Insulin is Insulin, or not?
(Using analogues: ultra rapid, basal, concentrated insulins)

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SPED President 2020-2021
100 Years of Insulin Therapy: A Long Successful Path
November 14, 2021. La Concha Renaissance San Juan Resort

Disclosure

•Dr. Jose M. Garcia Mateo, endocrinologist, declares that he serves as a speaker and consultant for the following pharmaceutical companies: ***Eli Lilly, Astra Zeneca, Sanofi , Amgen, Bayer, Boehringer Ingelheim, Janseen and Abbvie.***

Objectives

- Review the different modifications in the insulin molecule to obtain insulin analogues that mimics normal pancreatic insulin release.
- Discuss insulin analogues more physiologic PK and PD profiles.
- Present the advantages of insulin analogues clinical use for the appropriate patient.
- Compare the different profiles of prandial and basal insulin analogues as onset of action, time to peak and duration when used in diabetes management.
- Explain the rationale of using concentrated insulins, specially in the very insulin resistant patient.

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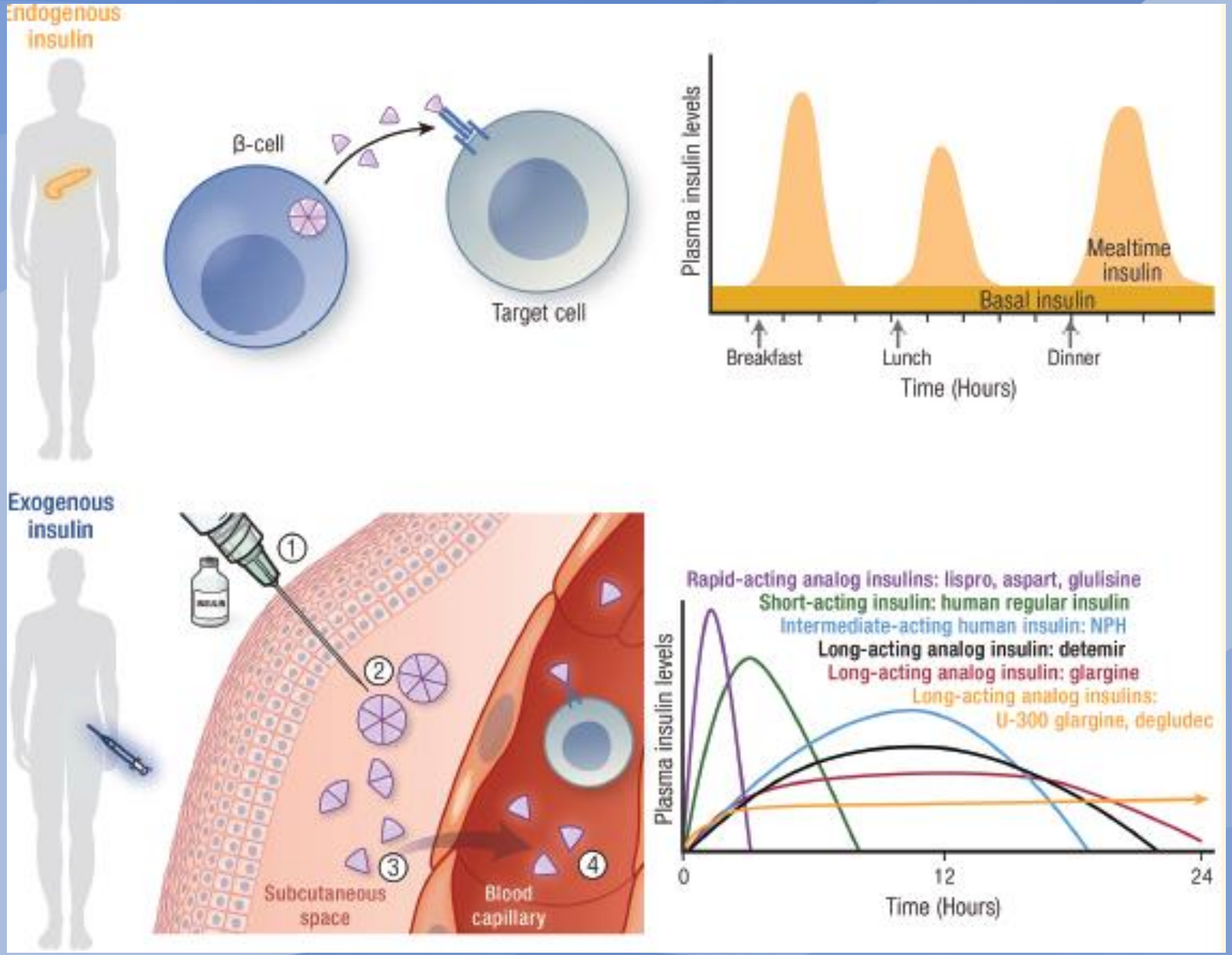

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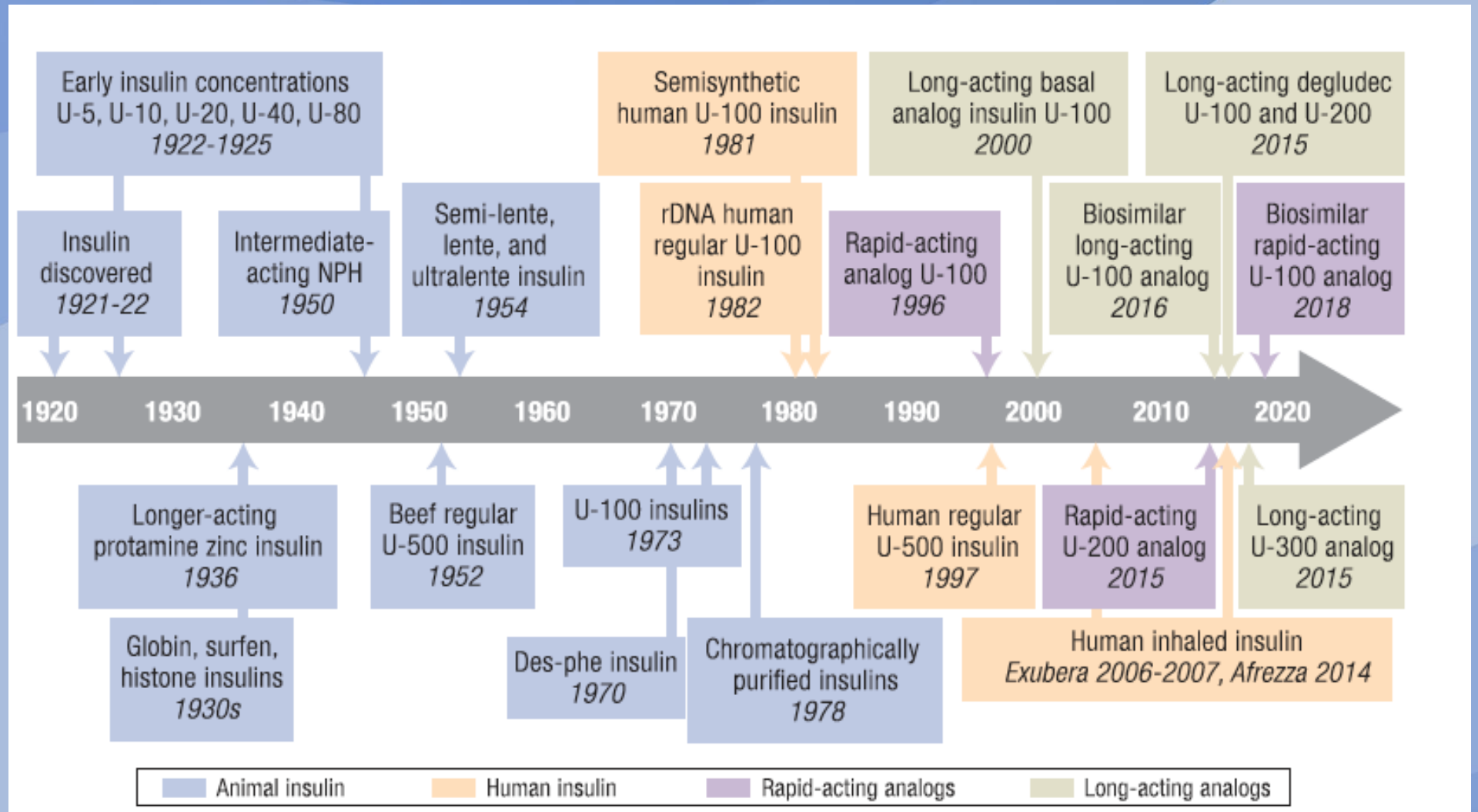

Figure 1. Timeline of insulin development with approximate historical dates. Abbreviations: NPH, neutral protamine Hagedorn; rDNA, recombinant DNA; U = units.

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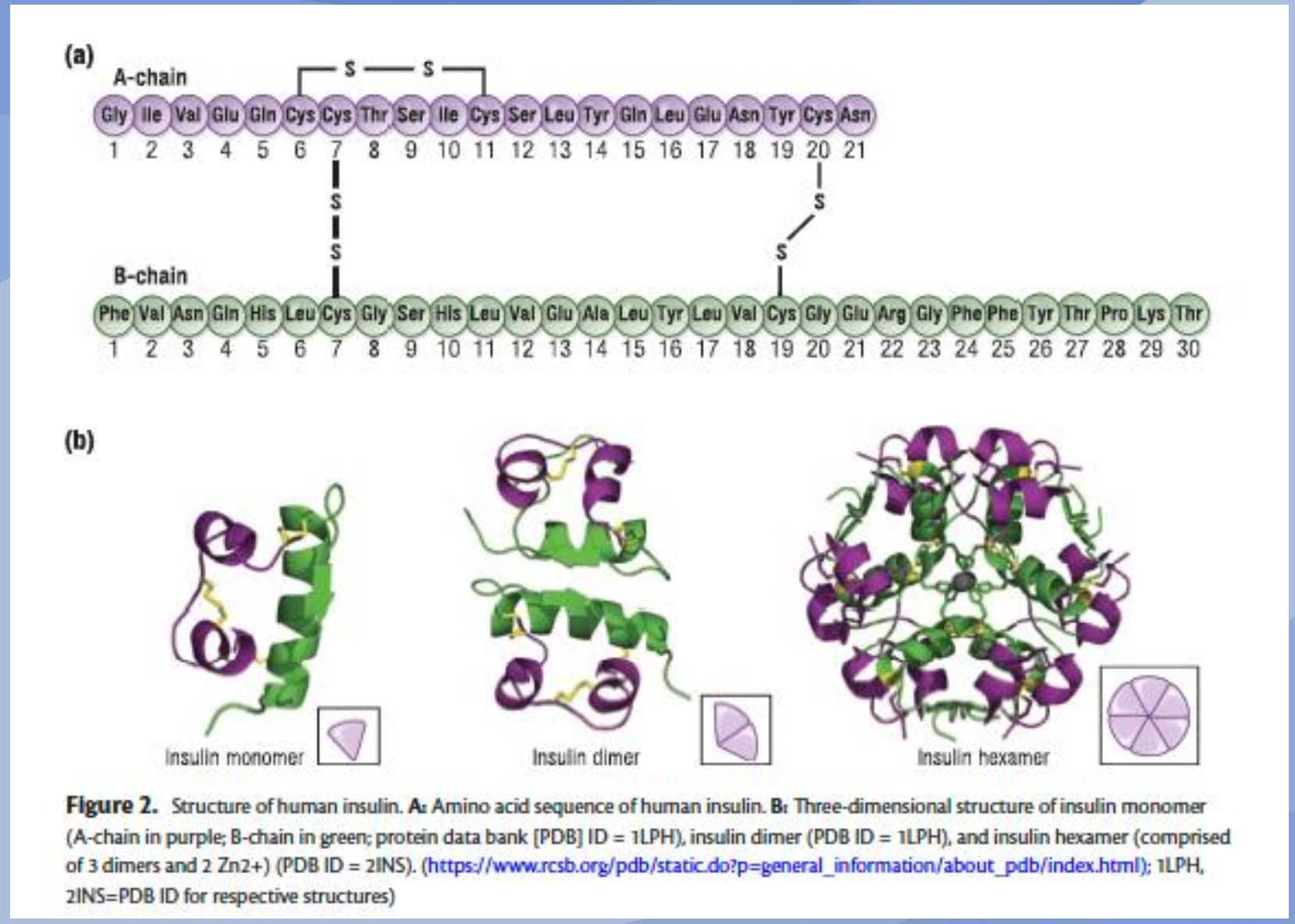

