AN INTRODUCTION TO INSULINS

Dr .Anahita Zakeri

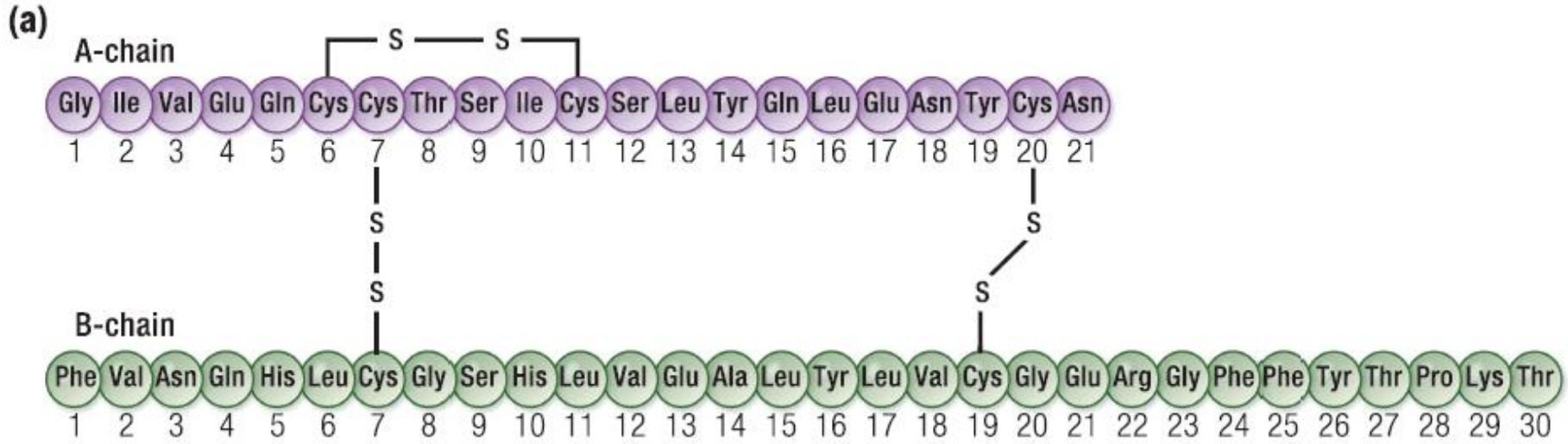
Agenda:

- INTRODUCTION
- SHORT-ACTING INSULIN
- INTERMEDIATE & LONG-ACTING INSULIN
- INSULIN MIXTURES
- CONCENTRATED INSULINS
- BIOSIMILAR INSULINS
- INDICATION OF INSULINS
- STARTING&TITRATION

INTRODUCTION

- **Human insulin**
- Basis of all modern insulin analogs/derivatives and insulin formulations
- Small protein of 51 amino acids consisting of 2 chains,
  - A-chain, composed of 21 amino acid
  - B-chain, composed of 30 amino acids.
  - Two interchain disulfide bridges covalently link chains A and B.
  - Chain A also contains an intrachain bridge

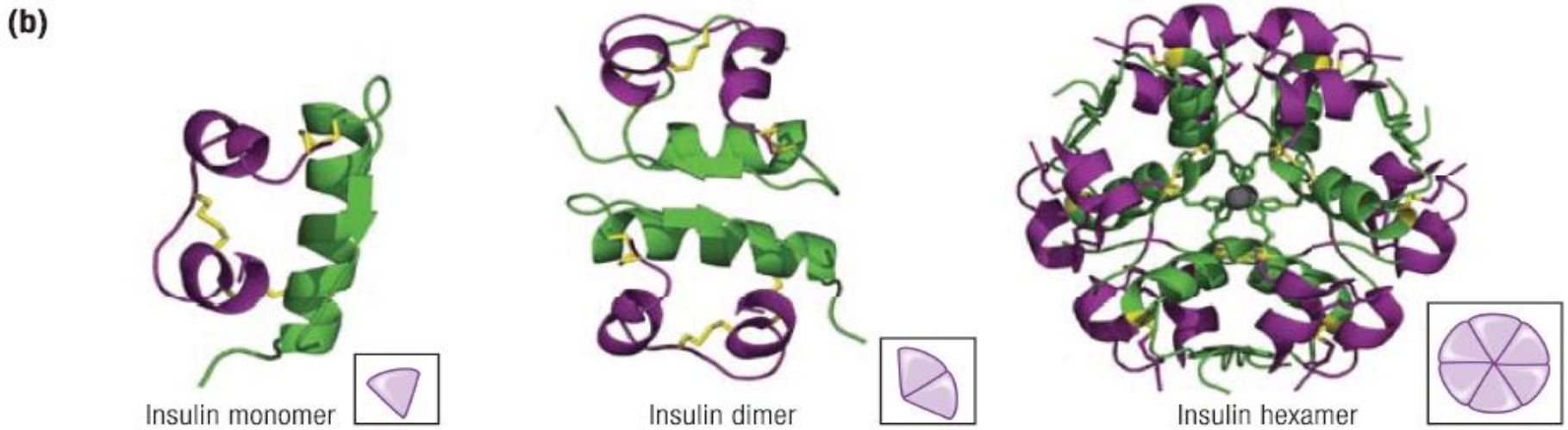
INTRODUCTION



INTRODUCTION

- Insulin is stored within the pancreatic β-cells as hexamers;
  - 6 monomers form 3 dimers
  - Assemble into hexamers
  - Stabilized by zinc ions
- When secreted
  - zinc-insulin hexamers dilute in the blood stream,
  - zinc to be released,
  - Hexamers disassembling into monomers (active state of insulin)

