Insulin and Insulin analogues

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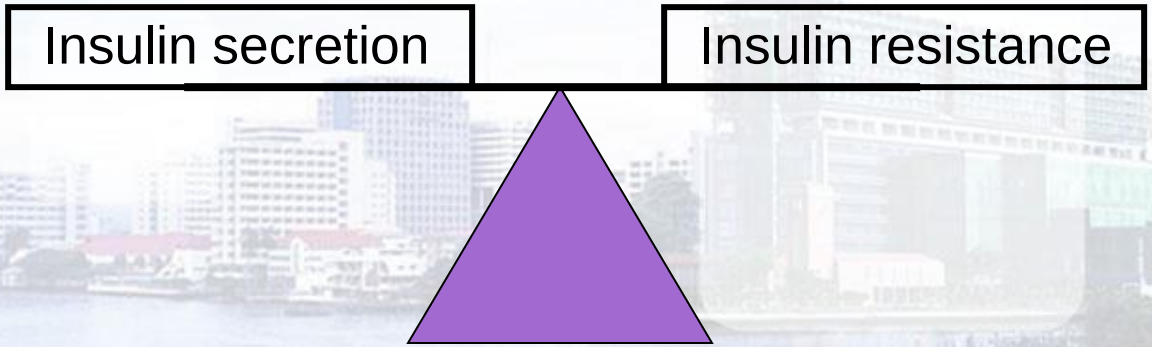
Insulin

- The oldest and best studied treatments for diabetes mellitus
- Can be used to treat patients with all types of diabetes



Insulin

- amino acid peptide hormone
- synthesized and secreted by pancreatic beta cells
- stimulate insulin release: glucose, vagal stimulation, sulfonylurea drugs
- Inhibitors of insulin release: Alpha-adrenergic effect, Somatostatin, Drugs (Phenytoin, Vinblastin)

Proinsulin

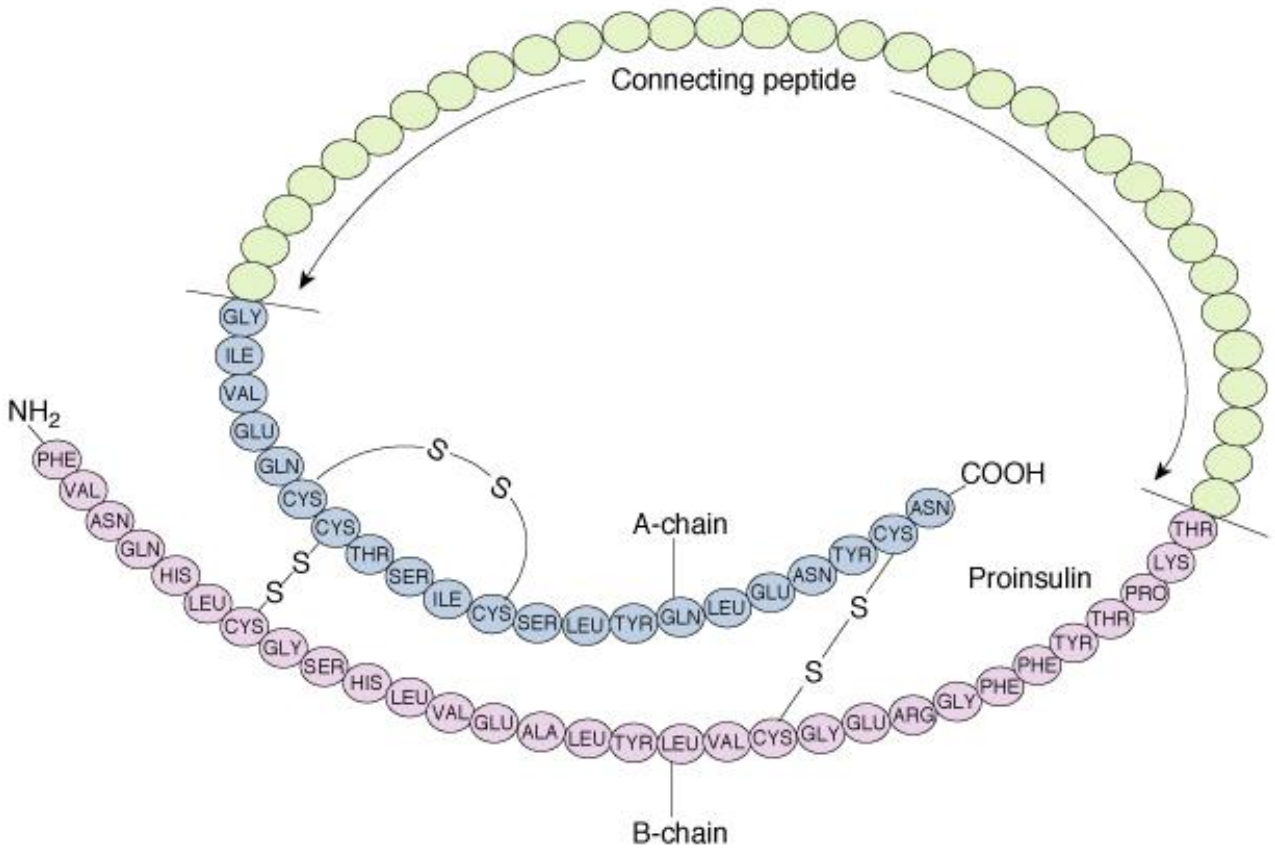


Figure 43-3 Structure of proinsulin. With removal of the connecting peptide (C-peptide), proinsulin is converted to insulin.

Indications for Insulin Therapy

- All patients with type 1 DM
- Type 2 DM that failure to achieve glycemic control with diet, exercise, and oral medications
- Acute illness or surgery
- Pregnancy
- Glucose toxicity (DKA,HHNS)
- Renal and hepatic disease

Physiology

- Basal insulin is secreted at an approximate rate of 0.5-1.0 U/h
- Postprandial insulin is released in a transient 2 to 5 minute burst (first phase)
- A slow but progressive increase in insulin secretion for 5-52 minutes (second phase)
- Insulin concentrations return to basal levels within 2-4 hours of a meal

Classifications of Insulin

1. แบ่งตามระยะเวลาในการออกฤทธิ์ : rapid, short, intermediate, long, very long acting
2. แบ่งตามวัตถุประสงค์ในการออกฤทธิ์ : basal, prandial insulin
3. แบ่งตามกลวิธีการผลิต : conventional insulin, insulin analogues

Major types of insulin (duration)

- Rapid-acting insulin
- Short-acting insulin
- Intermediate-acting insulin
- Long-acting insulin
- No peak insulin (Very long-acting)
- Pre-mixed (Combination) insulin

