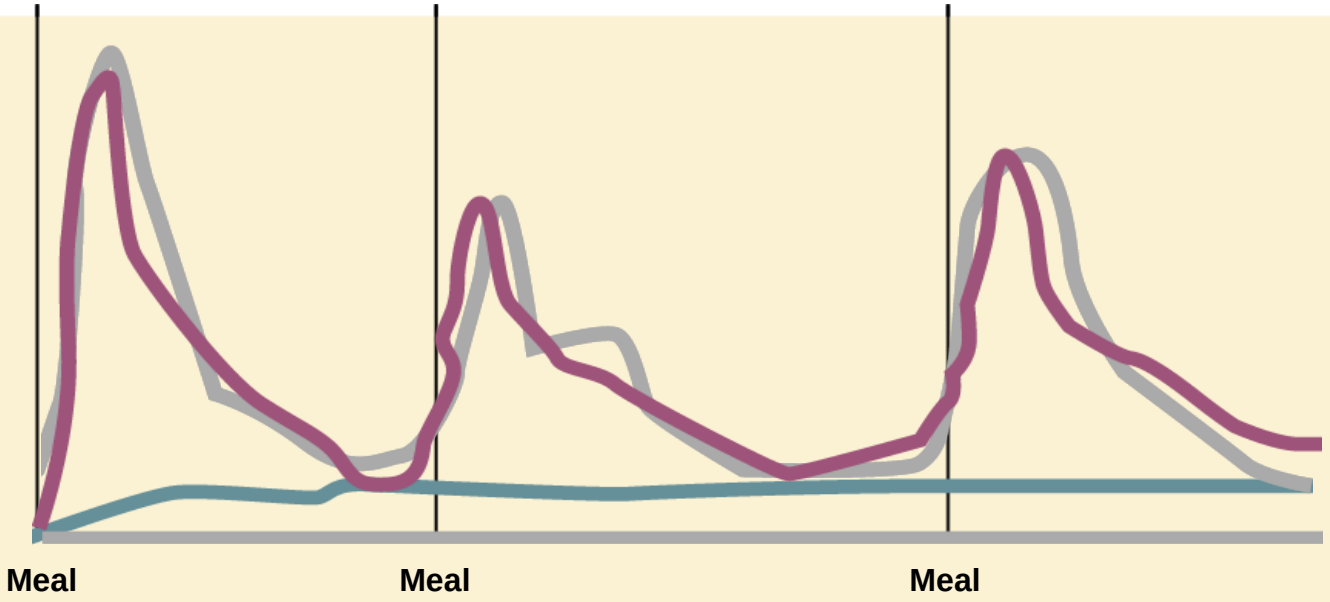
Case Summery

- Patient’s concerns – listen and address
- Pre-mixed insulin - when convenience and “compromise” are considerable
- Easy to use, less interruptions with routine
- A single injection facilitates basal insulin + prandial coverage for the main meal