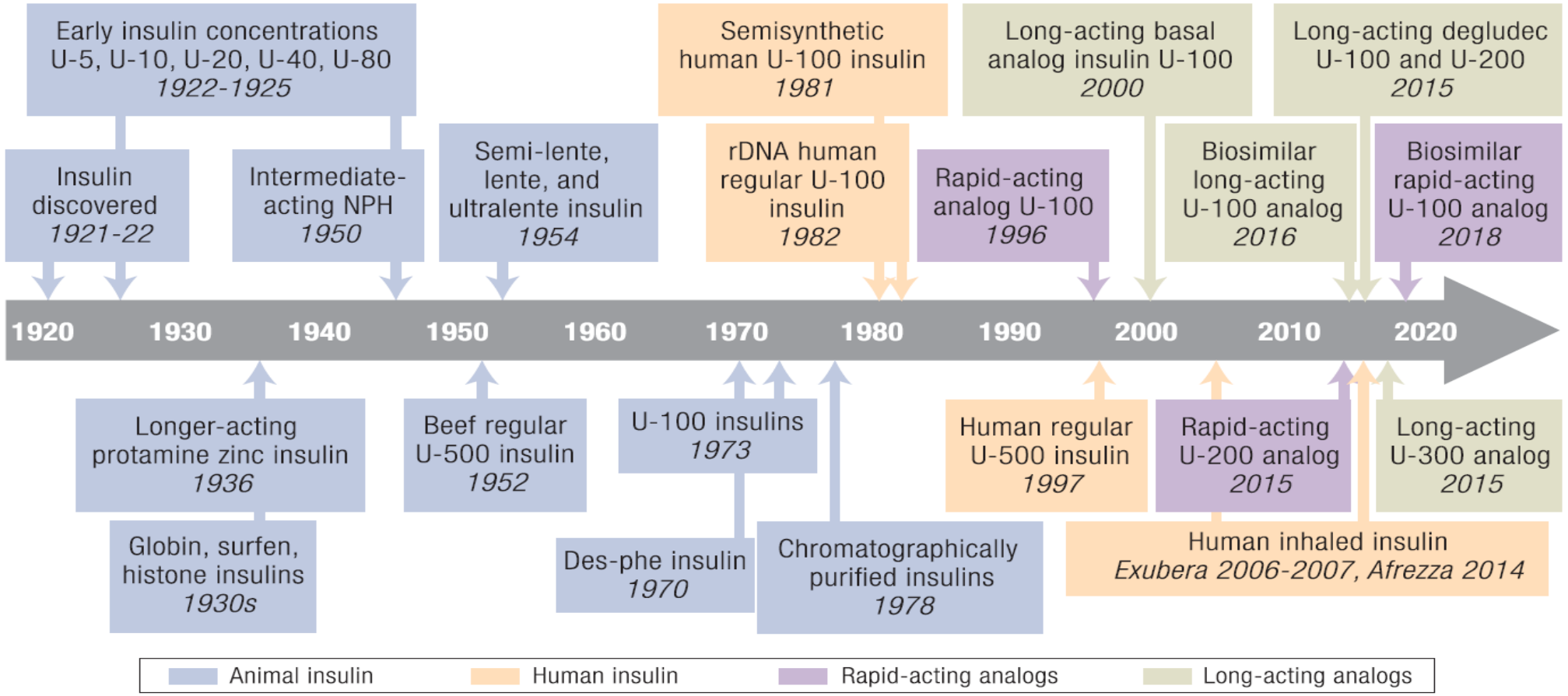
INTRODUCTION



INTRODUCTION

- ***Pharmacometric*** profiles define 3 features of the time-action profile:
- Onset of action
  - Time after injection when blood glucose-lowering activity is observed
  - Only insulin monomers (perhaps dimers) can pass through capillary walls
  - dependent on the strength of the interactions that bind the insulin hexamers together in the SC environment
- Time to peak
  - Time after the injection to reach maximum effect
- Duration of action
  - How long after injection the insulin action lasts.

INTRODUCTION



SHORT-ACTING INSULIN

SHORT-ACTING INSULIN

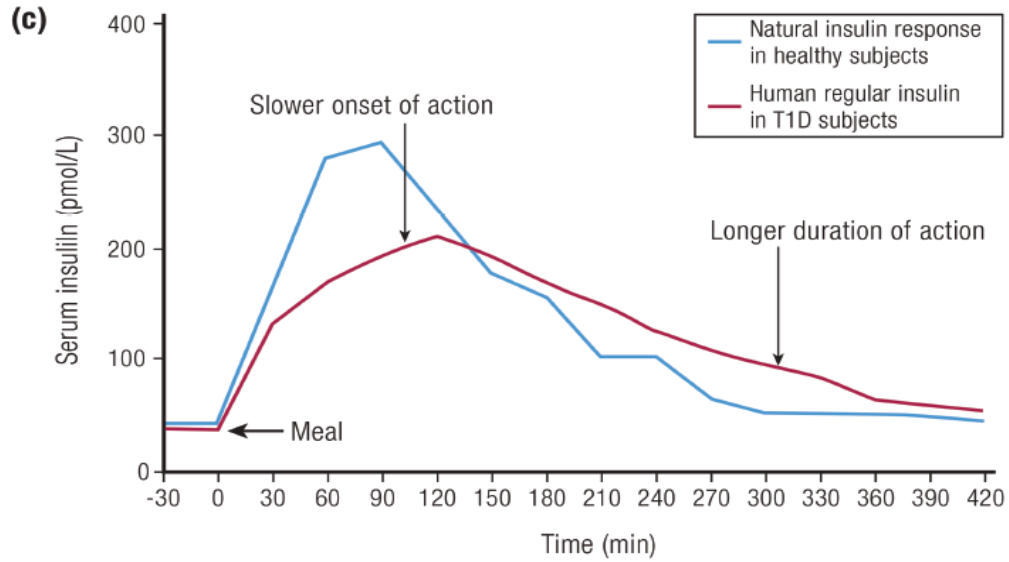
Table 1. Time-action of rapid-acting insulin analogs versus human regular insulin.

Insulin Type	Brand name	Onset of Action (min)	Peak Action (hr)	Duration of Action (hr)
Short-acting				
Human regular insulin	Humulin® R Novolin® R Insuman® R	30–60	2–4	5–8
Rapid-acting				
Insulin lispro	Humalog®, Admelog	15–30	0.5–2.5	≤5
Insulin aspart	Novolog® (26)	15	1–3	3–5
Insulin glulisine	Apidra®	12–30	1.5	~5.3
Faster rapid-acting				
Faster insulin aspart	Fiasp® (30)	~16–20	~1.5–2.2	~5–7
Inhaled human insulin	Afrezza® (34)	~12	0.5–0.9	1.5–3