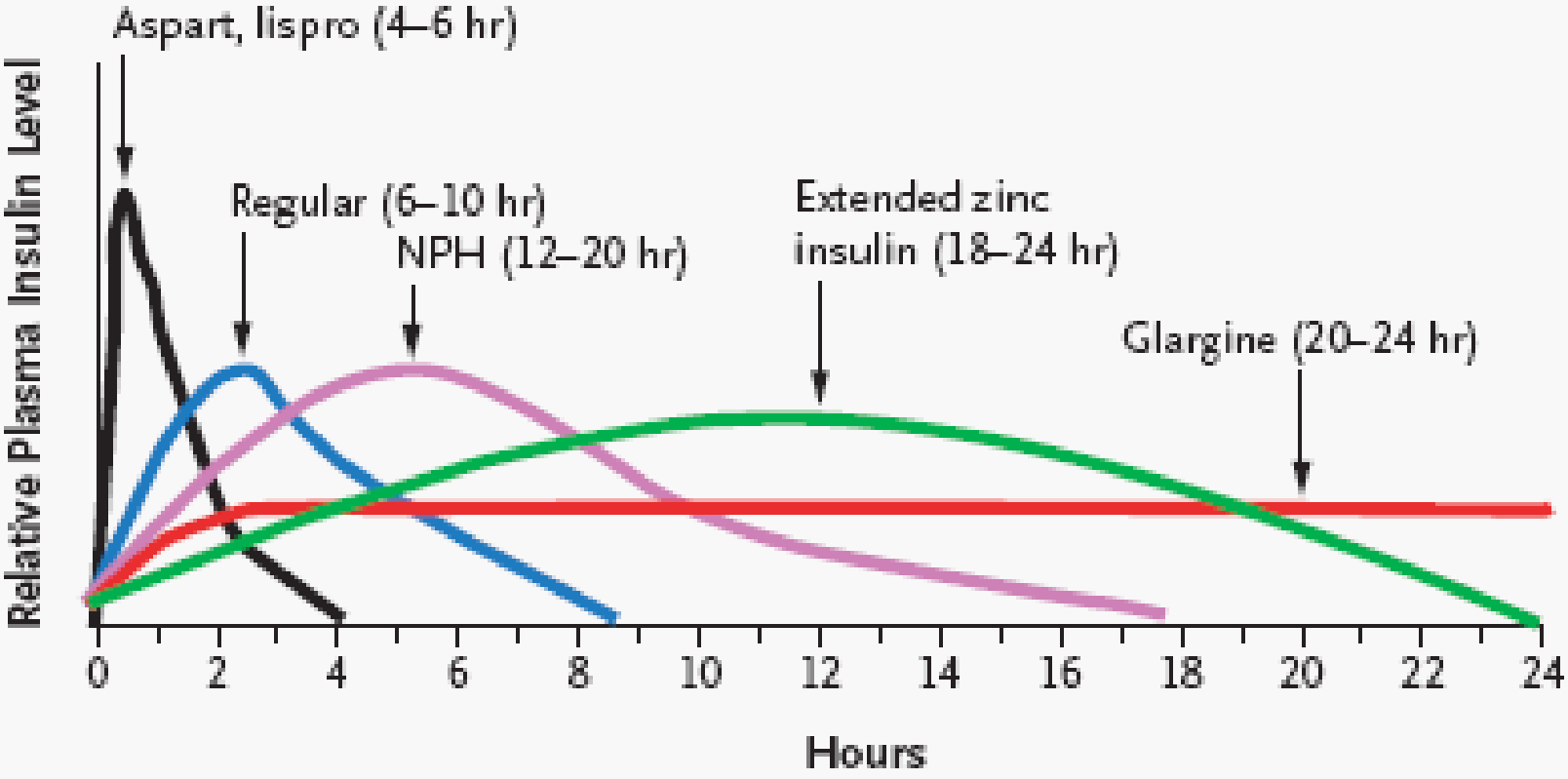


Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

Insulin Preparations (purpose)

1. **Basal Insulin** (Basal supplement)
2. **Prandial Insulin** (Premeal bolus dose)

Insulin Preparations (purpose)

Basal Insulin

- As a **basal supplement**
- intermediate- to very long-acting preparation (NPH, lente, ultralente, or glargine)
- suppress hepatic glucose production and maintain near normoglycemia in the fasting state

Insulin Preparations (purpose)

Prandial Insulin

- As a **premeal bolus doses**
- rapid-acting (regular or short-acting) or very-rapid-acting (lispro, aspart) insulin
- cover the extra requirements after food is absorbed

Insulin Preparations (Methods)

- Conventional insulins (Human Insulin)
- Insulin analogues

Conventional insulins preparations

- short-acting regular insulin, intermediate-acting insulins (NPH insulin) and long-acting insulin (insulin ultralente)
- limitations in the time-action profile

Insulin Analogues

- recombinant DNA technology
- overcome the limitations of conventional insulins
- simulate physiological insulin profiles
- Rapid-acting insulin analogues: insulin lispro, insulin aspart and insulin glulisine
- Basal insulin analogues: insulin glargine and insulin detemir

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Conventional Insulins

Short-acting insulin

- Regular Insulin (RI)
- Pk after subcutaneous injection
  - ❖ Onset: 0.5-1 hours
  - ❖ Peak effect: 2-3 hours
  - ❖ Duration: 8-12 hours
  - ➢ **IV or IM in diabetic emergency**

Short-acting insulin

- Injected 30-60 minutes before a meal
- inconvenient for most patients
- insulin concentration falls slowly after peaking

Intermediate-acting insulin

- Isophane insulin suspension or Neutral Protamine Hagedorn **(NPH)**
- Addition protamine to regular insulin: slowly absorbed

❖ Onset: 1-1.5 hours

❖ Peak effect: 4-12 hours

❖ Duration: 24 hours

Intermediate-acting insulin

- distinct peak and trough effect
- wide variations in blood glucose
- two or more injections a day (basal insulin)