Figure 2. Structure of human insulin. **A:** Amino acid sequence of human insulin. **B:** Three-dimensional structure of insulin monomer (A-chain in purple; B-chain in green; protein data bank [PDB] ID = 1LPH), insulin dimer (PDB ID = 1LPH), and insulin hexamer (comprised of 3 dimers and 2 Zn2+) (PDB ID = 2INS). (https://www.rcsb.org/pdb/static.do?p=general_information/about_pdb/index.html); 1LPH, 2INS=PDB ID for respective structures)

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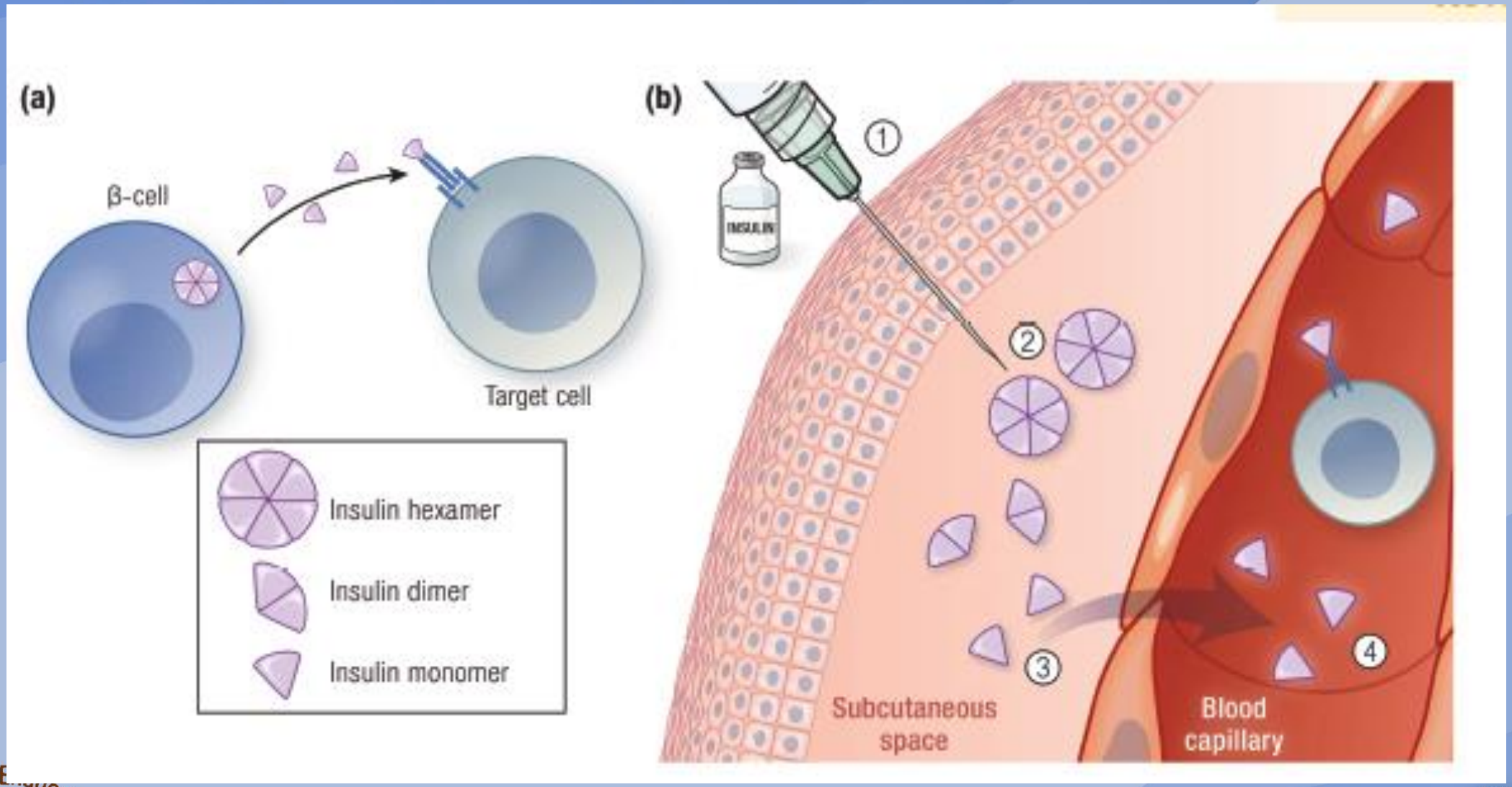
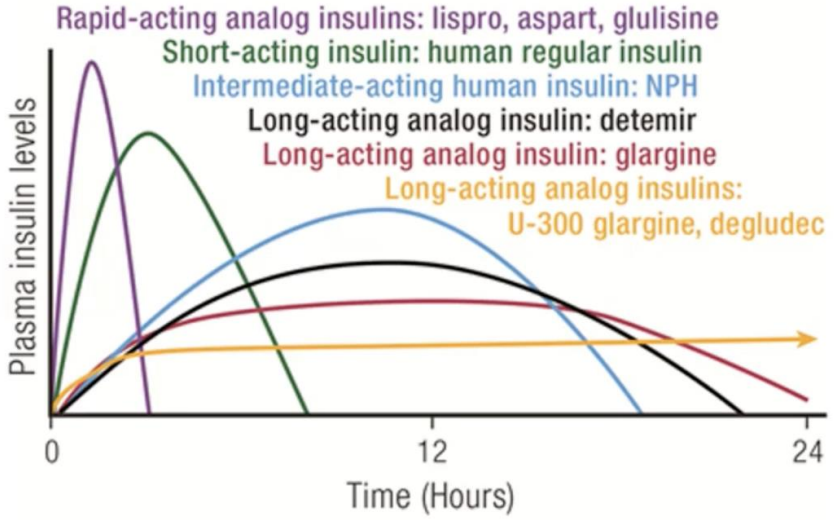

(a)
β-cell
Target cell
Insulin hexamer
Insulin dimer
Insulin monomer
(b)
1
2
3
4
Subcutaneous space
Blood capillary


Insulin Insuline
1921

Insulins

- Rapid analog – lispro, aspart, glulisine
- Short acting - R
- Intermediate - NPH
- Long – detemir, glargine
- Longer – glargine U300, degludec