SHORT ACTING INSULINS

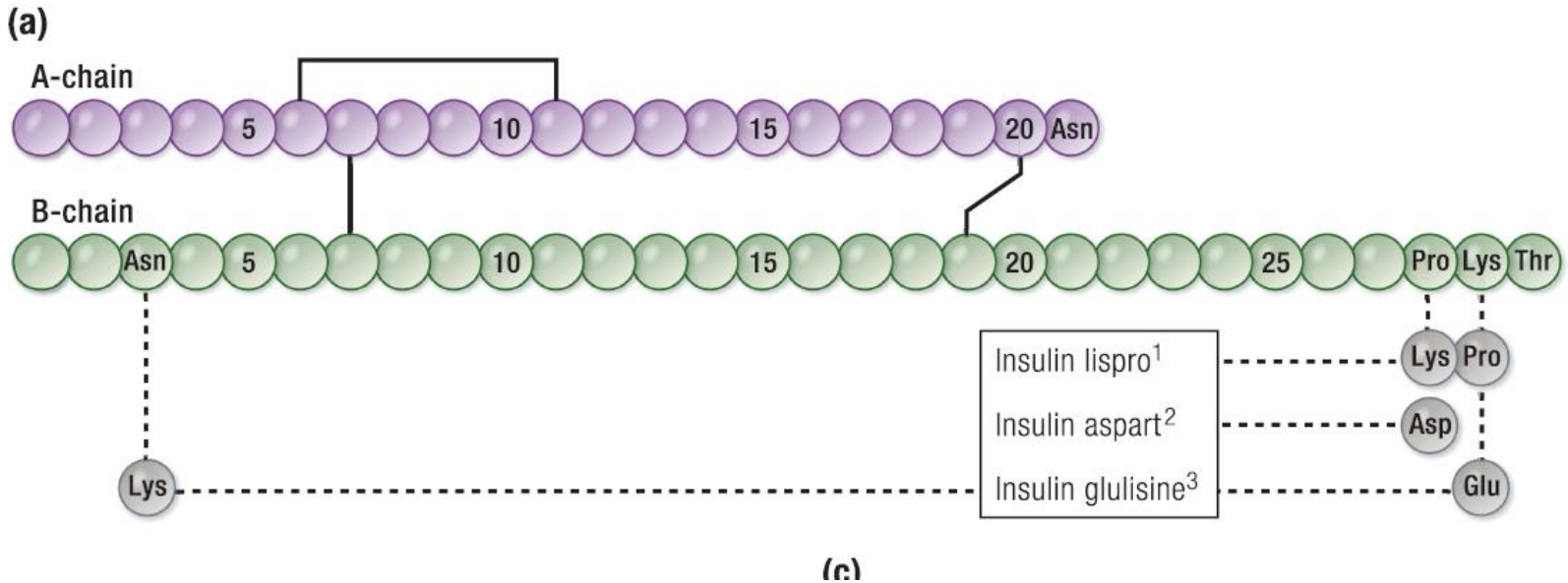
biosynthetic human insulin

- Discovery of the insulin gene and commercialization of recombinant DNA technology
  - large-scale manufacturing of biosynthetic human insulin(REGULAR)
- Even with human insulin,
  - Low titers of anti-insulin antibodies in most patients
  - Without consequence



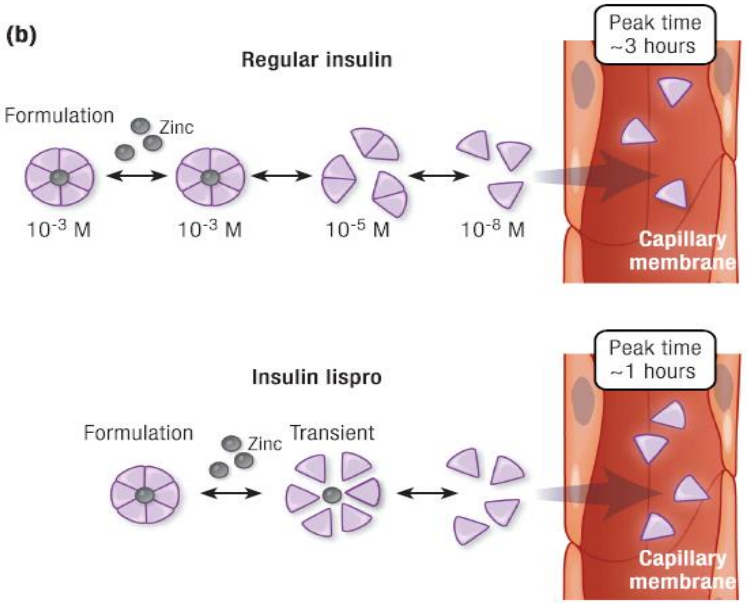
SHORT-ACTING INSULIN

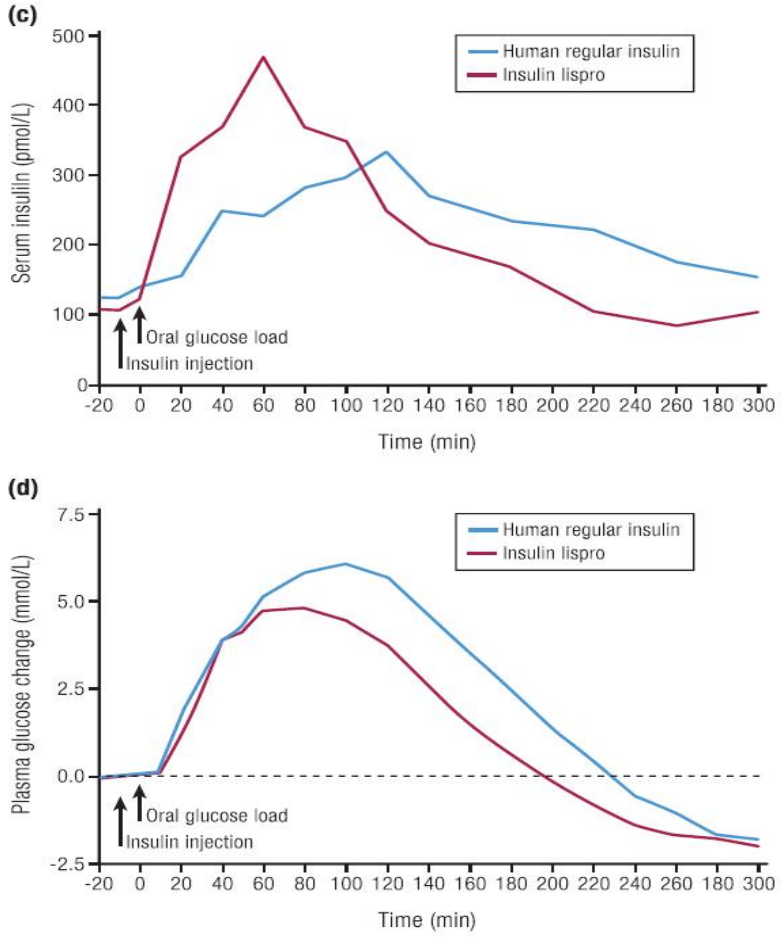
Rapid-acting Analog Insulins



SHORT-ACTING INSULIN

Rapid-acting Analog Insulins





SHORT-ACTING INSULIN

ULTRA-RAPID ACTING INSULINS

- Inhaled insulin
  - Approved in 2014
  - Recombinant human ***regular*** insulin (Not an analog)
  - Formulated as a dry powder to be inhaled
  - Compared with both regular insulin or rapid-acting analog
    - Rapid onset of action
    - Quick time to peak action
    - Shorter duration of action

INTERMEDIATE & LONG-ACTING INSULIN

INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs

Table 2. Time-action of intermediate-acting and long-acting insulins (100 U/mL).