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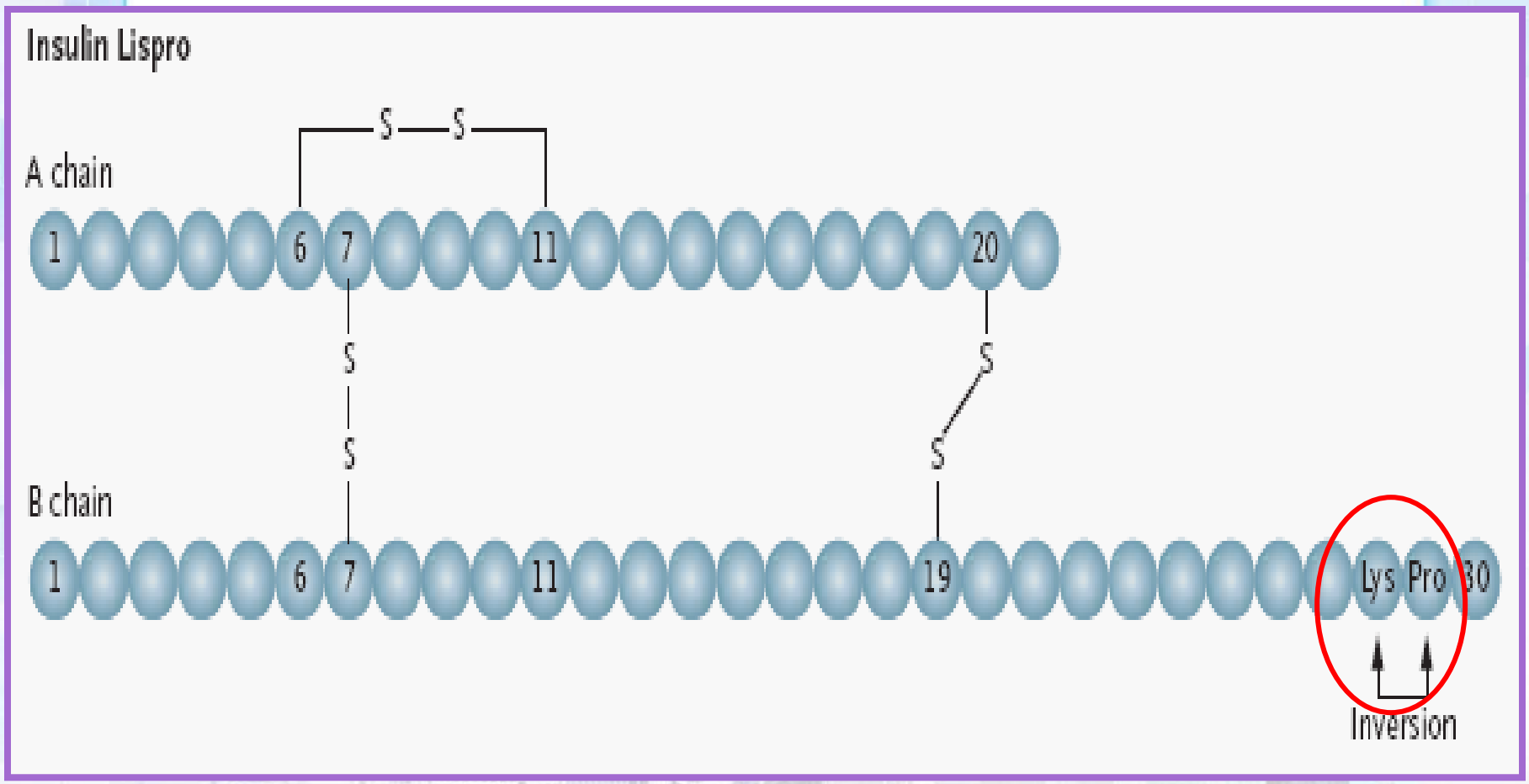
Insulin Analogues

Rapid-acting insulin

- Insulin lispro
- Insulin aspart
- Insulin glulisine

Insulin lispro

- substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain
- injected 5-15 minutes before a meal or immediately after a meal
- better postprandial glucose control and less frequent late hypoglycaemia


Insulin Lispro
S
S
A chain
1
6
7
11
20
S
S
S
B chain
1
6
7
11
19
Lys
Pro
30
Inversion

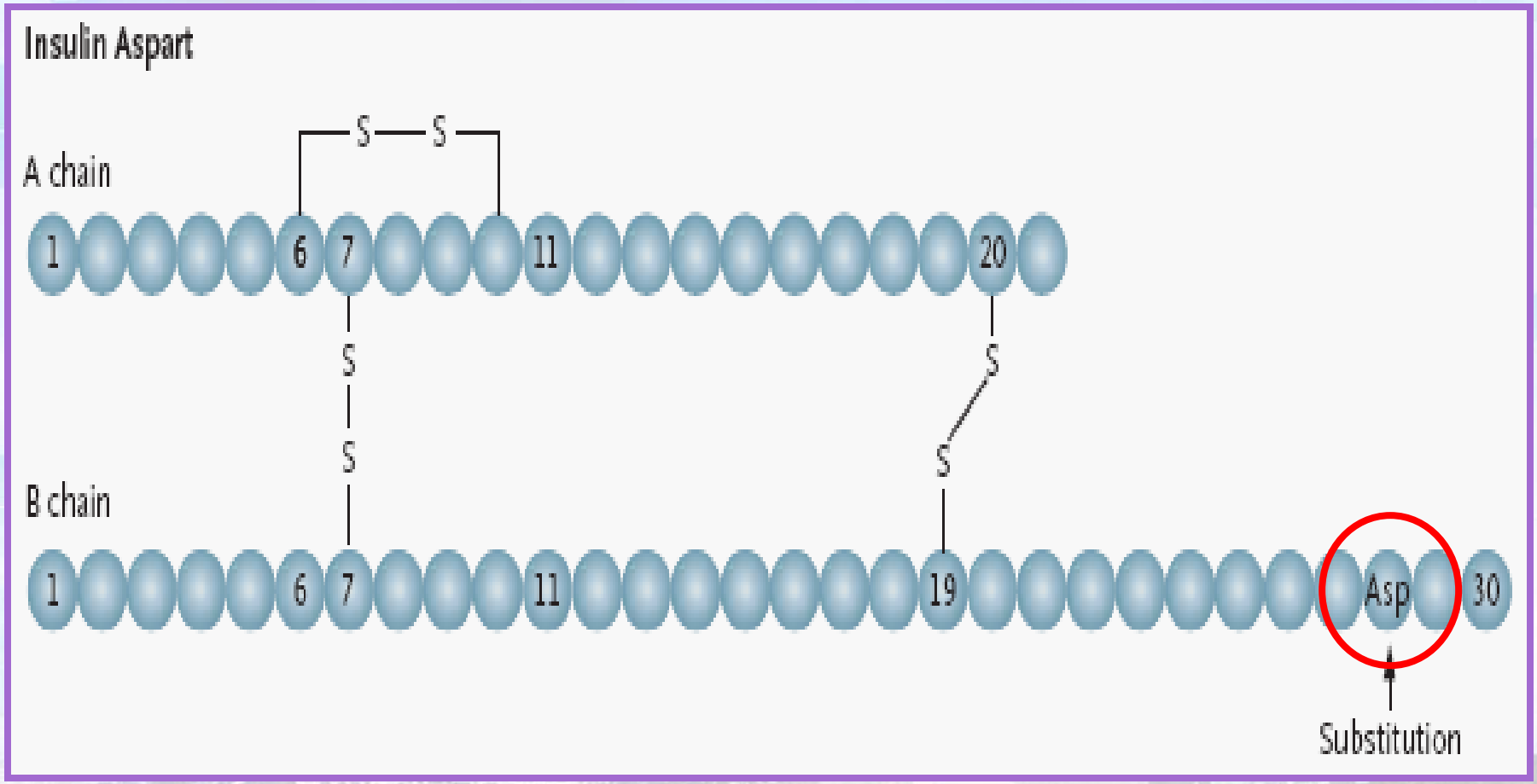
Insulin Aspart

- single replacement of the amino acid proline by aspartic acid at position 28 of the insulin β-chain
- Pk and Pd profiles of insulin lispro and insulin aspart were minor differrences