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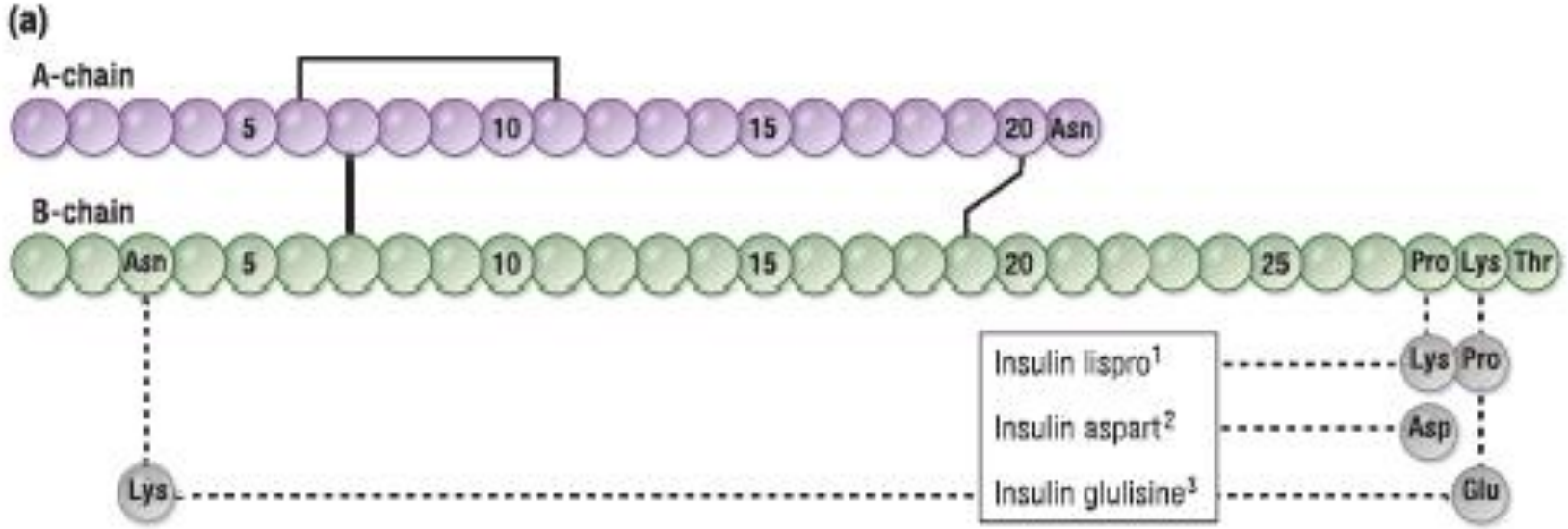
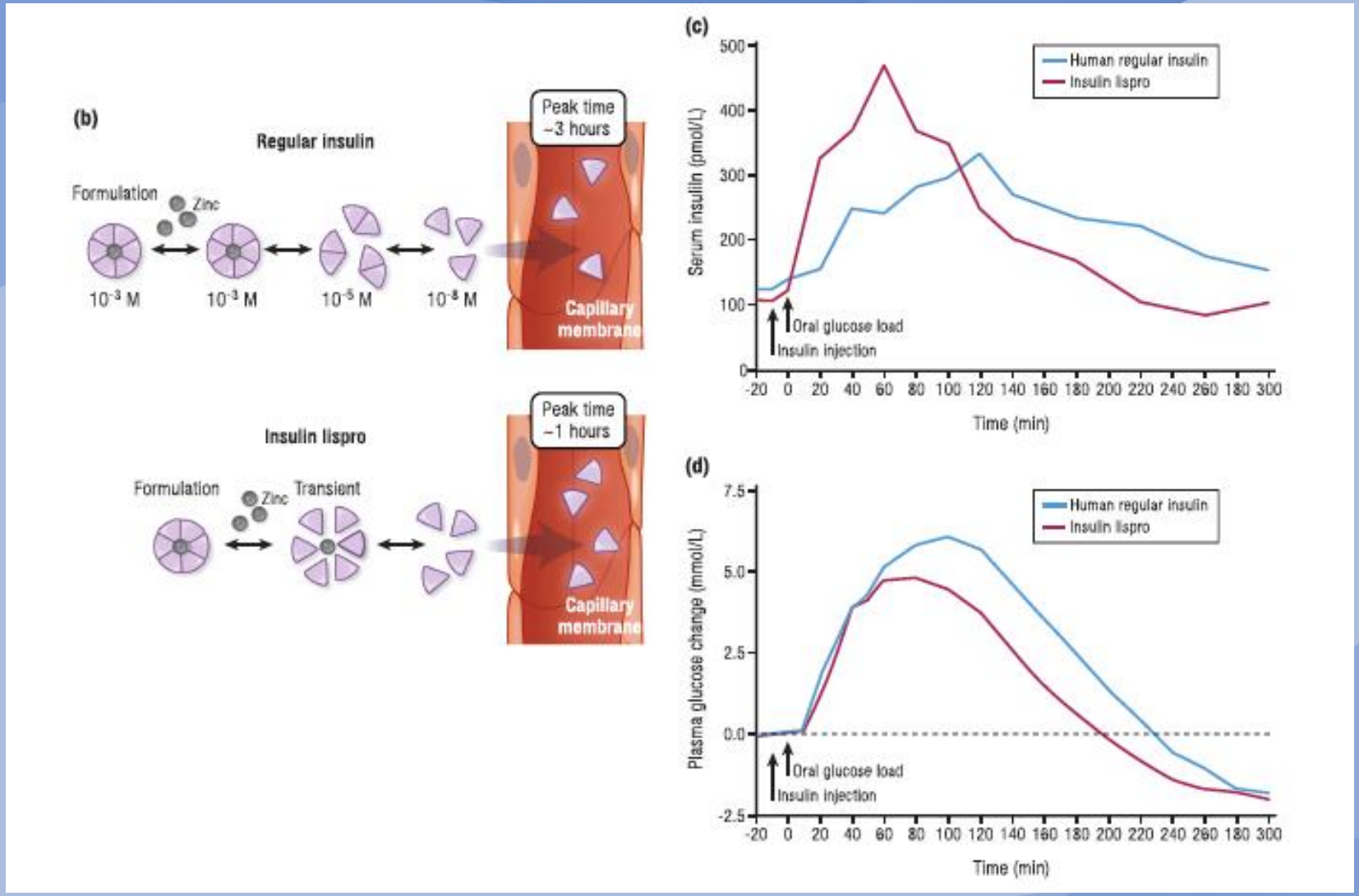
Prandial Insulin Analogues

- Rapid acting
- Ultra rapid acting
- Inhaled insulin

Rapid Acting Analogues: lispro, aspart and glulisine





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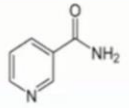
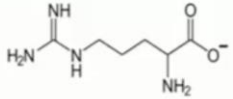
Fast Insulin Aspart

Niacinamide: absorption modifier



Vitamin B3

L-Arginine: added for stability

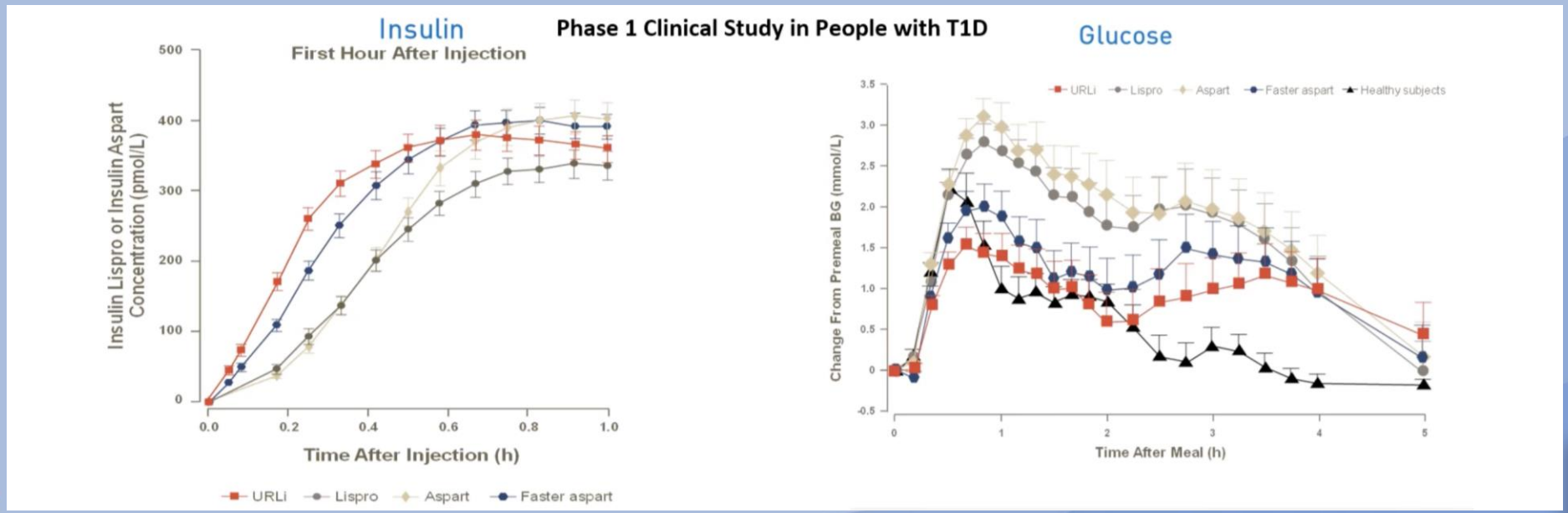


Naturally occurring amino acid

Ultra Rapid Lispro (aabc)

URLi contains the following excipients[2,3]

- **Citrate:** Speeds insulin absorption by enhancing local vascular permeability
- **Treprostinil:** A prostacyclin analogue currently approved for treatment of pulmonary arterial hypertension (Remodulin®). Further enhances the absorption of insulin lispro via local vasodilation



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Inhaled Insulin Powder

- Rapid acting
- Easy to use with small device
- Needs basal in T1D and very insulin deficient T2D
- Fixed doses
- Expensive
- Not widely available
- No commercial support in PR
- Needs assessment of PFT's
- Contraindicated in patients with respiratory pathology

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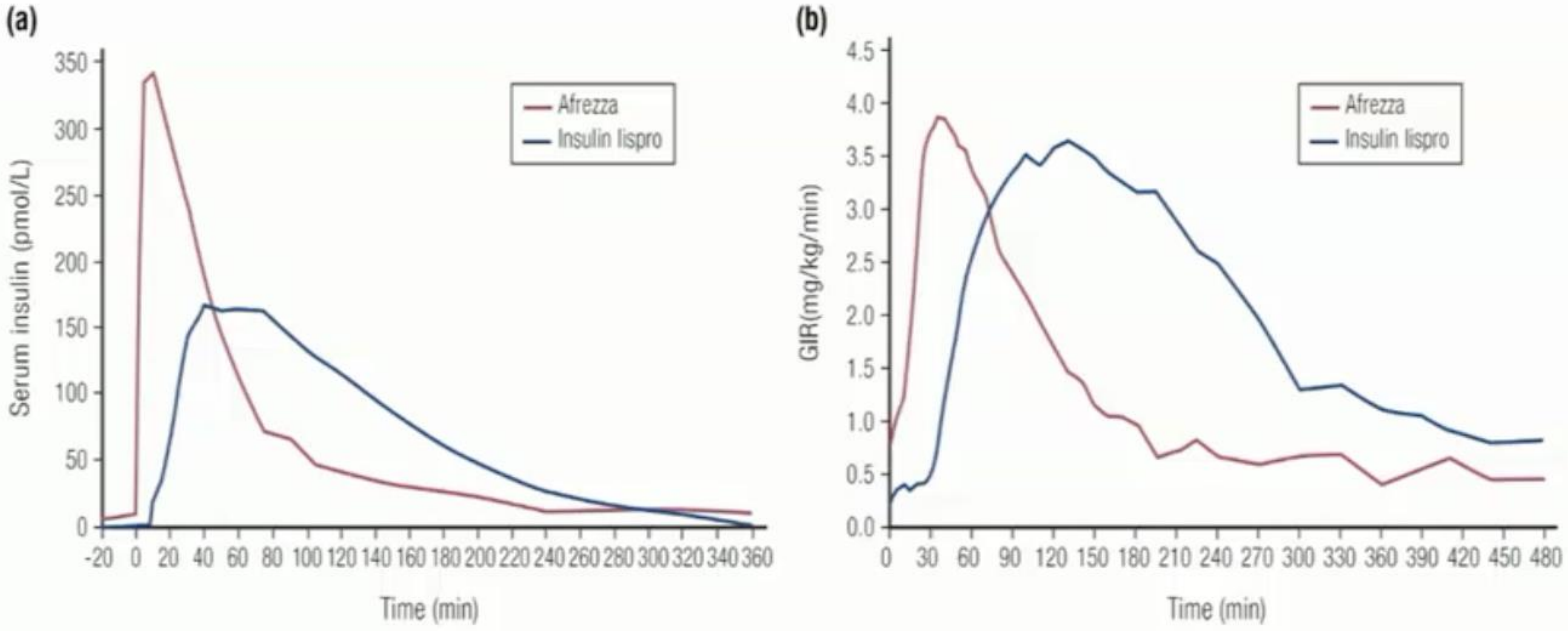
Ultra-rapid Insulin: Inhaled Human Insulin PK and PD (vs lispro)