Case 4

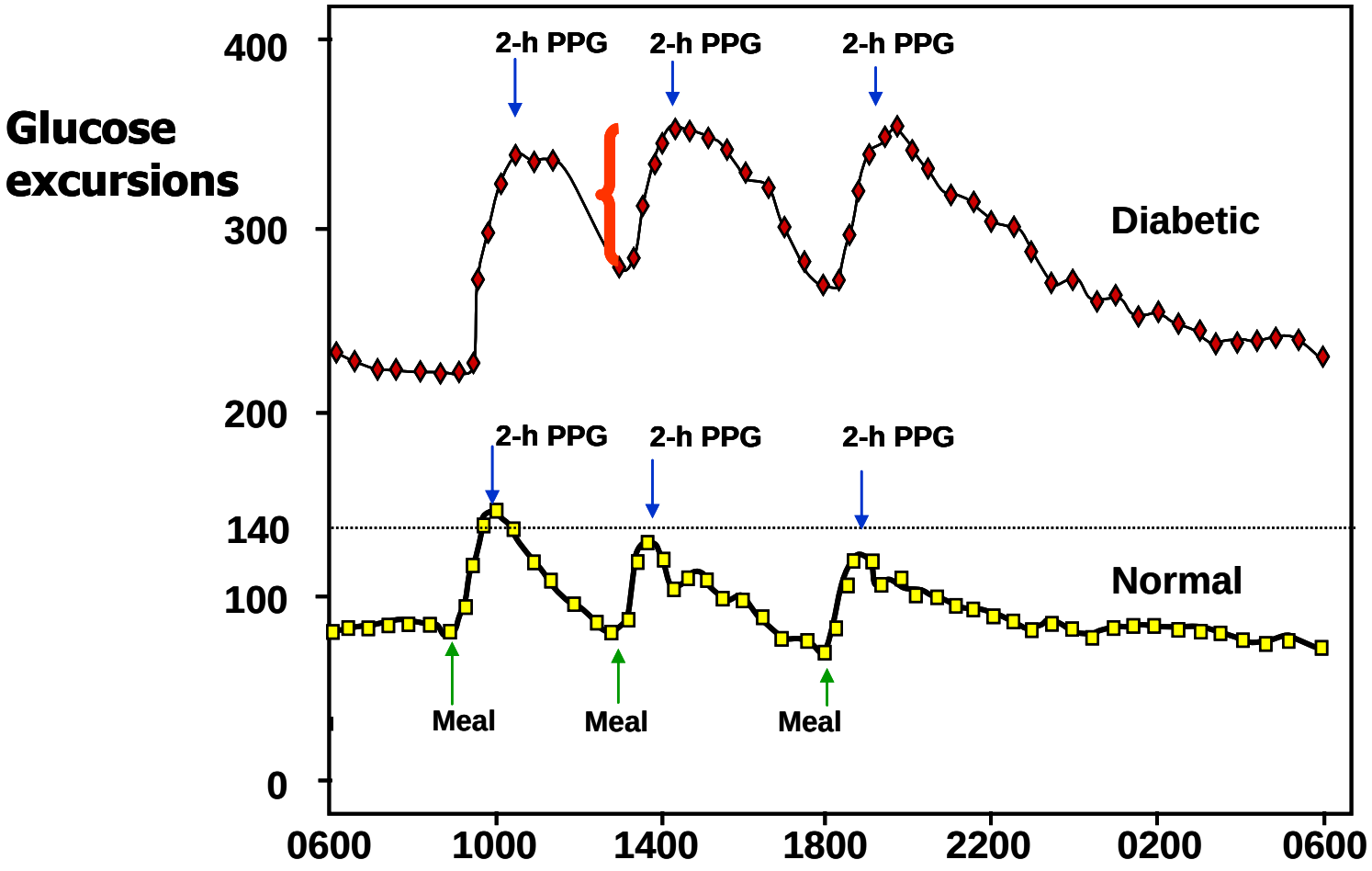
- 59 y.o. man
- 15 years long DM-2
- Taxi driver, irregular meals
- Significant postprandial hyperglycemia (320)
- Maximal O.A.D. including DPP-4 INH.
- Willing to start insulin, limit injections to BID