❖ Onset: 0.17-0.33 hours

❖ Peak effect: 1-3 hours

❖ Duration: 3-5 hours


Insulin Aspart
A chain
S
S
1
6
7
11
20
S
S
S
S
B chain
1
6
7
11
19
Asp
30
Substitution

No peak insulin (Very long acting)

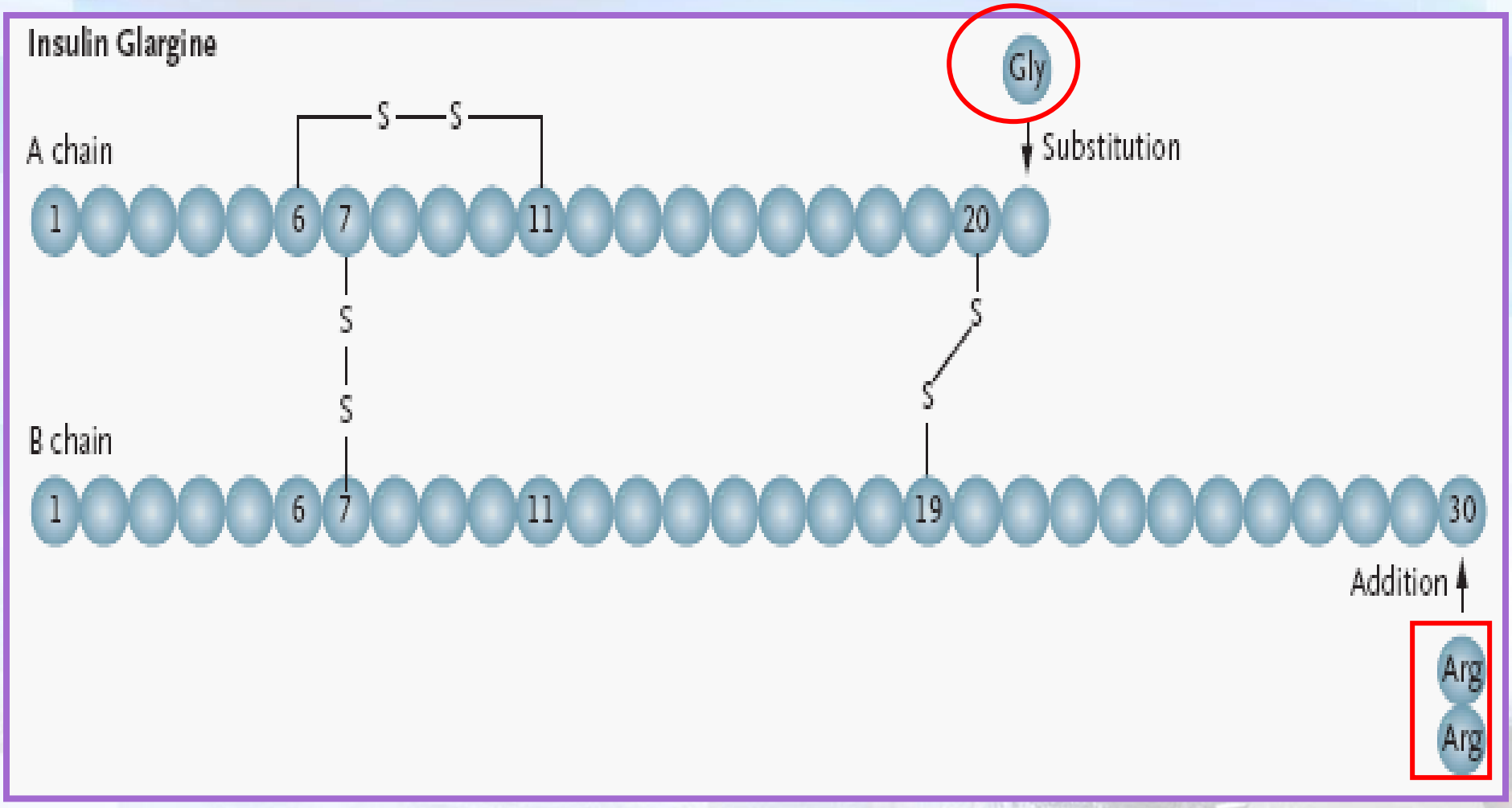
- Insulin glargine
- Insulin detemir

Insulin glargine

- the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the β-chain
- onset of action of approximately 2 hours
- reaching a plateau of biological action at 4-6 hours

Insulin glargine

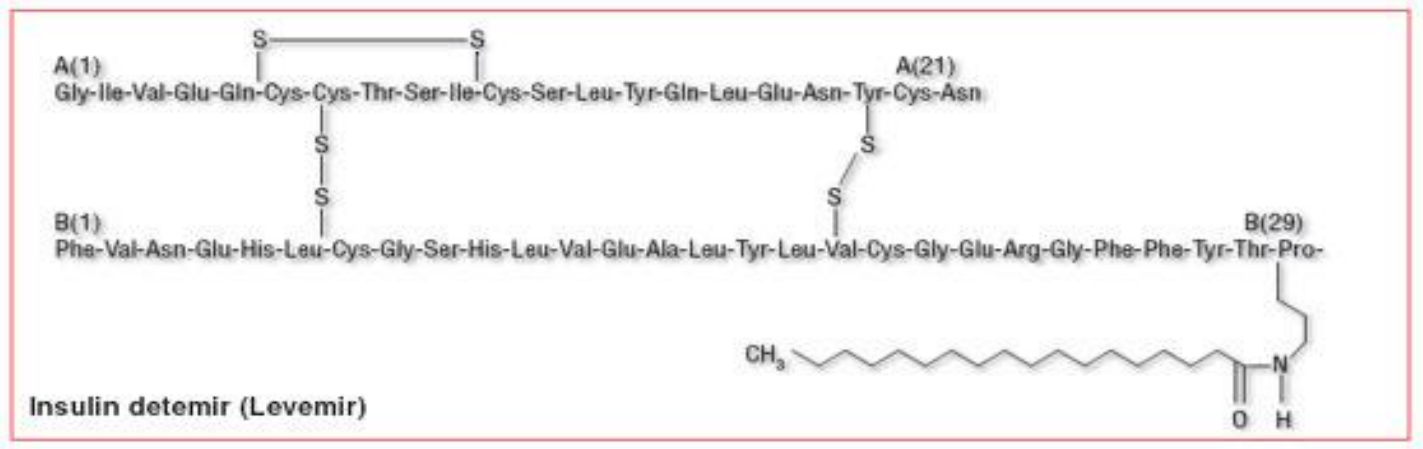
- lasting up to 24 hours
- ‘flat’ and peakless
- less nocturnal hypoglycaemia
- administered once daily, at any time of day
- administered at the same time each day
- Cannot be diluted or mixed with any other insulin or solution