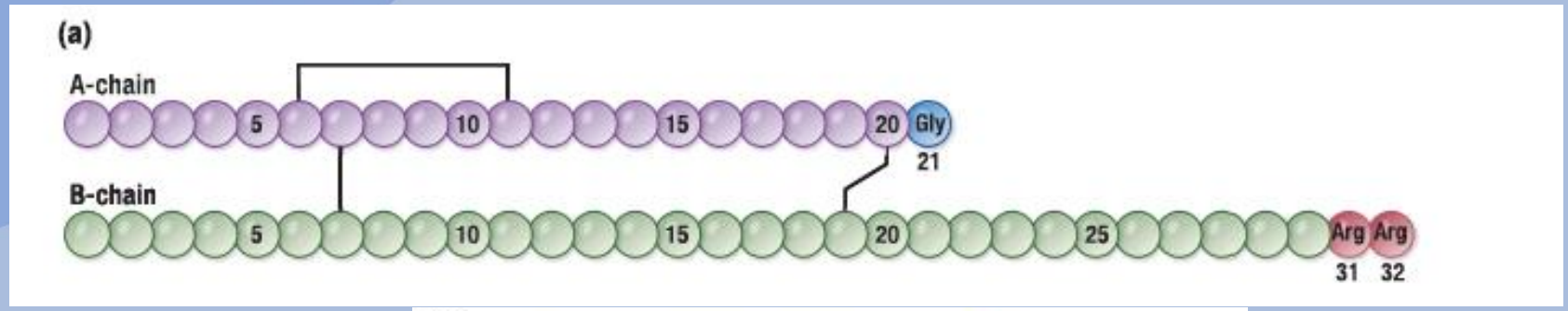
Endocr Rev, Volume 41, Issue 5, October 2020, bnaa015, https://doi.org/10.1210/endrev/bnaa015

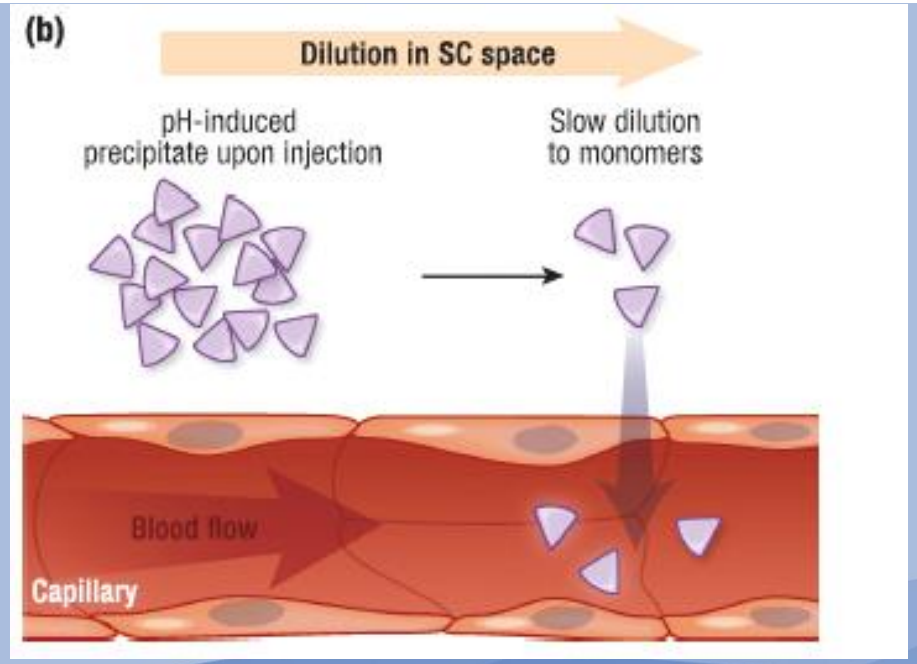
PRANDIAL INSULIN	Time to Onset	Time to peak	Duration of Action	Delivery Options	Advantages	Disadvantages
Human regular U-100	30-45 min	~3 hr	~8 hr	Vial only	Cheapest, OTC	Doesn't match meal well More delayed hypos
Lispro U-100 (original, biosimilar)	20 min	~90-120 min	~5 hr	Vial or pen	Faster than R, matches meal better, less delayed hypo	Expensive
Lispro U-200				Pen only		
Aspart				Vial or pen		
Glulisine				Vial or pen		Glulisine < 48 h in pump
Faster aspart	15-20 min	~90-120 min	~5 hr	Vial or pen	Less post-meal hyperglycemia	No differences in A1C-lowering or hypo
Lispro-aabc *(FDA-approved, coming to market)*	*13 min*	*90-120 min*	*4.5 hr*	*Vial or pen*	*Less post-meal hyperglycemia*	*No differences in A1C-lowering or hypo*
Human insulin inhalation powder	<15 min	45-60 min	~ 1.5 hr	Single-use cartridges for specific inhaler	Faster on and off Matches meal well	Expensive Limited dose intervals Contraindications, Spirometry required Need basal insulin

Basal Insulin Analogues

- Long acting: glargine, detemir
- Ultra Long acting: U300 glargine, degludec
- Weekly insulin (not available yet): icodec, BIF

Glargine: First True Basal Insulin: Lauched 2000





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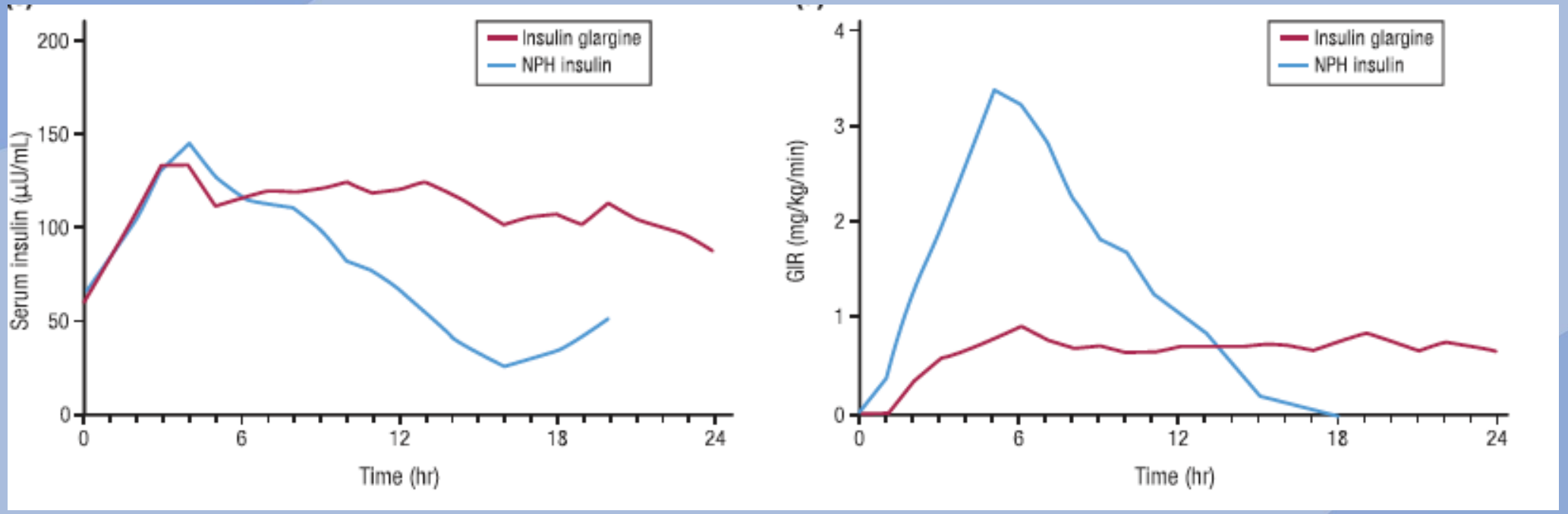
Glargine: First True Basal Insulin: Lauched 2000