Physiologic Insulin Pattern



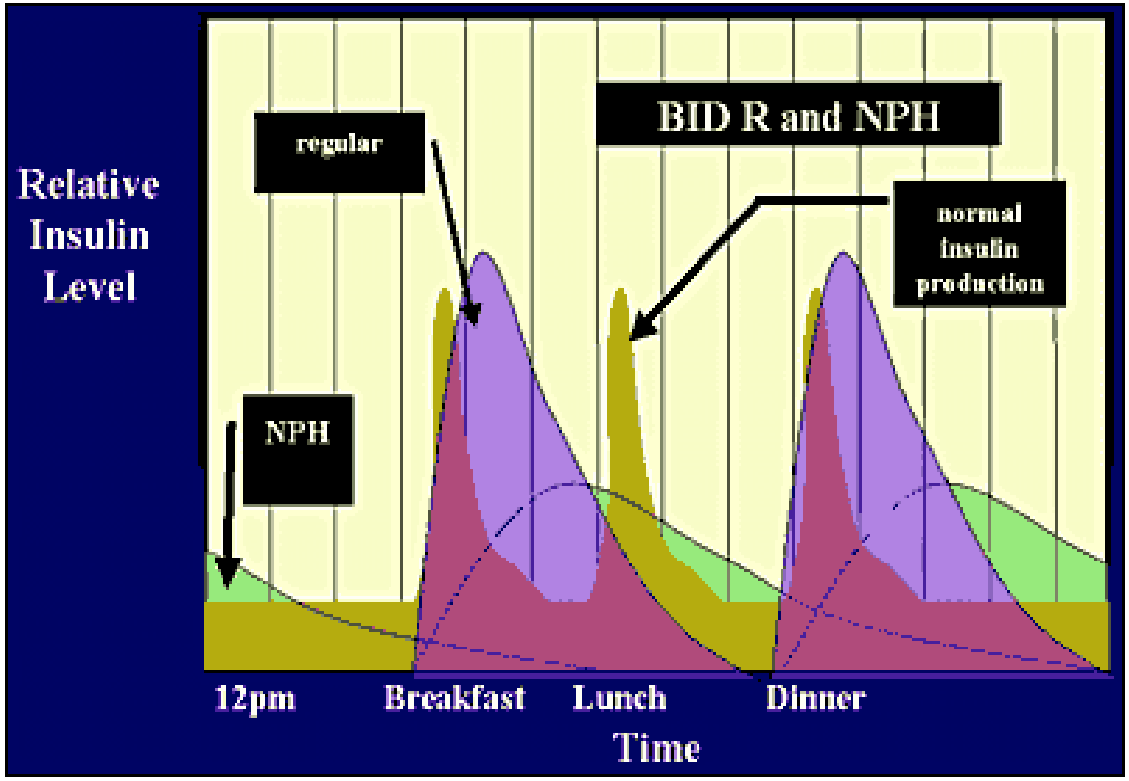
Insulin effect images are theoretical representations and are not derived from clinical trial data.

Normal vs DM-2



Adapted from Polonsky KS, et al. N Engl J Med 1988;318(19):1231-9.

BID Premixed Insulin Regimens



- Non-physiologic
- **Compromise** on glucose control
- Reduced flexibility

Case Summery

- B.I.D. premixed insulin - a good solution for patients willing to inject and monitor BG to a limited level
- Easier to use for many patients
- Better than no insulin in many cases
- Suboptimal, non-physiological compromise compared to basal-bolus