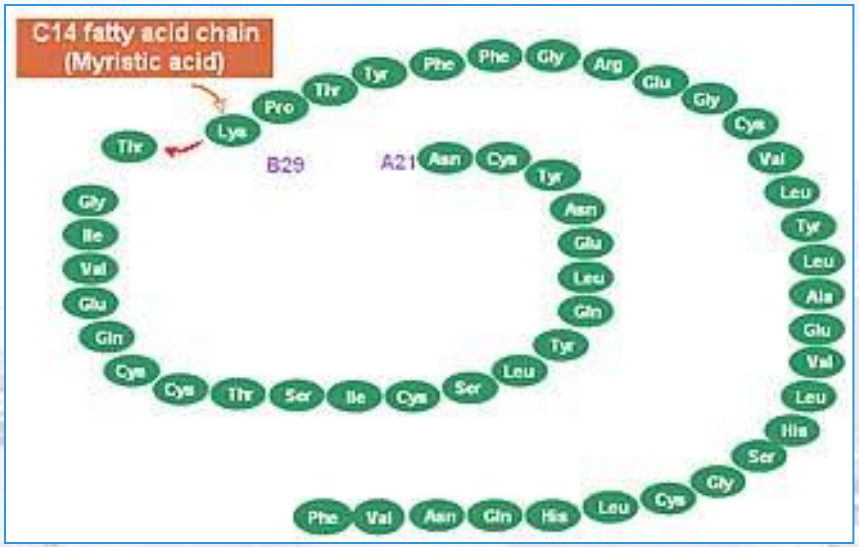

Insulin Glargine
Gly
Substitution
A chain
S
S
1
6
7
11
20
S
S
S
B chain
1
6
7
11
19
30
Addition
Arg
Arg

Insulin Detemir

- a soluble, long-acting basal insulin analog
- the amino acid threonine in position B30 has been removed
- a 14-carbon fatty acid (myristic acid) has been acylated to lysine at B29

Insulin Detemir





Insulin Detemir

- more predictable pharmacokinetic profile than NPH insulin
- 98–99% albumin bound in plasma
- reducing the risk of hypoglycaemia

Insulin Analogues

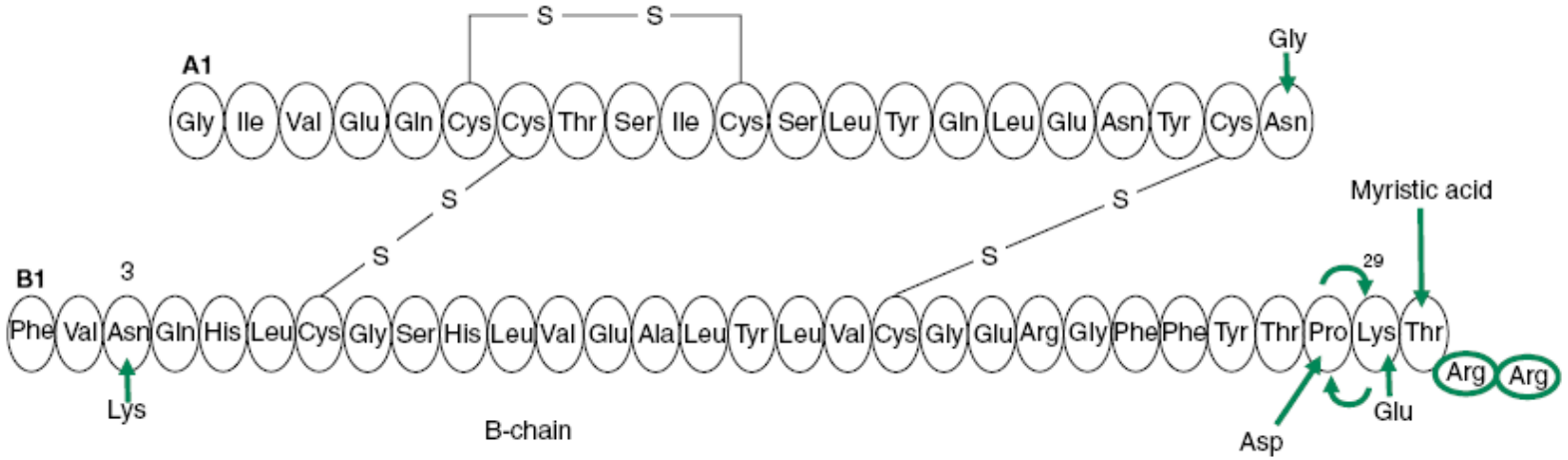


Fig. 1. The structural modifications of insulin found in some insulin analogues. Insulin lispro differs from human insulin by the substitution of proline with lysine at position 28 and lysine with proline at position 29 of the insulin β-chain; insulin aspart is designed with the single replacement of the amino acid proline by aspartic acid at position 28 of the human insulin β-chain; insulin glulisine is designed with the substitution of the amino acid lysine with asparagine at position 3 of the human insulin β-chain and by substitution of the amino acid lysine at position 29 with glutamine; insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the β-chain; insulin detemir is designed to bind albumin in plasma after absorption, threonine is omitted from position 30 of the insulin β-chain and replaced by myristic acid, a C14 fatty acid chain.

Pre-mixed(Combination)Insulin

- pre-meal insulin in addition to basal insulin
- draw up pre-meal and basal insulins in the same syringe or commercial preparation
- Combination NPH/RI eg. 70/30, 50/50 or NPH/Rapid acting eg.

  Humalog 75/25 = NPH(75%):Lispro (25%)
- Onset, peak and duration are variable (proportion and type of insulin)

Table 1. Rapid-acting, long-acting, and premixed insulin analogs.