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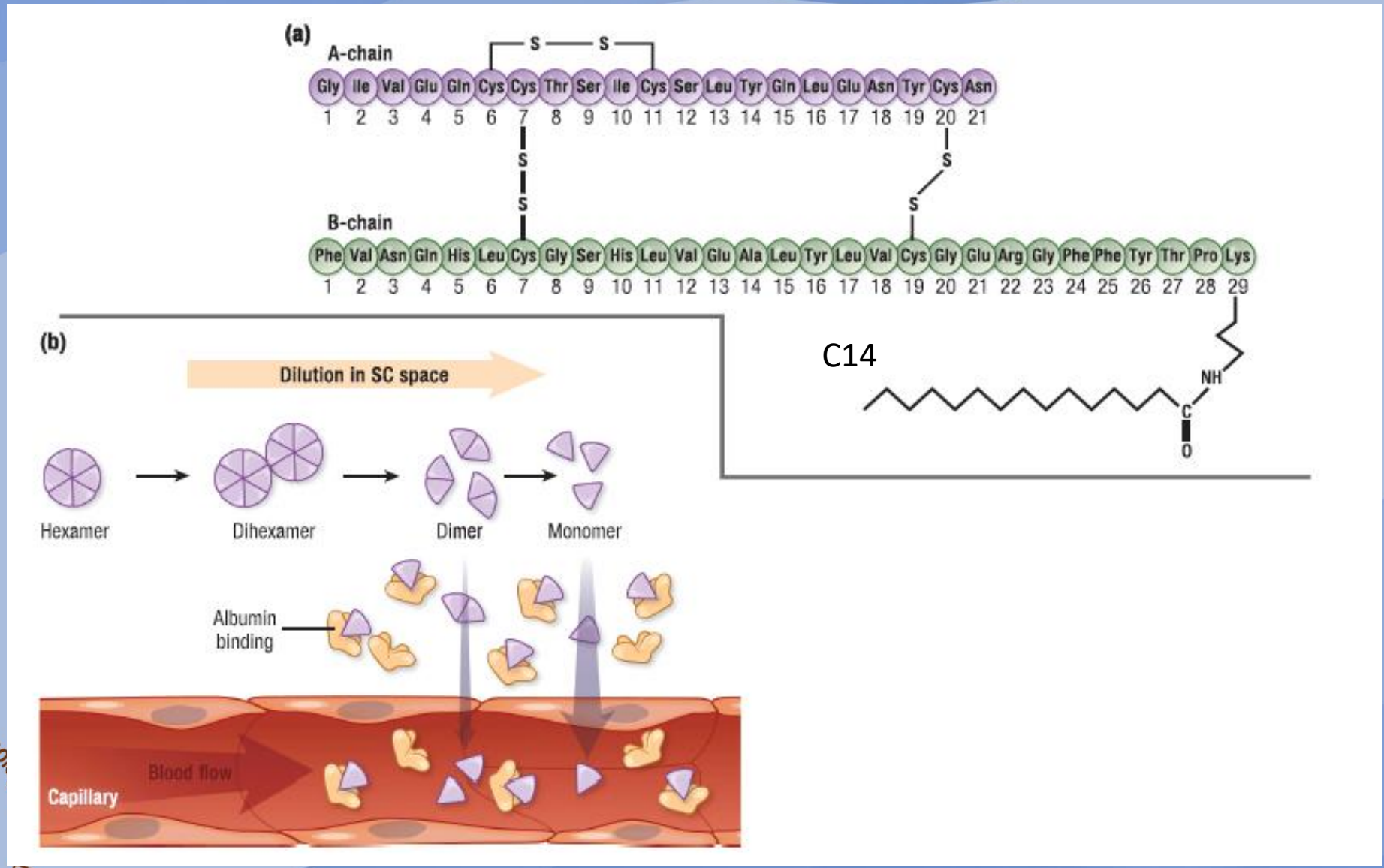
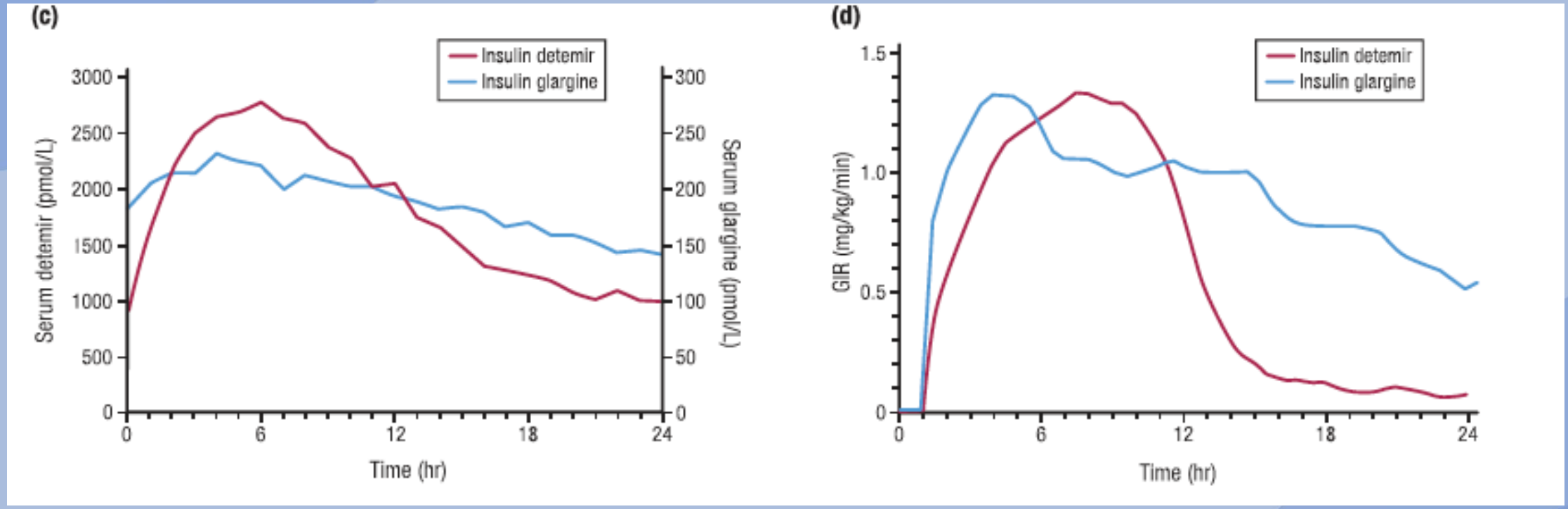
Insulin detemir

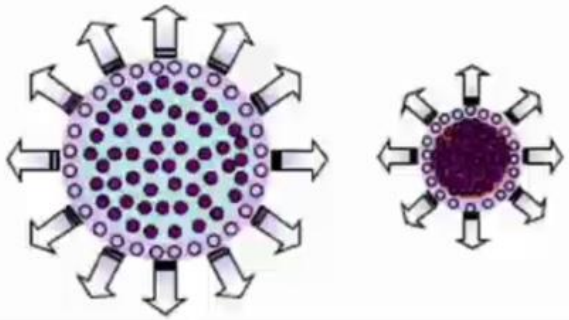


Insulin Detemir



Glargine U300: concentrated but classified as ultra basal

U-300 Glargine has 2/3 less Volume than U-100 Glargine



- Three-fold more concentrated formulation of glargine
- Reduced volume (1/3) and reduced surface area (1/2) of subcutaneous depot
- Slower and more constant rate of absorption

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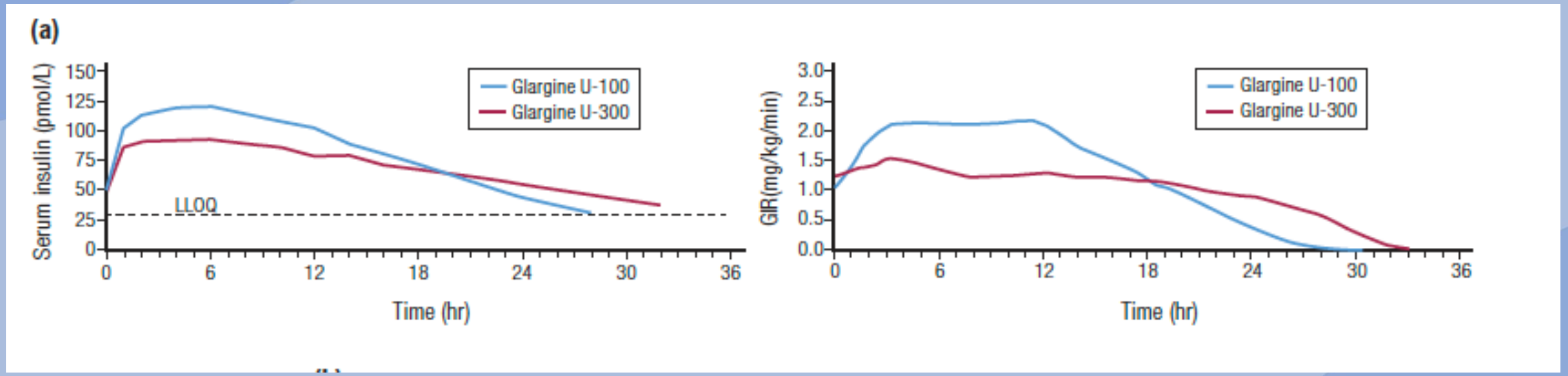
Glargine U300: concentrated but classified as ultra basal



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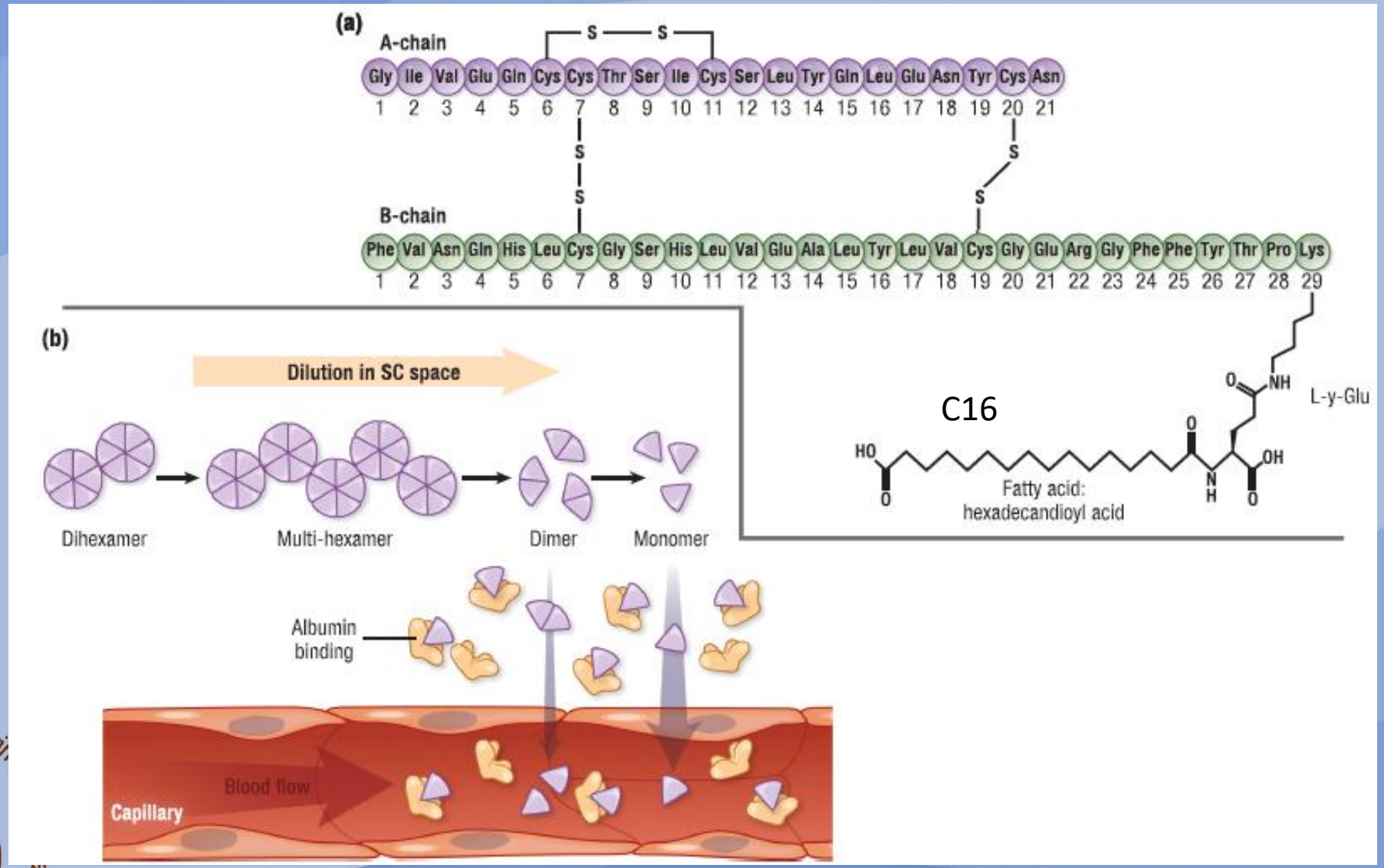
Insulin Degludec