Insulin Type	Brand name	Onset of Action (hr)[a]	Peak Action (hr)	Duration of Action (hr)
Intermediate-acting U-100				
NPH insulin	Humulin® N (40), Novolin® N (41)	1–2	2–8	14–24
Long-acting U-100				
Insulin glargine	Lantus® (43), Basaglar®	NA	No pronounced peak	24
Insulin detemir	Levemir® (52)	NA	No pronounced peak	7.6–>24
Insulin degludec	Tresiba® (59)	NA	No pronounced peak	42

[a] The onset of action is not relevant for long-acting insulins.

INTERMEDIATE & LONG-ACTING INSULIN

NPH

- NPH insulin
  - Made with human regular insulin
  - Precipitate with protamine and zinc
  - Protamine
    - Obtained from the semen of trout
    - Positive-charged protein
    - Crystalizes with insulin hexamers, causing precipitation
    - Result in a suspension formulation

INTERMEDIATE & LONG-ACTING INSULIN

NPH

- When injected
  - Protamine/insulin crystals dissolve slowly,
  - Delaying the dissociation of insulin hexamers
  - Slowing the absorption of Insulin monomers into circulation
- Needs resuspended by rolling 12 to 15 times prior to injection
- If not,may cause day-today variability
- Duration of action of 13 hours
- Not sufficient to mimic daily physiological basal insulin
- Needs to be administered twice-daily

INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs

- Insulin glargine
  - First approved in the US in 2000
  - Differs from human insulin in :
    - Amino acid asparagine in position A21 was substituted with glycine
      - chemical stability in a low pH solution
    - 2 arginine residues added at positions B31 and B32
      - Shifted the isoelectric point to near neutral
  - Upon injection into the neutral pH SC space,
    - Undergoes pH-induced precipitation
  - pH-induced precipitate dissolves slowly
    - time-action profile with a flattened peak
    - median duration of action of up to 24 hours

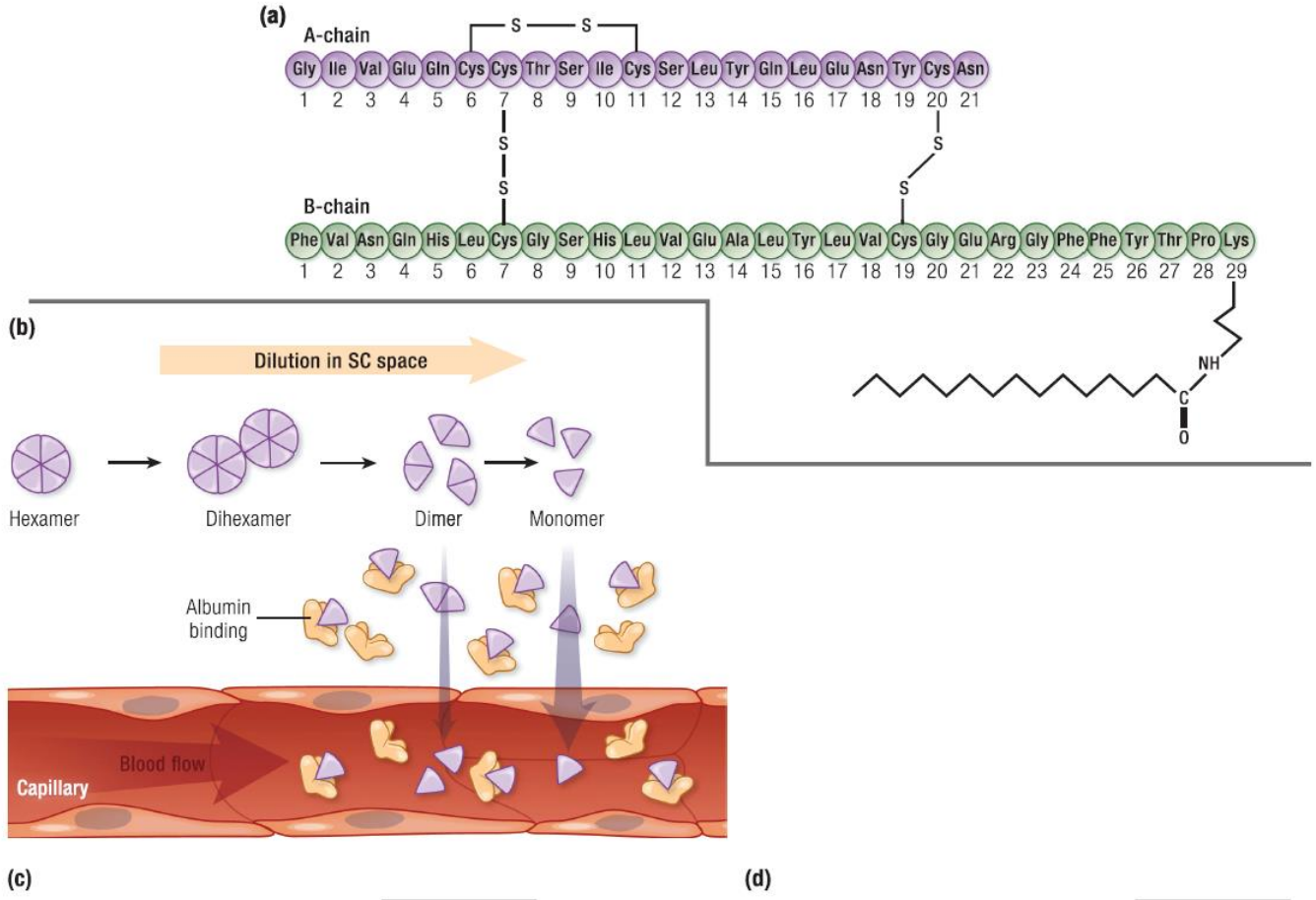
INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs

- Insulin detemir
  - Approved in 2005
  - Insulin detemir molecule has
    - Amino acid threonine at B30 omitted
    - 14-carbon fatty acid covalently attached to the lysine at B29
  - Formulated as a solution of hexamers at neutral pH.
  - After injection Fatty acyl side chain
    - Stabilizes the hexamers
    - Promotes self-association of hexamers to dihexamers.
      - Prolongs persistence at injection site
    - Also enables binding to serum albumin
      - Slowing the disposition of detemir to peripheral tissues
      - Slowing Clearance from the body
      - Reduced Injection to-injection glycemic variablity