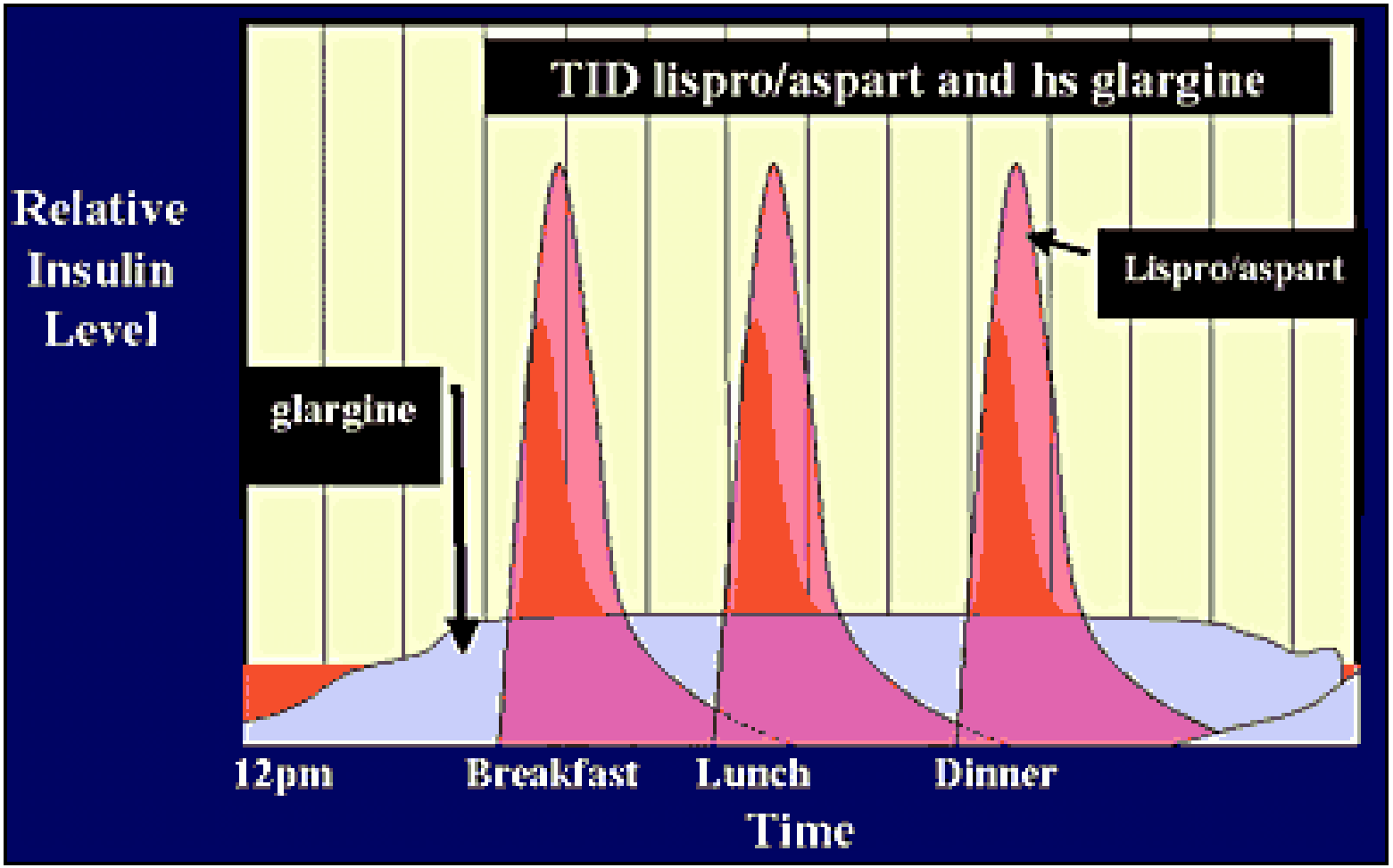
Case 5

- 50 YO obese woman,13 years DM-2
- Worried about CVS complications (family)
- Current therapy: 2 Metformin / D + 3 Gluben 5 mg / d + 12 units Lantus every evening

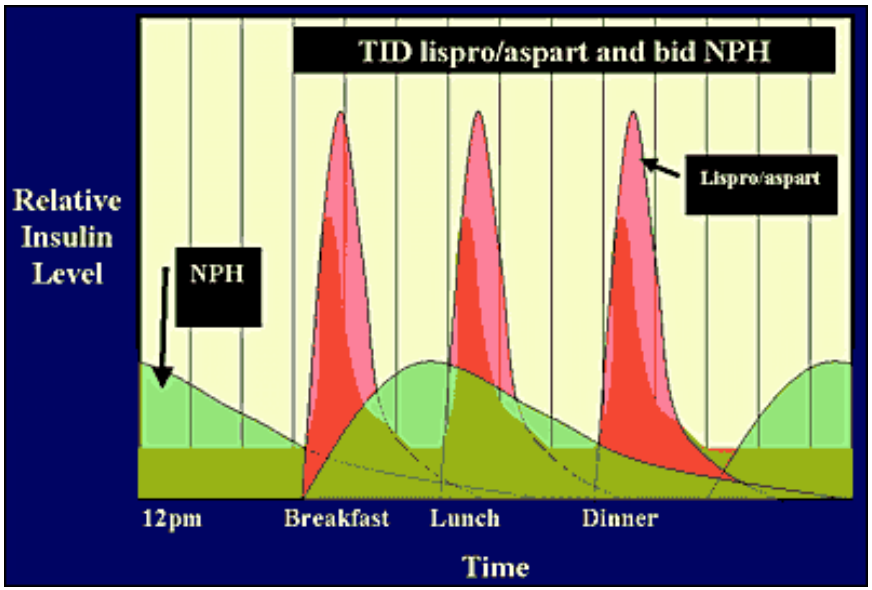
- HBA1c=9.5
- Retinopathy, microalbuminuria
- Willing to make an effort needed for diabetes control