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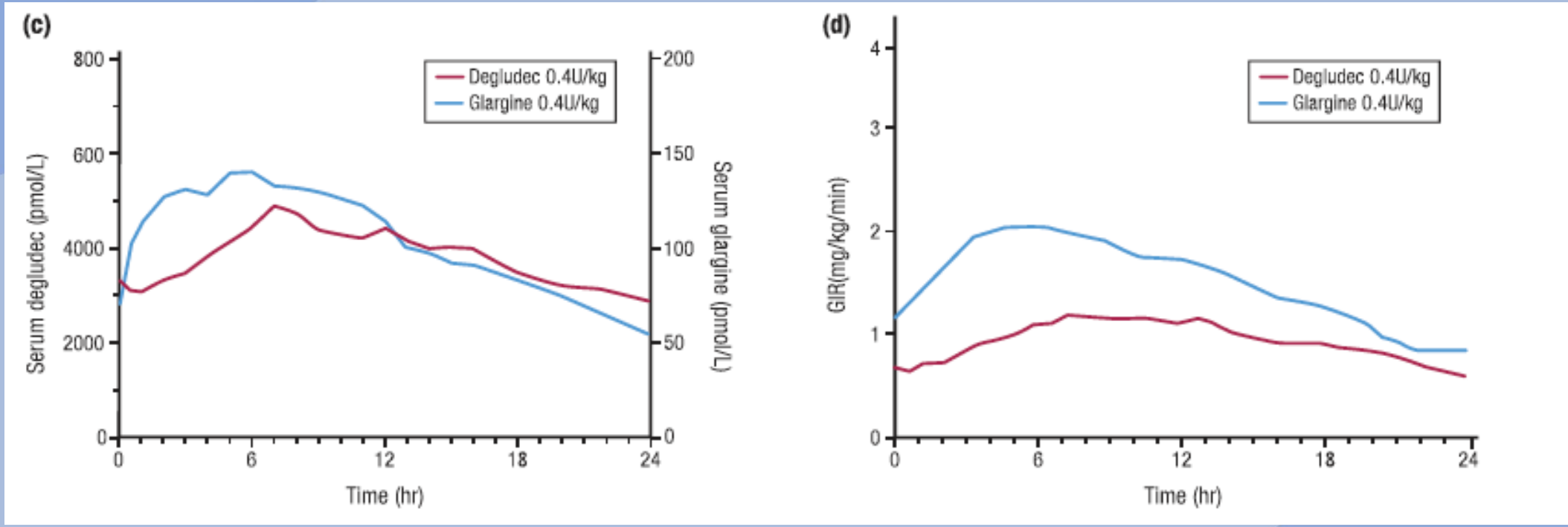
Insulin Degludec



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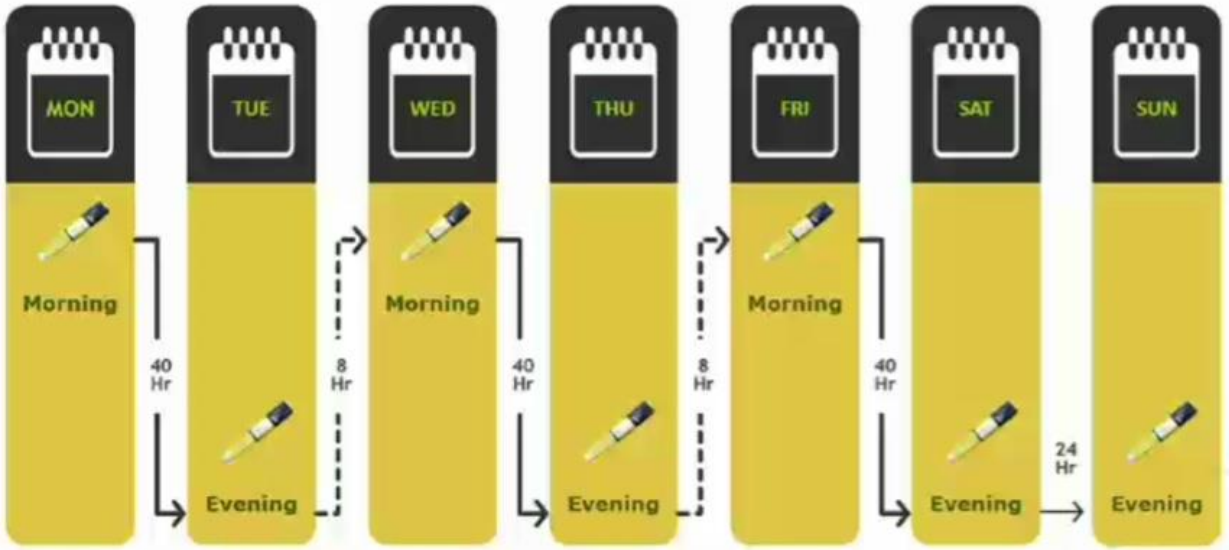
Insulin Degludec

BEGIN FLEX T1D Study:

- Degludec U-100 Alternating times once daily AM vs. PM, 8-h to 40-h intervals
- Degludec U-100 Fixed timing once daily
- Glargine U-100 Fixed dose, once daily

Open label Randomized



1. J Clin Endocrinol Metab. 2013 Mar;98(3):1154-62. doi: 10.1210/jc.2012-3249. Epub 2013 Feb 7.
2. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc; September 2015.

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Insulin Degludec

Degludec Alternating Times Achieved Comparable A1C Efficacy and Degludec Fixed Numerically Lower FPG vs Insulin Glargine U-100 and Degludec Alernating Times.

A1C (%)

	Degludec U-100 Alternating	Degludec U-100 Fixed	Glargine, Fixed
A1C Reduction	-.40	-.41	-.58

FBG (mg/dl)

	Degludec U-100 Alternating	Degludec U-100 Fixed	Glargine, Fixed
FBS Reduction	-23.04	-45.72	-23.04

Insulin Degludec met the prespecified non-inferiority margin of 0.4%

Baseline A1C: Degludec Alternating Times 7.7%; Degludec Fixed 7.7%; insulin glargine U-100 7.7%.
Baseline FPG: Degludec Alternating Times 173 mg/dL; Degludec Fixed 180 mg/dL; insulin glargine U-100 175 mg/dL.
Mean ± SEM used for the full analysis set; Last observation carried forward was used for each postbaseline time point.
Comparison estimates adjusted for multiple covariates.

1. J Clin Endocrinol Metab. 2013 Mar;98(3):1154-62. doi: 10.1210/jc.2012-3249. Epub 2013 Feb 7.
2. Degludec [package insert]. Plainsboro, NJ. Novo Nordisk Inc; September 2015.

Clinical Guidelines for Switching to & from Concentrated Insulins

Current Therapy	Switch to U-100 Glargine	Switch to U-300 Glargine	Switch to Degludec
U-100 Glargine	--	Initial switch no dose change; likely need to up-titrate	Consider↓ dose by 10%
U-300 Glargine	Consider↓ dose by 10%	--	Consider↓ dose by 15%
Degludec	Initial switch no dose change; likely need to up-titrate	Initial switch no dose change; likely need to up-titrate	--

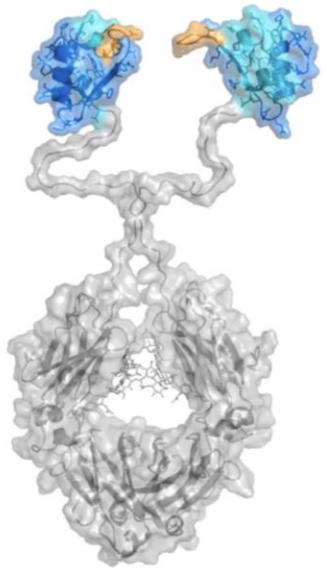
BASAL INSULIN	Time to Onset	Time to Peak	Duration of Action	Delivery Options	Advantages	Disadvantages
NPH	2-4 hr	4-10 hr	12-18 hr	Vial, pen (?)	Cheapest; OTC	Erratic action Marked peak More hypos (esp T1D)
Glargine U-100 (Original, biosimilar)	2-4 hr	"Flat"	20-24 hr	Vial, pen Biosimilar: pen only	Less peak Fewer hypos than N (T1D)	Expensive Not truly 24-hr insulin
Glargine U-300	N/A	More "Flat"	Up to 36 hr	Pen only	Flatter and longer than glargine U-100	Expensive Steady state takes 5 days 27% less potent than U-100 Only 80 units/shot
Detemir	2-4 hr	"Flat"/ Broad	6-24 hr, dose-dependent	Vial, pen	Flatter than N	Expensive Often twice-daily
Degludec U-100 Degludec U-200	N/A	Most "Flat"	>42 hr	Pen only U100 vial now available	Flatter, longer-acting Less hypo than glargine U-200 pen: 160 u/shot	Expensive Steady state 3-4 days

new max pen offers 160 units /shot

Coming soon… weekly basal insulins

Weekly Basal Insulin Fc (BIF)

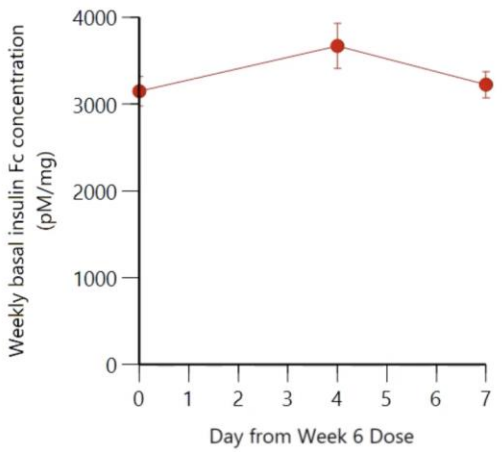
BIF is a fusion protein that combines a novel single-chain variant of insulin with a human IgG Fc domain



Attributes

- Selective insulin receptor agonist
  - >1000x selectivity versus IGF-1 receptor
  - Low mitogenicity potential
- Pharmacokinetic profile consistent with once weekly subcutaneous dosing
- Very low peak-to-trough profile (1.1 at steady state)
- Formulation compatible with single-use or multi-use devices. Can be co-formulated with weekly incretins
- Low immunogenicity risk

Phase 1 PK data
(weekly dosing)



BIF achieved flatter peak-to-trough profile than daily basal insulins and may demonstrate lower nocturnal hypoglycemia

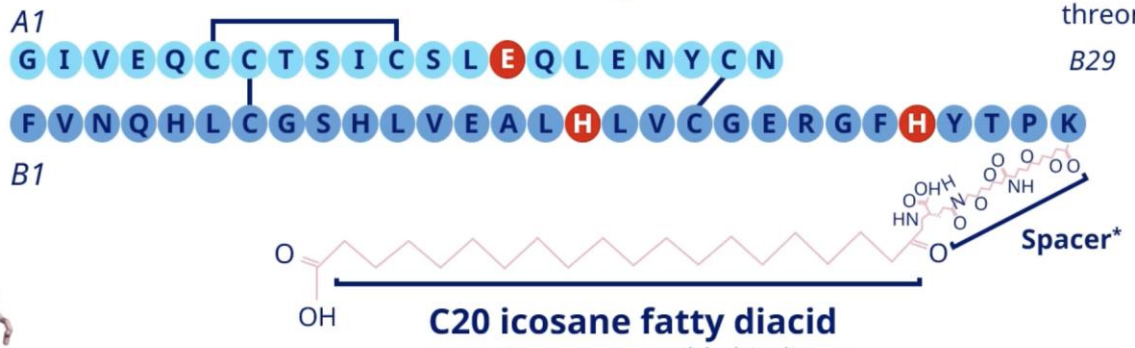
Coming soon... weekly basal insulins

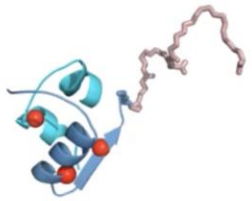
Molecular structural engineering of once weekly subcutaneous insulin icodec