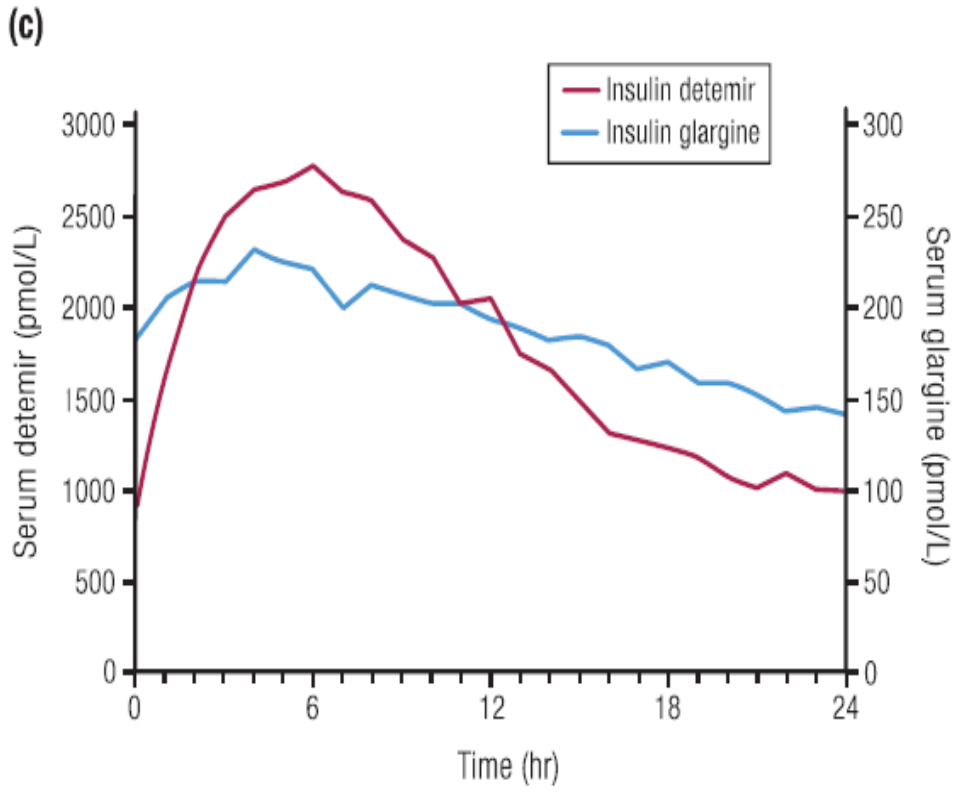
INTERMEDIATE & LONG-ACTING INSULIN

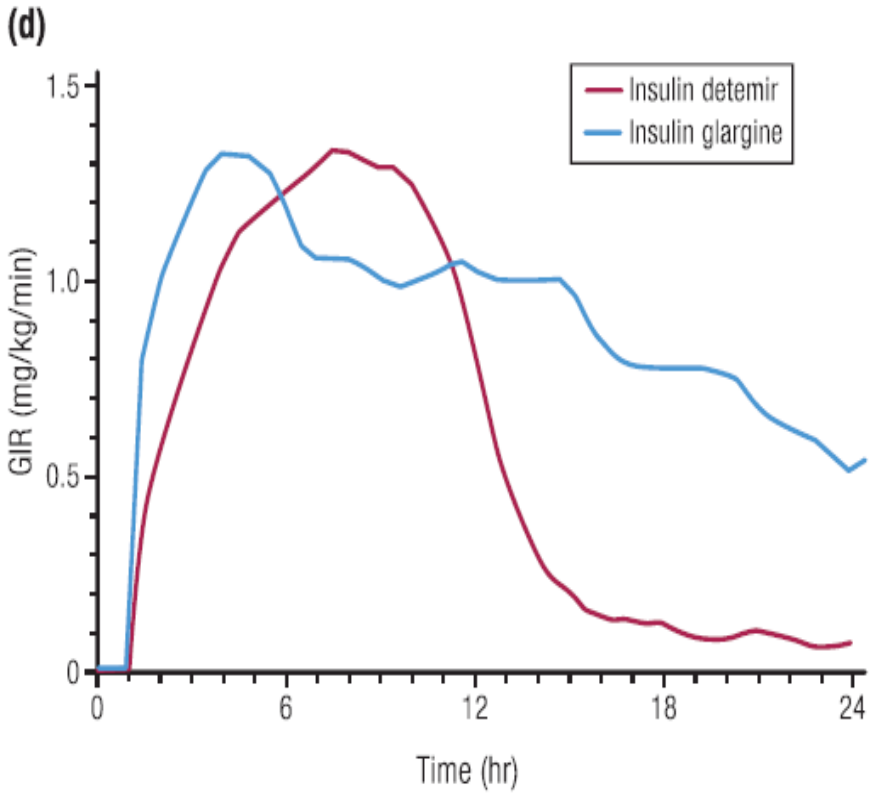
Long-acting insulin analogs



INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs





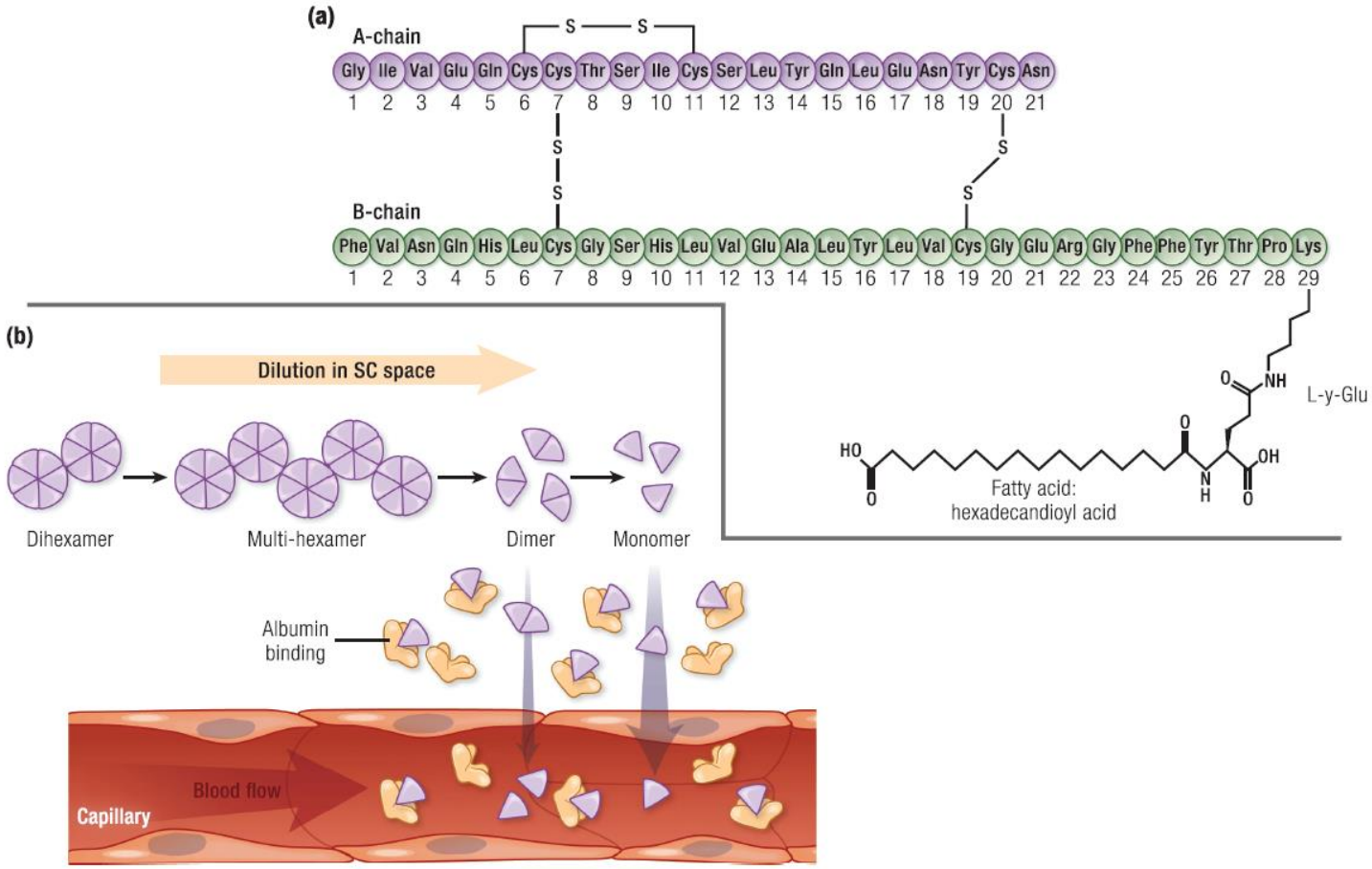
INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs

- Insulin degludec
  - Approved by the FDA in 2015
  - longest-acting insulin analog in the market today.
  - duration of action of at least 42h at steady state
- In insulin degludec molecule,
  - B30 threonine is omitted
  - side chain is attached to the B29 lysine consisting of
    - glutamic acid
    - 16-carbon fatty acid with a terminal carboxylic acid group
    - Promotes association into dihexamers under formulation conditions.
- After injection
  - dihexamers self associate, forming multihexamer complexes
  - binding of monomers to albumin in the circulation also
    - slows the disposition to peripheral tissues
    - slows Clearance from the body

INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs



INTERMEDIATE & LONG-ACTING INSULIN

Long-acting insulin analogs

- Overall, time-action profiles of long-acting insulin analogs
  - Flattened peaks
  - Prolonged duration of action,
  - Better mimicks endogenous basal insulin secretion compared to intermediate-acting insulins,
  - Reduce the risk of hypoglycemia

INSULIN MIXTURES

- Premixed insulins can be based on
  - Human insulins
    - NPH insulin (70%) combined with regular insulin (30%).
    - Needs to be injected 30 to 45 minutes before the meal
  - Analog insulins
    - Mixtures of insulin lispro,with its protamine suspension, neutral protamine lispro (NPL)
      - 75/25(Mix 75/25)
      - 50/50 percent (Mix 50/50)
    - Insulin aspart, with its protamine suspension (70/30)
    - Mixture of aspart (30%)with degludec (70%)

CONCENTRATED INSULINS

- Rising number of people requiring high doses of insulin
  - Due to obesity and type 2 diabetes
- **Concentrated Insulins** deliver more insulin with
  - Lower volume
  - Fewer injections
  - Less pain at the injection site
  - Potentially improving adherence

CONCENTRATED INSULINS

- Switching from a U-100 insulin to concentrated insulin