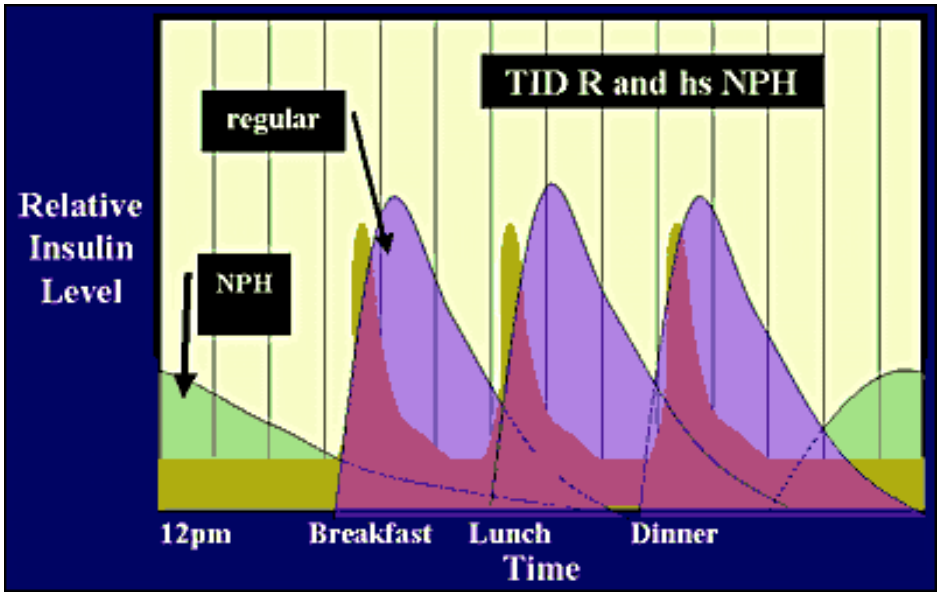
	FBG	**PPG** breakfast	**Pre-dinner**	**PPG** Bedtime
	146	**201**	**159**	**325**
Target	<130	<180	<130	<180