Three amino acid substitutions

- Molecular stability
- Reduced enzymatic degradation
- Slow receptor-mediated clearance

Removal of terminal threonine *B29*





C20 icosane fatty diacid

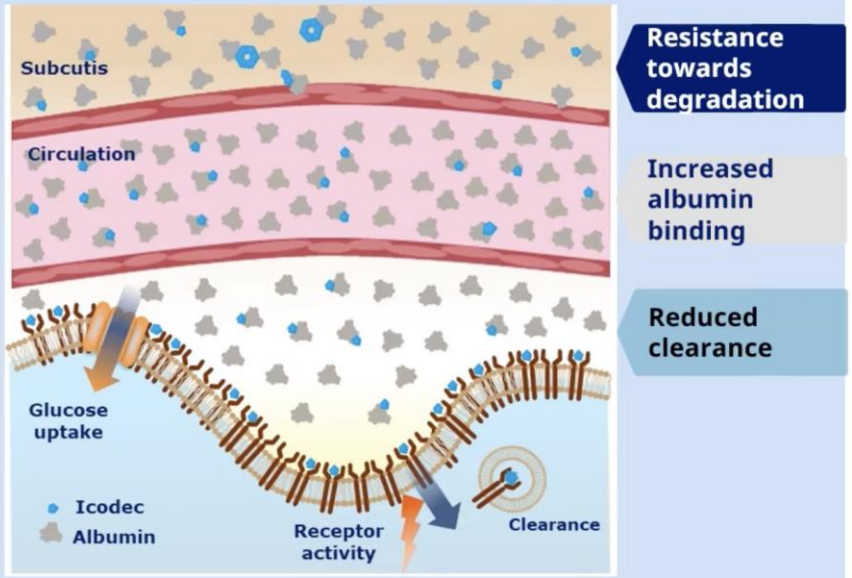
- Strong, reversible binding to albumin
- Slow receptor-mediated clearance

*2x (oligoethylene glycol(OEG)) γ-L-Glu spacer.
Nishimura et al, Diabetes (2020) 69 (Supplement 1) 236–OR
Rosenstock et al, N Engl J Med (2020) 383, 2107-2116

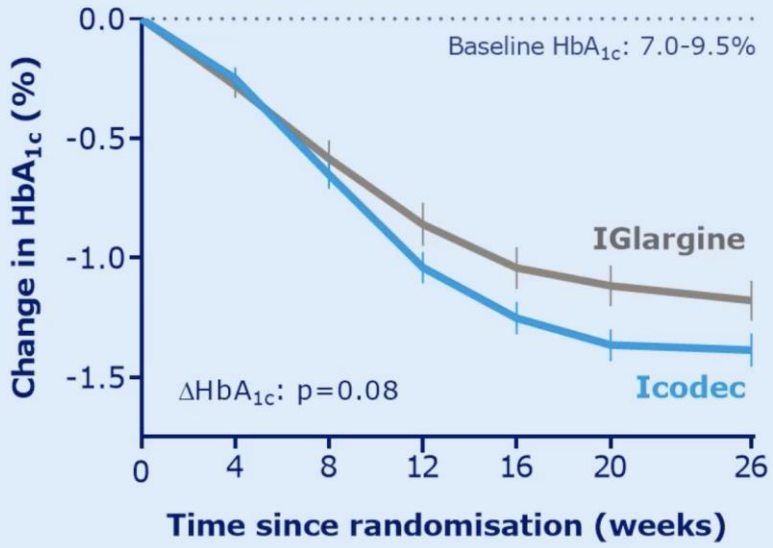
Coming soon... weekly basal insulins

First-in-class once-weekly icodec shows excellent glycaemic control in type 2 diabetes, 72% at ADA target

Albumin binding and lower receptor affinity secures a long-lived icodec depot



Once weekly icodec vs once daily glargine U100, phase 2



Rosenstock et al, N Engl J Med (2020) 383, 2107-2116

100 Years of Insulin Therapy: A long Successful Path

Concentrated Insulins

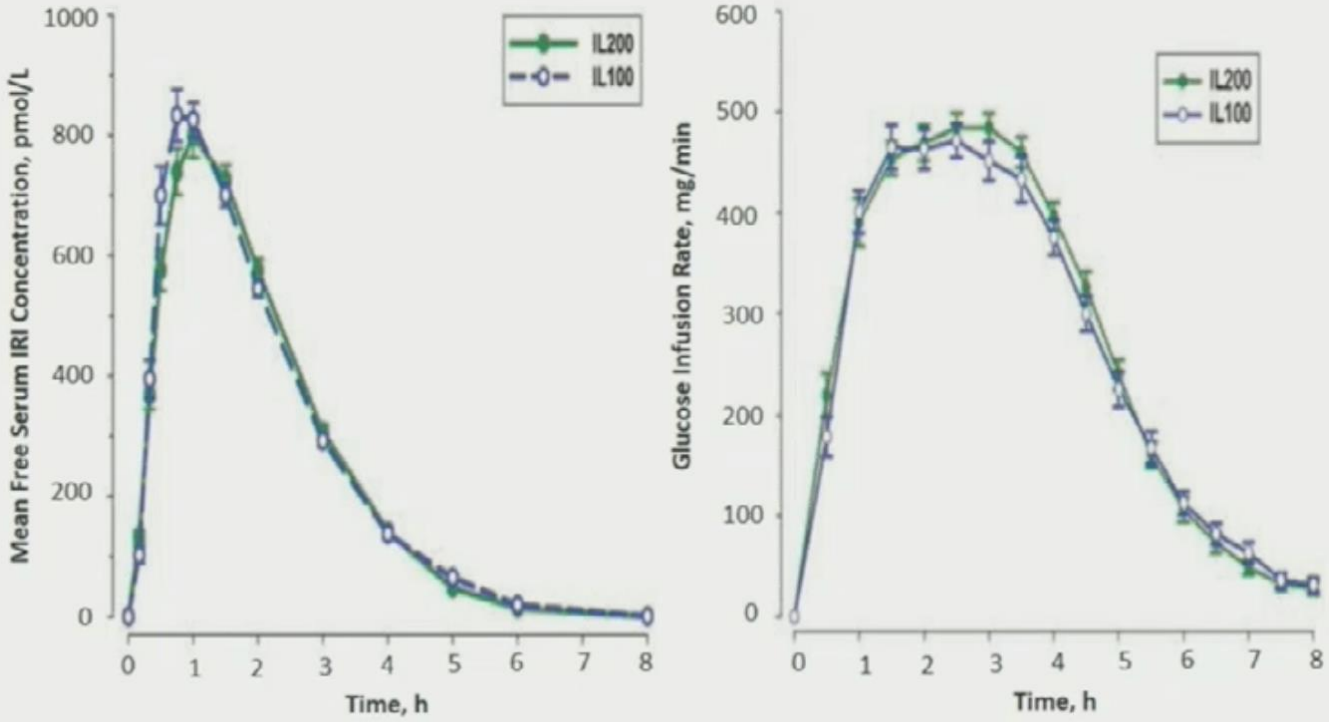
- Basal
  - Insulin degludec U-200
  - Insulin glargine U-300 (already discussed as an ultrabasal insulin)
- Bolus
  - Insulin lispro U-200
- Basal and bolus
  - U-500 human regular (now available as a pen)

Rationale for Concentrated Insulin Use

- When single dose of insulin exceeds 80 units (pen) or 100 units (syringe)
  - Physically too large for single subcutaneous administration
  - Multiple injections are required to deliver a single dose
- Increased # of injections may lead to adherence issues
- Discomfort
- Unpredictable absorption of large volume injections (rate limiting step in insulin activity)

U200 lispro

PK/PD Profiles of Lispro: U100 vs U200



De la Pena, et al. *Clin Pharmacol Drug Dev* 2016;5:69-75

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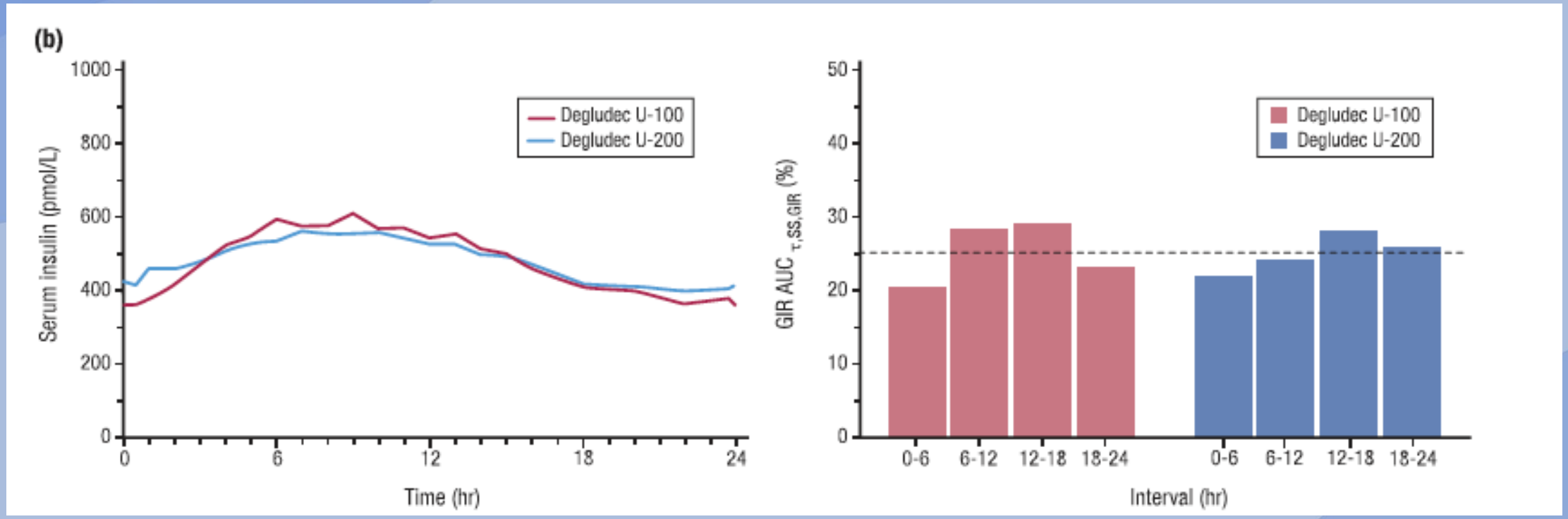
Insulin lispro (U-200)

- No difference in kinetics from U-100 lispro
  - Half-life 1 hour
  - Duration of action: 3 hours
- Available only in a pen
  - 600 units/3ml pen
  - Maximum 60 units per injection
  - Once opened 28 day shelf life
  - 2 pens per box
- Addresses the problem of frequent pen turnover.