  - Requires knowledge of the bioequivalence of the concentrated insulin to its U-100 counterpart
- Bioequivalence implies
  - Equivalent efficacy (PK and PD) when delivering the same units in a reduced volume
- Bioequivalent insulins:
  - U-200 and U-100 insulin lispro
  - U-200 and U-100 insulin degludec
  - Volume of insulin can be reduced by 50% for U-200 with similar results
- Not Bioequivalent insulins
  - U-300 and U-100 Insulin glargine
  - U-500 and U-100 Insulin regular

CONCENTRATED INSULINS

- Insulin glargine U-300 (300 U/mL)
  - Approved in 2015
  - Higher concentration of glargine in the same volume
  - Further slows the dissolution of glargine precipitate
  - Leading to a better basal insulin
- Concentrated U-300 compared to U-100
  - Lower peak
  - Longer duration of action

CONCENTRATED INSULINS

- Glucose-lowering effects of U-300 insulin glargine
  - lower than U-100 insulin glargine at the same dose level
- For the same glycemic effect : In a study
  - In type 1 diabetes, subjects needed 17.5% more U-300 than U-100 insulin glargine
  - in type 2 diabetes, subjects needed an average of 12% more U-300 than U-100
- 20% dose reduction is recommended when switching from U-300 to U-100 insulin glargine

CONCENTRATED INSULINS

- U-500 R
  - Similar onset and time to peak action
    - Provides prandial (mealtime) coverage
  - lower peak action
  - Prolonged duration of action
    - Provides basal insulin properties
  - Facilitates its use as insulin monotherapy,
  - Improve HbA1c in patients with type2 DM inadequately controlled on high doses of U-100R therapy (> 200 units/day)

When is Insulin Appropriate?

- A1C>10% or blood glucose levels >300 mg/dL
- Any time glycemic control is inadequate on other therapies
- Type 1 DM is suspected
- Ongoing metabolic catabolism
  - Weight loss
  - Ketosis
  - Very high triglycerides
- Pregnancy

American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

When to introduce insulin therapy

A1C persistently above target

↓

Lifestyle
Patient compliant with agreed modifications?
Any further modifications that can be considered?

Oral hypoglycaemic medication
Is patient taking as prescribed?
Can these be maximised further?