Physiologic Regimens
Basal & Bolus

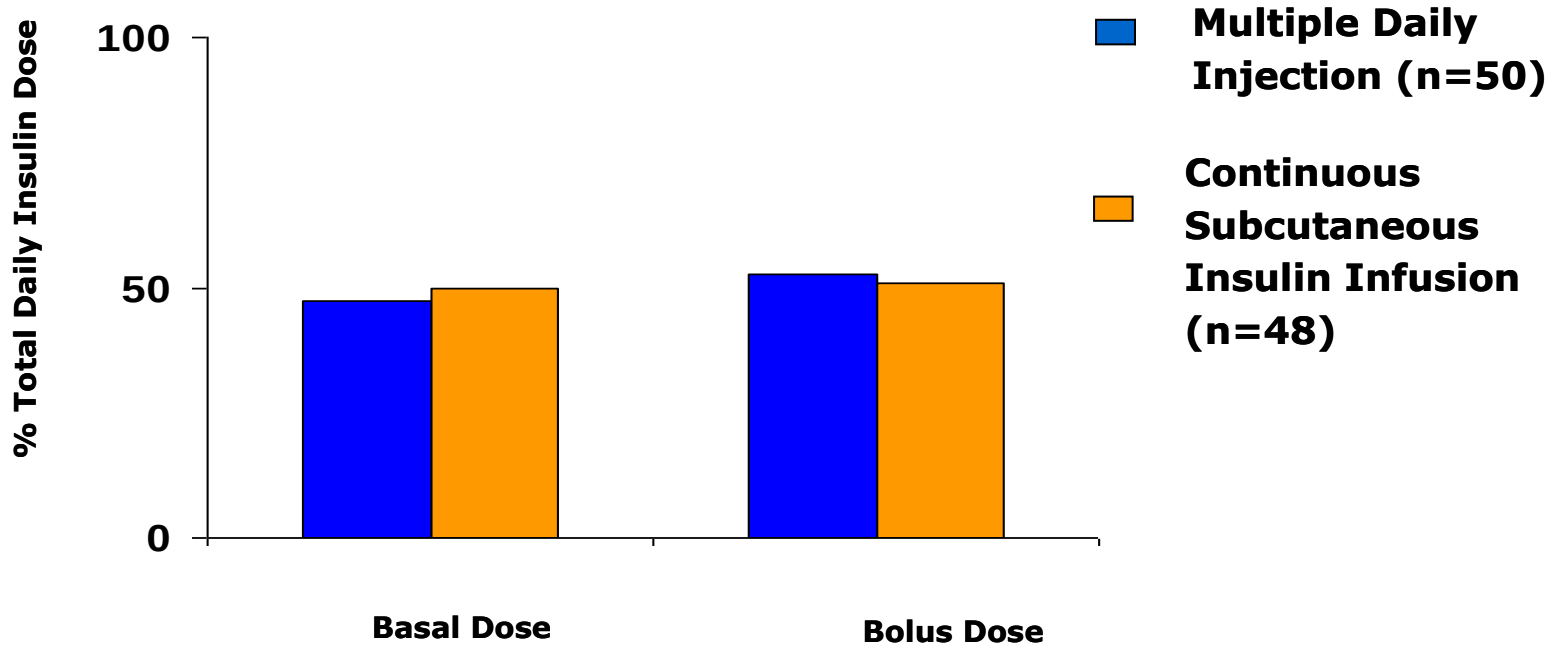


Basal & Bolus Regimens



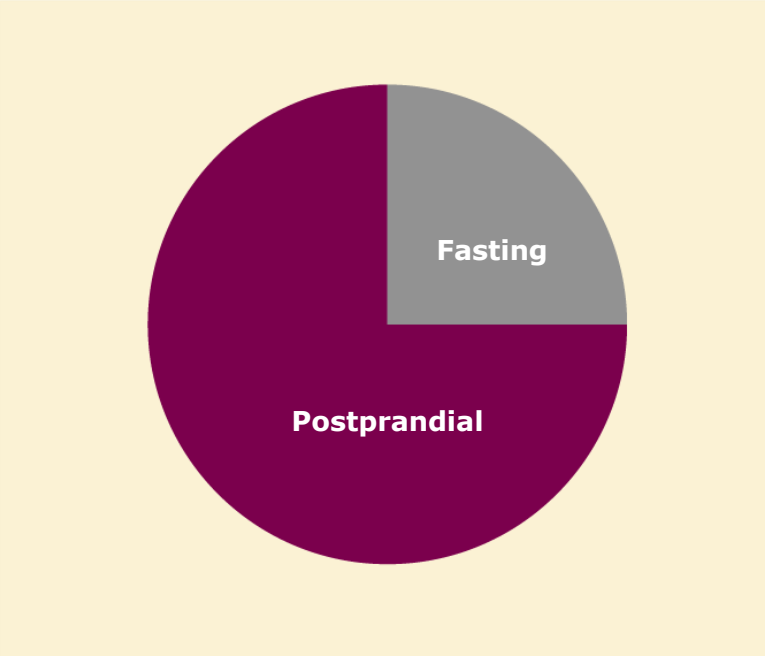


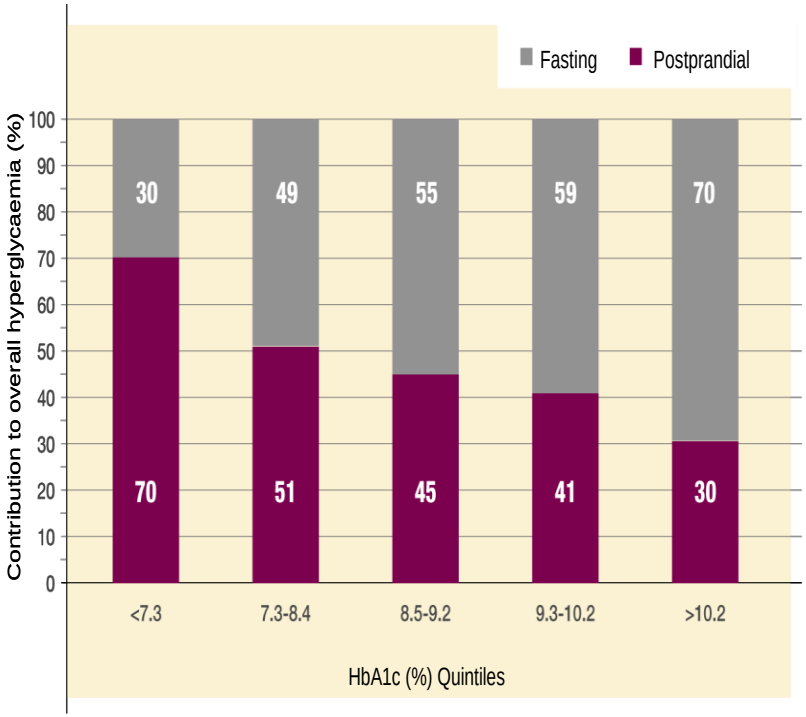
Basal & Bolus proportion



Doses adjusted to achieve target preprandial and bedtime BG levels

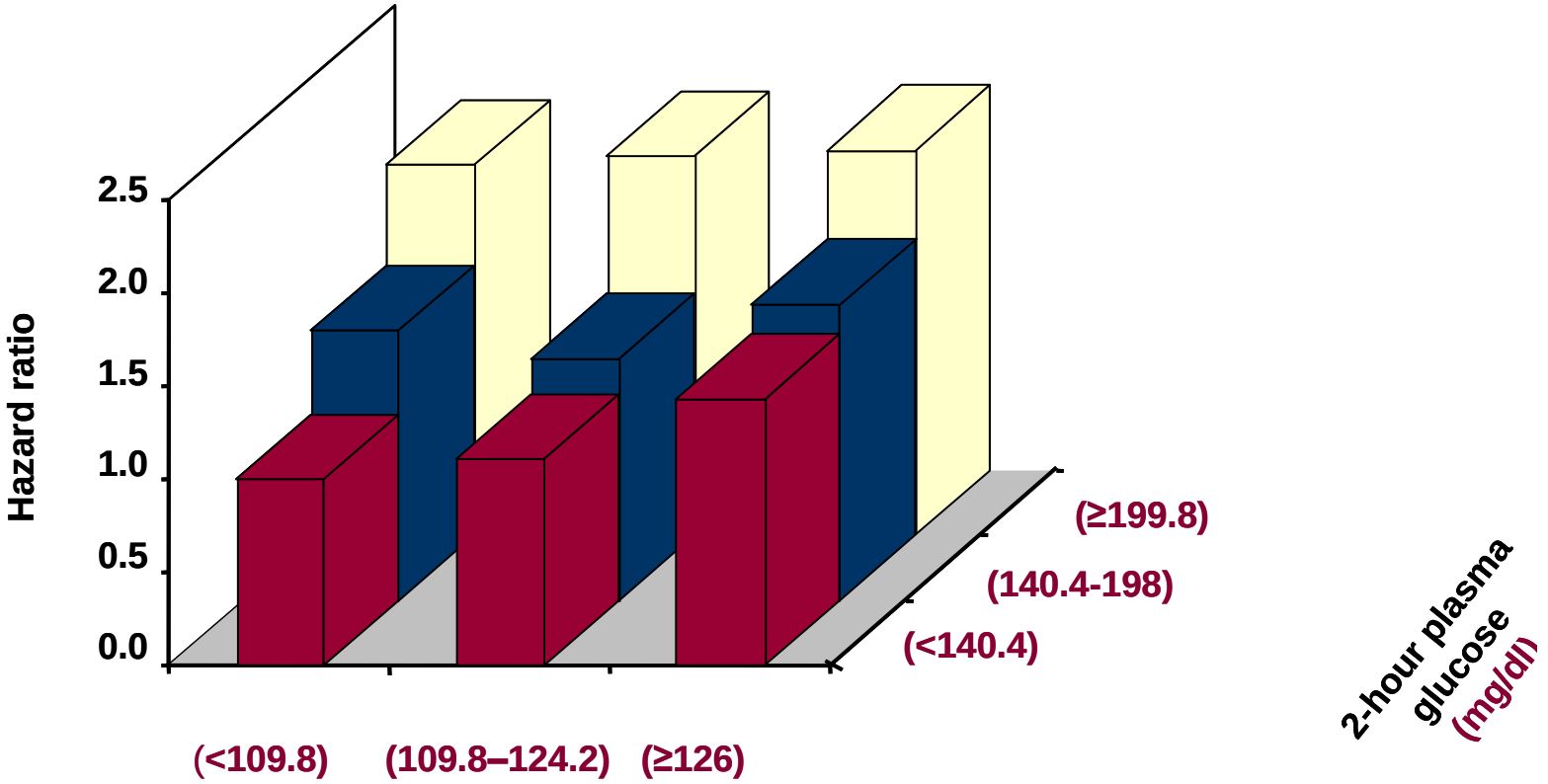
Post Prandial Glycemia





Data derived from American Diabetes Association. *Diabetes Care.* 2001;24(4):775-778 and Monnier L, et al. Diabetes Care. 2003;26:881-885