Analog	Trade name/manufacturer	Insulin molecule modifications
Rapid-acting analogs		
Lispro	Humalog/Eli Lilly	Pro(B28)/Lys(B29) switched
Aspart	Novolog/Novo Nordisk	Asp replaces Pro(B28)
Glulisine	Apidra/Sanofi-Aventis	Asp(B3) replaced by Lys; Lys(B29) replaced by Glu
Long-acting analogs		
Glargine	Lantus/Sanofi-Aventis	Asp(A21) replaced by Gly; 2 Arg added to C-terminus of B-chain
Detemir	Levemir/Novo Nordisk	Thr(B30) omitted; C14 fatty acid chain added at B29
Premixed analogs		
75% neutral protamine lispro, 25% lispro	75/25 Humalog/Eli Lilly	NA
50% neutral protamine lispro, 50% lispro	50/50 Humalog/Eli Lilly	NA
70% protamine aspart, 30% aspart	70/30 Novolog/Novo Nordisk	NA

Asp, aspartic acid; Arg, arginine; Glu, glutamic acid; Lys, lysine; Pro, proline; Thr, threonine; NA, not applicable.

Pharmacokinetics of Most Commonly Used Insulin Preparations

Insulin type	Onset of action	Time to peak effect	Duration of action
Lispro, aspart, glulisine	5 to 15 min	45 to 75 min	2 to 4 h
Regular	About 30 min	2 to 4 h	5 to 8 h
NPH or Lente	About 2 h	6 to 10 h	18 to 28 h
Ultralente	About 4 h	10 to 20 h	12 to 20 h
Insulin glargine	About 2 h	No discernable peak	20 to >24 h

TABLE 1

Description of Onset, Peak, and Duration of Insulins

Insulin	*Onset*	*Peak (hours)*	*Usual effective duration (hours)*	*Usual maximum duration (hours)*
Bolus or mealtime insulin				
Aspart (NovoLog)	5 to 10 minutes	1 to 3	3 to 5	4 to 6
Lispro (Humalog)	< 15 minutes	0.5 to 1.5	2 to 4	4 to 6
Regular (Humulin R, Novolin R)	30 to 60 minutes	2 to 3	3 to 6	6 to 10
Basal insulin				
NPH (Humulin N, Novolin N)	2 to 4 hours	4 to 10	10 to 16	14 to 18
Lente (insulin zinc suspension)	3 to 4 hours	4 to 12	12 to 18	16 to 20
Ultralente (extended insulin zinc suspension)	6 to 10 hours	Peakless	18 to 20	20 to 24
Glargine (Lantus)	1 hour, 6 minutes	Peakless	24	24
Combinations				
50% NPH/50% regular	30 to 60 minutes	Dual	10 to 16	14 to 18
70% NPH/30% regular (Humulin R 70/30, Novolin R 70/30)	30 to 60 minutes	Dual	10 to 16	14 to 18
75% NPL/25% lispro (Humalog 75/25)	< 15 minutes	Dual	10 to 16	14 to 18
70% NPH/30% aspart (NovoLog 70/30)	5 to 10 minutes	Dual	10 to 16	14 to 18


10 ml
Actrapid® HM 100 i.u./ml
Neutral Insulin Injection
Biosynthetic Human Insulin
Remove protective cap
Novo Nordisk
Novo Nordisk
Actrapid® HM
100


10 ml
Insulatard® HM
Isophane Insulin Injection
Biosynthetic Human Insulin
100
iu/ml
Novo Nordisk
Novo Nordisk
Insulatard® HM
100


Regular Insulin(RI)
NPH


P050
GENSULIN R
Insulinum humanum
100 IU/ml
solution for injections
1 vial of 10 ml
IBA BIOTON
100 IU/ml


P051
GENSULIN N
Insulinum isophanum humanum
100 IU/ml
suspension for injections
1 vial of 10 ml
IBA BIOTON
100 IU/ml


10 mL
HI 0710
Humulin® 70/30
U-100
100 IU/mL
70% human insulin isophane suspension
30% human insulin injection
(rDNA origin)
เก็บในตู้เย็น
10 mL
HI 0710
Humulin® 70/30
U-100
100 IU/mL
70% human insulin isophane suspension
30% human insulin injection
(rDNA origin)
เก็บในตู้เย็น

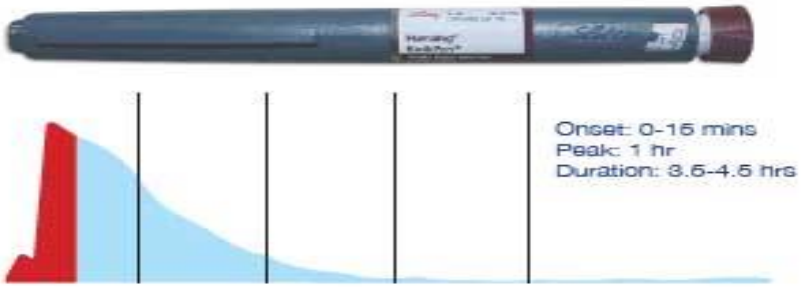
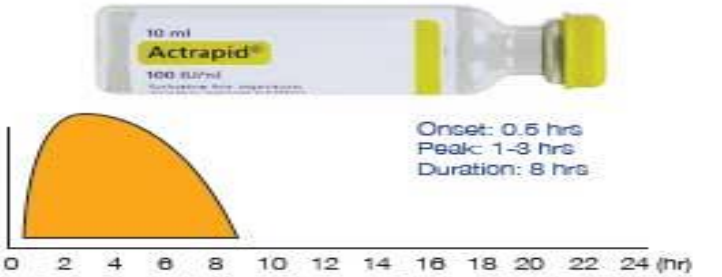

10 ml
Mixtard® 30 HM
Biphasic Isophane Insulin Injection 30/70
Biosynthetic Human Insulin
100
iu/ml
Novo Nordisk


P054
GENSULIN M30 (30/70)
Insulinum humanum + Insulinum isophanum
100 IU/ml
suspension for injections
1 vial of 10 ml
IBA BIOTON
100 IU/ml