Secondary causes for hyperglycaemia?
Medications (e.g. contraceptive pill, thiazides,beta-blockers, oral corticosteroids) Medical conditions (e.g. hyperthyroidisim, urinary or dental infections, occult malignancy)

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A1C still above target — Initiate insulin

Starting and Titration of Basal Insulin

Every 24 hour long-acting insulin OR bedtime intermediate-acting insulin

Daily dose: 10 units or 0.1-0.2 units/kg/day

Check FBG daily

Increase dose by 2-3 units every 2-3 days until FPG at desired goal

Check FBG daily

In the event of hypoglycemia or FPG level <70 mg/dL:

Reduce insulin dose by 4 units, or by 10-20%

OR

Check FBG daily

Treat to Target

FPG over last 2-3 days	Basal Insulin Adjustment
>180mg/dl	+8 units
140-180	+6 units
120-140	+4 units
100-120	+2 units
Below goal	-2 to -4 units

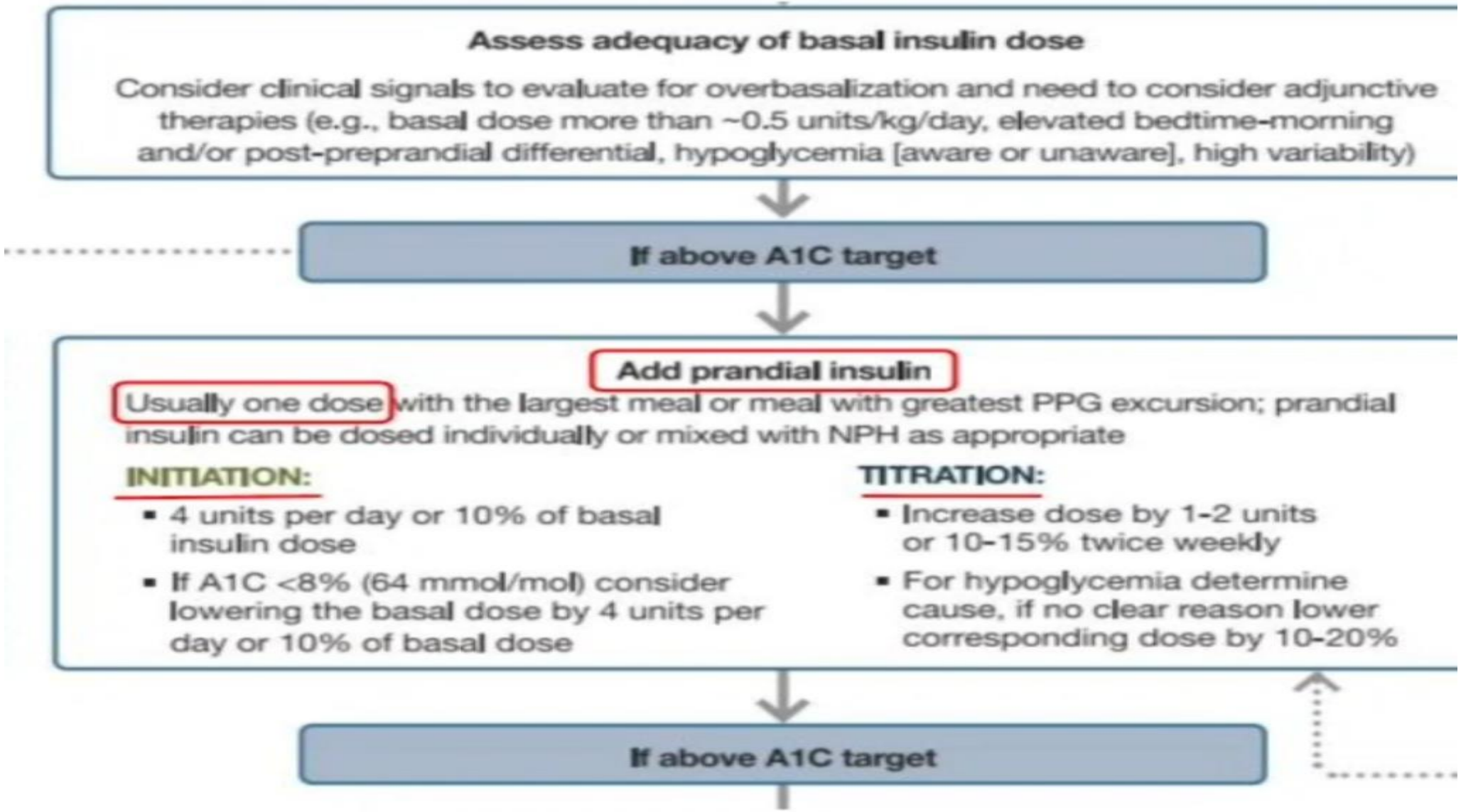
American Diabetes Association. *Diabetes Care*. 2021