PPG and Cardiovascular Complications

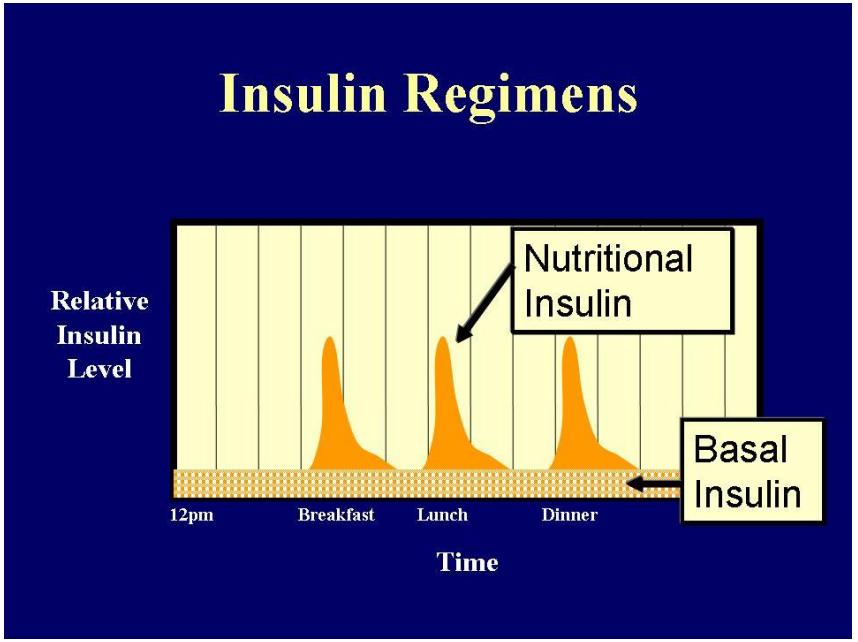


Adapted and reprinted from DECODE Study Group. *Lancet* 1999;354:617. Copyright 1999, with permission from Elsevier

Case Summery

- **Basal Bolus – physiologic regimen**
- High motivation
- Multiple BG checks
- Multiple injections
- Pts knowledge

  diet, carbs etc
- Better glycemic control



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	146	**201**	**159**	**325**
Target	<130	<180	<130	<180

- 13 years DM-2
- 2 Metformin / D
- **3 Gluben 5 mg / d**
- 12 units Lantus every evening

Insulin Regimens In DM-2

- Age
- Type of diabetes
- Concurrent disease
- Lifestyle
- Patient's motivation / compliance
- Hb A1C
- Glycemic targets

למי להתחיל טיפול באינסולין ?

קווי הנחיה על בסיס פיזיולוגי

איך להתחיל טיפול באינסולין ?

סוגי אינסולין

בסיס פרמקולוגי

משלבים טיפוליים

מדידות סוכר – לא רק בבוקר!

חשיבות היפרגליקמיה שלאחר ארוחה

קשיים ואתגרים

תודה על ההקשבה, שאלות?...