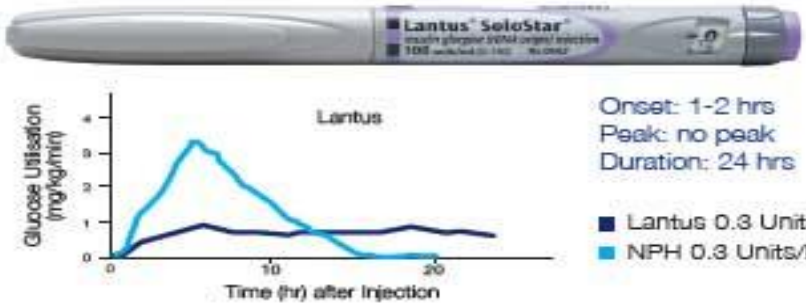
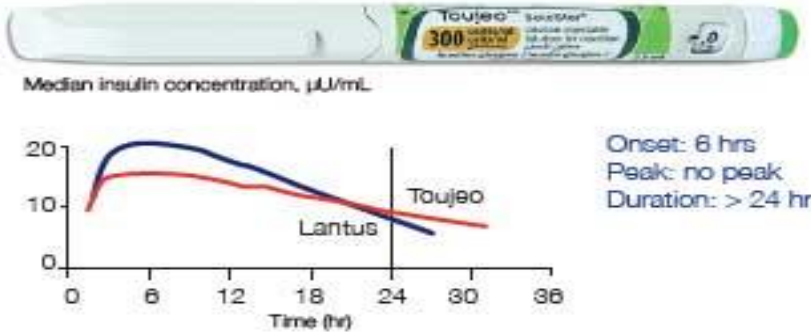

3mL
5 Cartridges
VL7394
Humalog® Mix25™ 100 IU/mL
25% insulin lispro and
75% insulin lispro
protamine suspension
(rDNA origin)
U-100
เก็บในตู้เย็น
Lilly

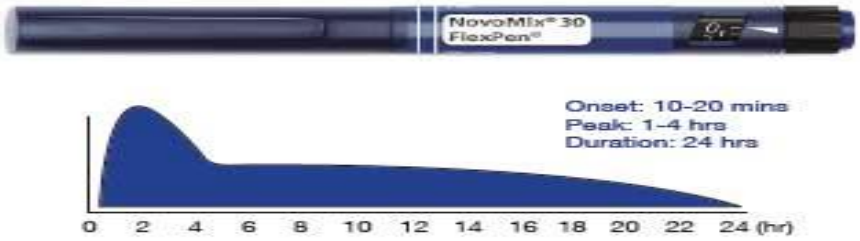
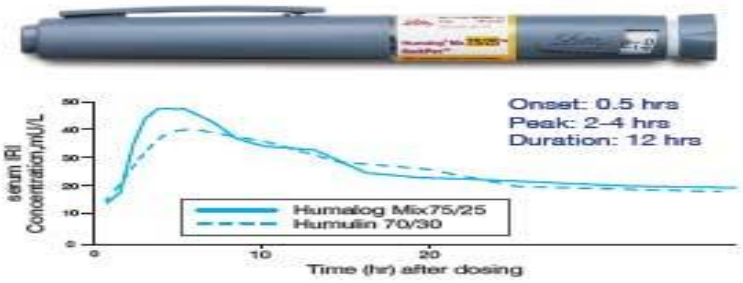
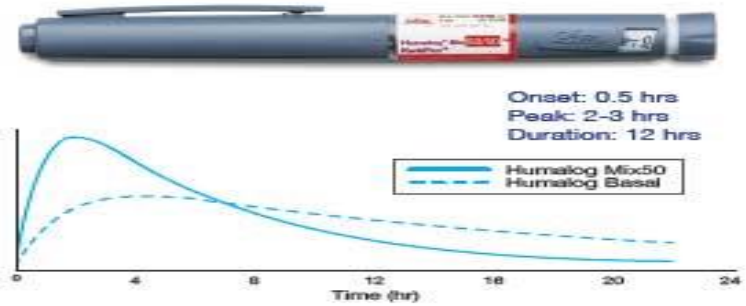

Lantus
insulin glargine
(rDNA origin)
injection
100
Aventis


Novo Nordisk
NovoRapid®

Onset of insulin action	Brand and type	Generic name	Type of insulin
15 min	Apidra® Solostar	Insulin Glulisine	
15 min	Humalog® KwikPen	Insulin Lispro	
15 min	NovoRapid® FlexPen	Insulin Aspart	
30 min	Actrapid®	Regular Insulin	

Onset of insulin action	Brand and type	Generic name	Type of insulin
60 min	Insulatard®	NPH Insulin	 

Onset of insulin action	Brand and type	Generic name	Type of insulin
> 60 min	Lantus® Solostar	Insulin Glargine	 Onset: 1-2 hrs Peak: no peak Duration: 24 hrs
> 60 min	Levemir® FlexPen	Insulin Detemir	 Onset: 1-2 hrs Peak: 3-14 hrs Duration: 24 hrs
> 60 min	Toujeo® SoloStar 300 units/ml	Insulin Glargine	 Onset: 6 hrs Peak: no peak Duration: > 24 hrs