Basal Insulin Goals

1. Control Fasting Plasma Glucose Levels

2. Avoid overbasalization
   -Reassess benefit if >0.5 units/kg
   -Bedtime SMBG to AM SMBG is a high number

3. Consistent FPG readings (Low Fasting Glucose Glycemic Variability



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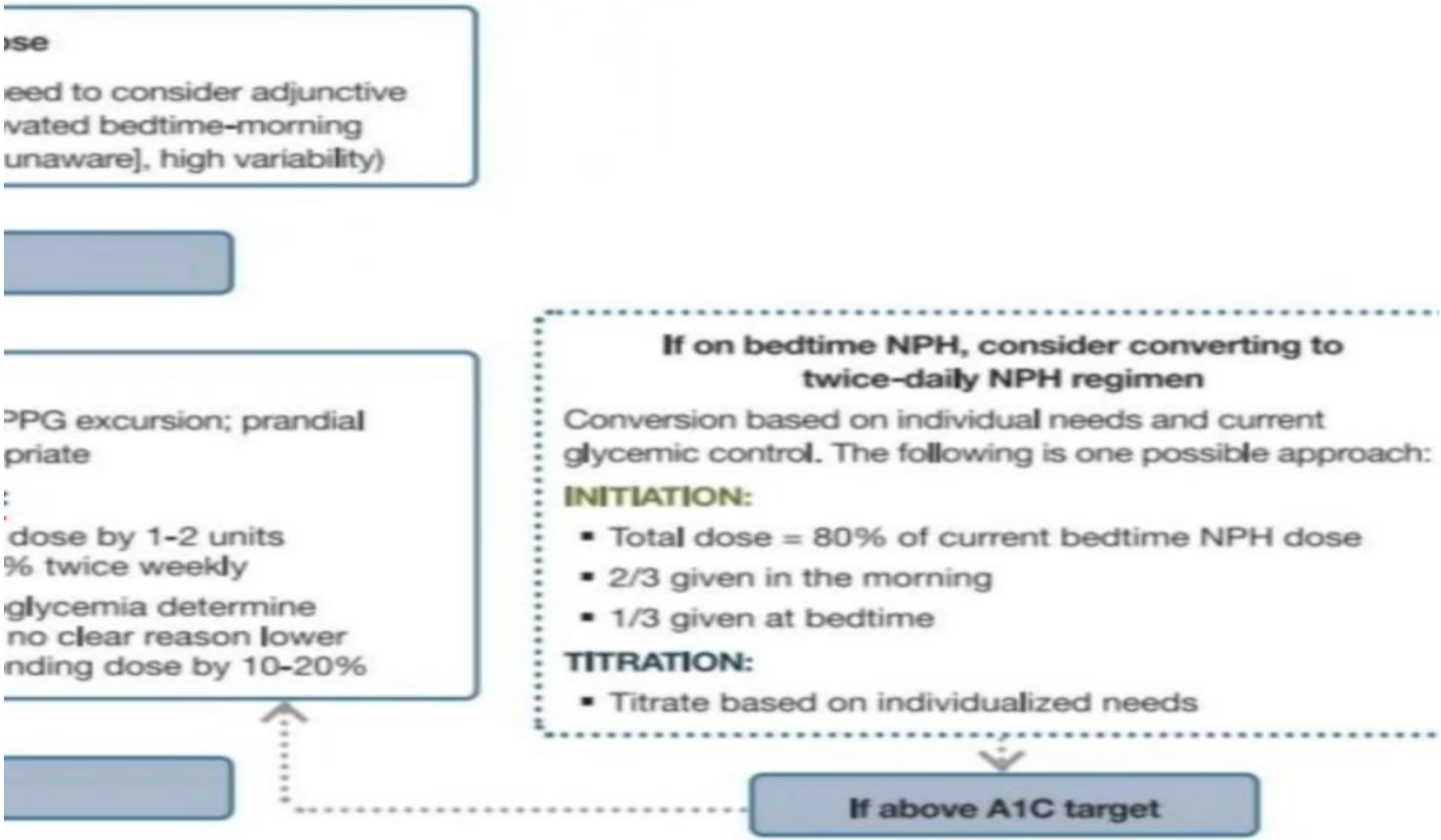
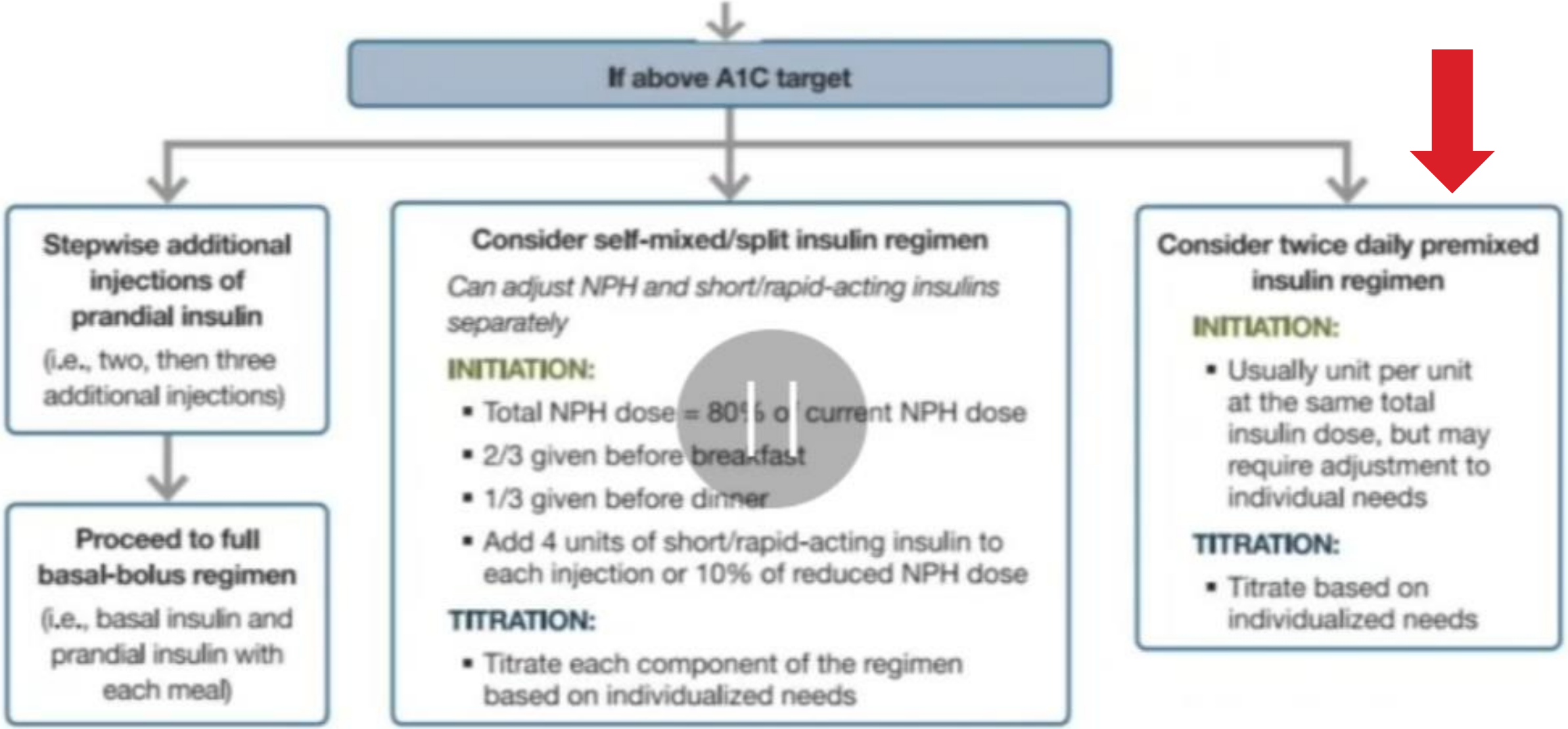


ommittee. *Diabetes Care* 2022;45(Suppl. 1):S125-S143



American Diabetes Association Professional Practice Committee. Diabetes Care 2022;45(Suppl. 1):S125-S143

OD to BID

- **Split the OD dose into equal breakfast and dinner doses (50:50)**
- Titrate the doses preferably once a week according to the algorithm
- Discontinue sulphonylureas
- Continue metformin
- Consider discontinuing TZDs as per local guidelines and practice
- Administer BIAsp 30 just before meals

BID to TID

- **Add 2–6 U** or **10% of total dail BIAsp 30 dose** before lunch
- Down-titration of morning dose (-2 to -6 U) may be needed after adding the lunch dose
- Titrate the doses preferably once a week according to the algorithm
- Continue metformin
- Consider discontinuing TZDs as per local guidelines and practice
- Administer BIAsp 30 just before m

* mg/dL Pre-breakfast/pre-dinner value	dose adjustment (Units) Pre-dinner/pre-breakfast dose change
<80	-2
80–130	0
131–160	+2
161–180	+4
>180	+6

ne recommended target for titration is pre-meal value of 80-130mg/dl, pre-breakfast dose if titrated based on pre-dinner values and vice-versa

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