U200 degludec



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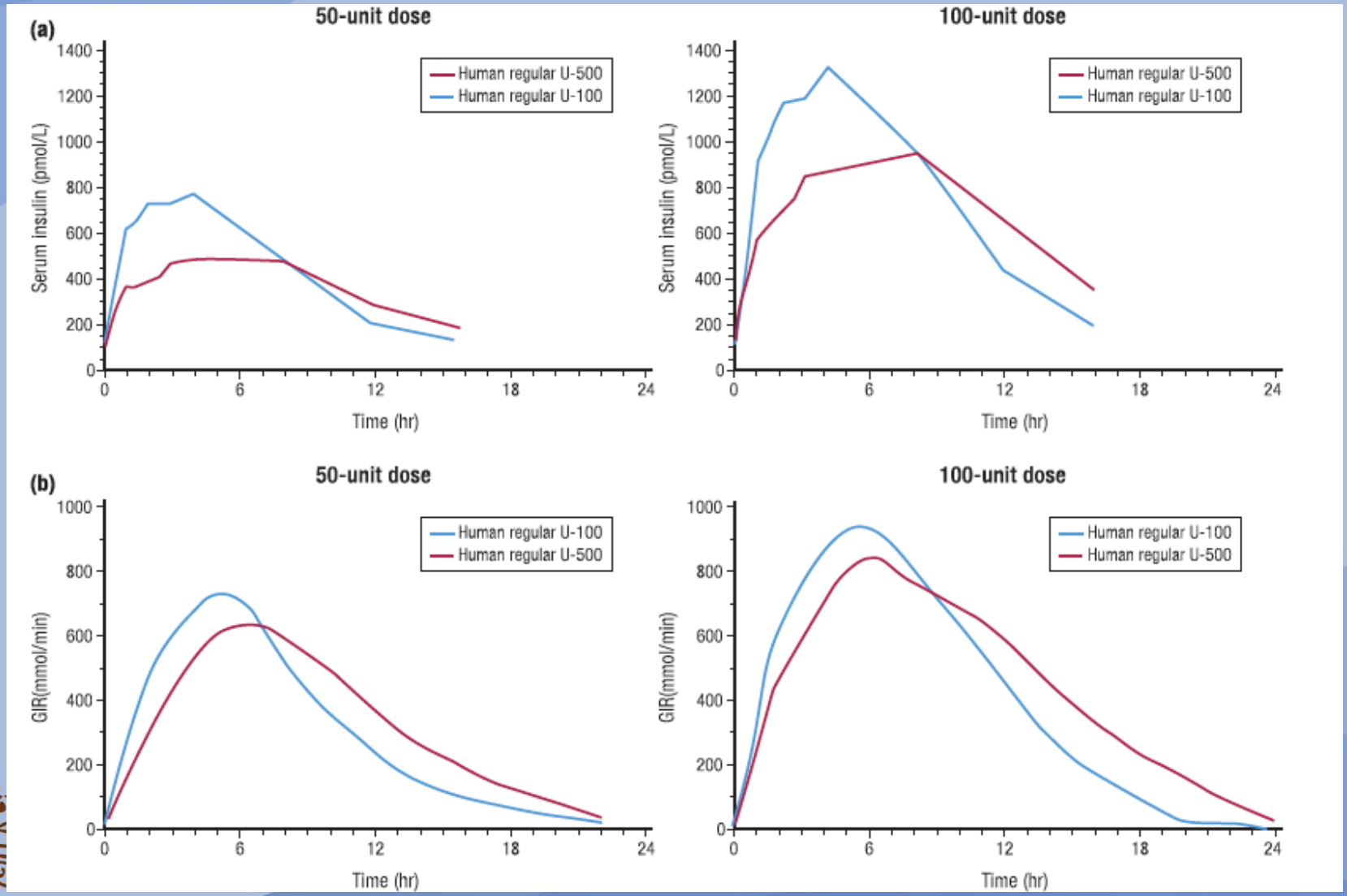
Insulin Human Regular U-500

- Characteristics
  - Five times as concentrated as U-100 insulin
  - Consider use with total daily insulin dose >200 units per day
- Pharmacokinetics/pharmacodynamics
  - Mean onset of action 30 - 35 minutes
  - Mean duration of action 21 hours (range 13 – 24)
- Clinical pearls
  - Time to onset similar to U-100 regular insulin
  - Duration of effect similar to NPH insulin
  - Has properties of pre-mixed short/intermediate acting insulin
  - Available as a pen (3ml = 1500 units/pen) or vial (20 ml = 10,000)
  - Once opened,
    - Pen: 28 day shelf-life
    - Vial: 40 day shelf-life

Humulin R U-500 Insulin PI, Eli Lilly & Company 2016

U500 regular insulin PK and PD



Regular U-100 to U-500 Dosing

- Converting from any U-100 insulin to U-500 human regular insulin
  - A1c $\leq 8\%$ $-$ *lower total daily dose by* $10 - 20\%$
  - A1c $\geq 10\%$ $-$ *consider increasing TDD by* $10 - 20\%$
- Dosing recommendations
  - BID (60:40) vs TID (40:30:30)
  - Titrate AM based upon pre-lunch and pre-dinner BG, PM based upon BG at bedtime and next AM
  - Administer at least 30 minutes before meals due to slow duration of action

Lane WS et al. Endocr Practice 2009;15:71-79
Cochran E et al. Diabetes Care 2005;28:1240-1244
Hood R et al. Endocrine Practice 2015;21:782-793

Despite advantages of insulin analogues over human insulin, it is not clinically meaningful for most patients

- Most of these are for the adequately insurance patient with good access in formularies.
- Most advantages are: compatibility with pumps, PPBS control and decreased hypoglycemia risk (specially nocturnal).
- Human insulin is ok if cost is an issue: use with caution and goals not as aggressive to prevent hypoglycemia.
- Most T2D patients can reach control with basal insulin, if used correctly with orals, decreasing the needs for complicated insulin regimens and costs.
- Individualization and patient education is the rule.

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Cost of Insulin is a Huge Problem for Many!

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Conclusions

- Modifications in the insulin molecule has lead to the development of more physiologic insulin regimens that mimics normal pancreatic insulin secretion with some advantages for our diabetic patients in need for insulin replacement.
- In those patients with adequate access to this better profile but costly insulin analogues, we should offer this opportunity. If not an option based on costs: human insulin is ok.
- Only U500 concentrated regular insulin is approved for insulin resistant patients requiring > 200 units of insulin daily.
- Discussion with patients about the mode and time of administration (vial, pen or pumps), onset, time to peak and duration of action of insulin therapy should be encouraged in daily clinical practice.
- Individualize therapy based on clinical judgement, patient characteristics and costs.

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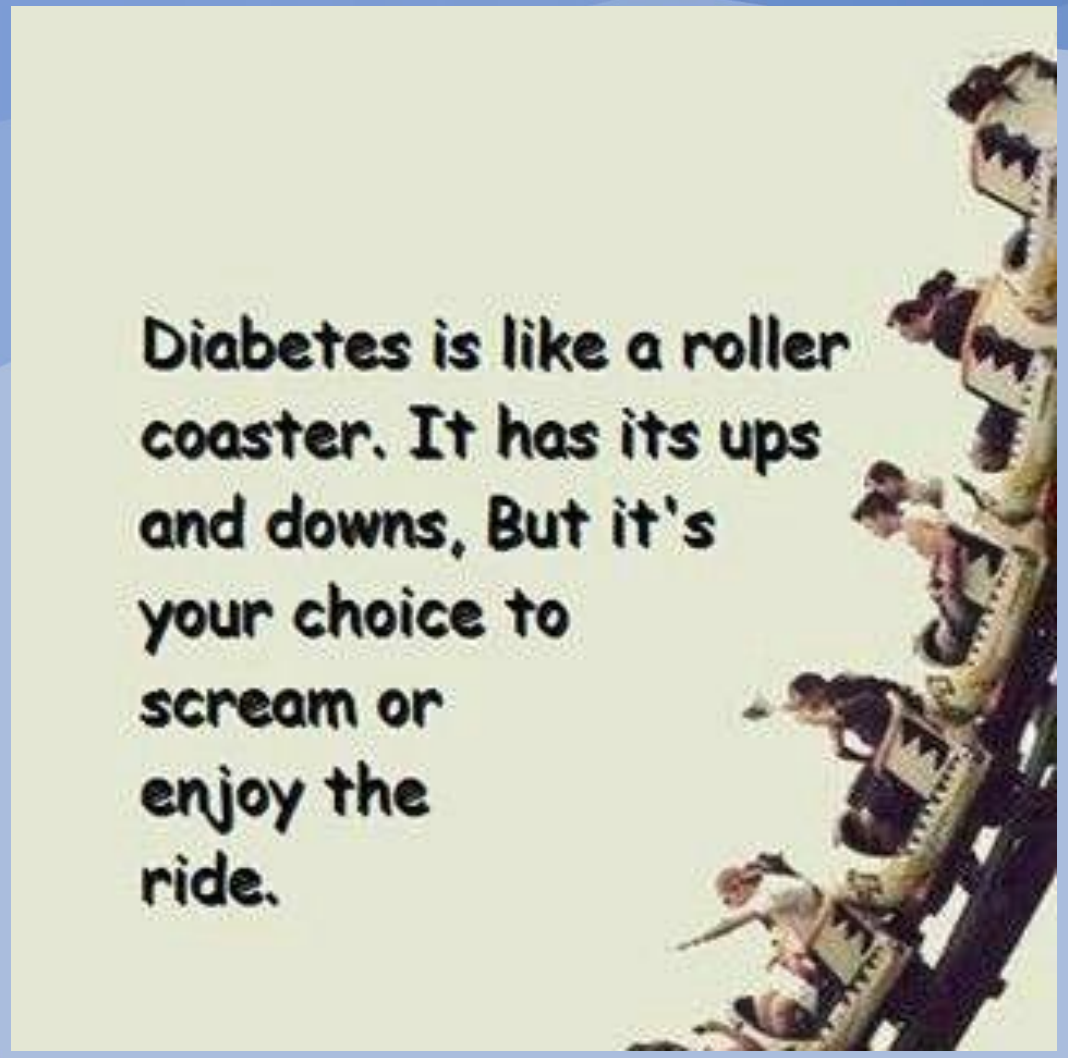

THANKS

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