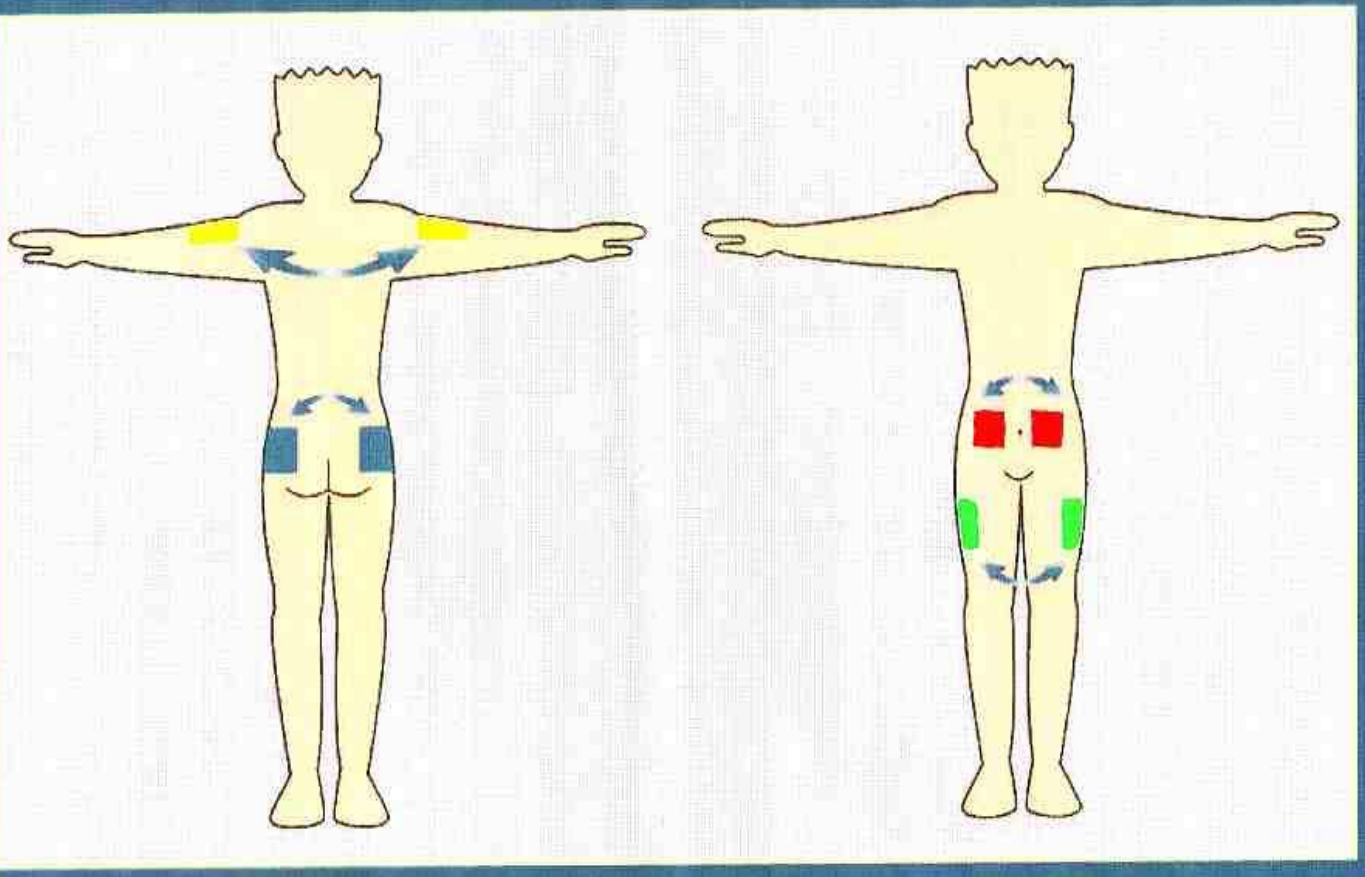
Onset of insulin action	Brand and type	Generic name	Type of insulin
15 min	NovoMix®30 FlexPen	Biphasic Insulin Aspart	
15 min	Humalog® Mix 75/25 KwikPen	Biphasic Insulin Lispro 25%/ Protamine 75%	
15 min	Humalog® Mix 50/50 Kwikpen	Biphasic Insulin Lispro 50%/ Protamine 50%	
15 min	Mixtard® 30	Biphasic 30% Soluble Human Insulin +70% NPH Insulin	

Daily Requirements

- Insulin production by a normal, thin, healthy person = 18 - 40 units/day or 0.2 - 0.5 units/kg of body weight per day
- ½ secreted in the basal state, ½ response to meals
- basal secretion is about 0.5 - 1 units/h

Administration

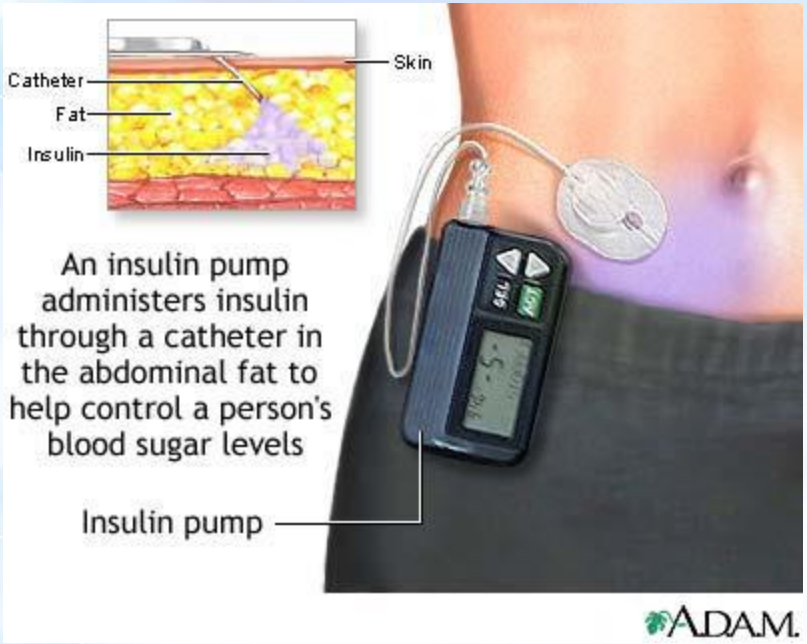
Injection Site Rotation



Administration

- Subcutaneous injection
- Intravenous and intramuscular (Only Emergency condition)
- Site of injection: abdominal wall (fastest), arm, leg and buttock (slowest)
- Tools: syringe, pen, pump

Insulin syringe



Insulin pump

Insulin pen

Factors That Affect Insulin Absorption

- site of injection
- the type of insulin
- subcutaneous blood flow
- regional muscular activity at the site of the injection
- the volume and concentration of the injected insulin
- depth of injection

Adverse reactions

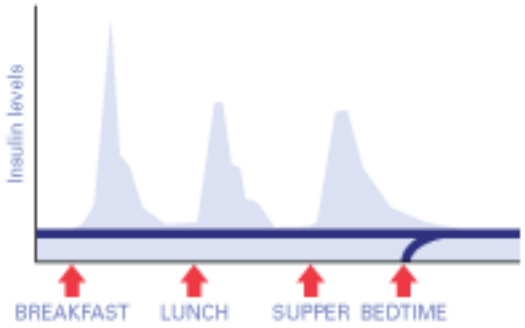
- **Hypoglycemia: most common**
- Cardiovascular: Palpitation, tachycardia, pallor
- Central nervous system: Fatigue, mental confusion, loss of consciousness, headache, hypothermia
- Dermatologic: Urticaria, redness
- Gastrointestinal: Hunger, nausea, numbness of mouth

Therapeutic Regimens

- Ideal insulin therapy regimen should mimic **normal physiologic insulin release**
- Tailored to the patient's degree of hyperglycemia, the risks associated with hypoglycemia, comorbid conditions, the ability to adhere to a routine, understand and master the information and skills, and the cost

BASAL (Lantus®)

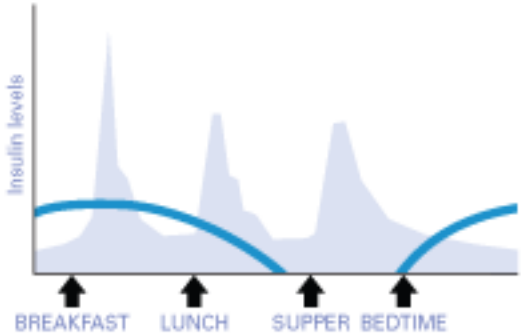
LONG-ACTING INSULIN



Onset
2-4 hours

Duration
24 hours

INTERMEDIATE-ACTING INSULIN (NPH)

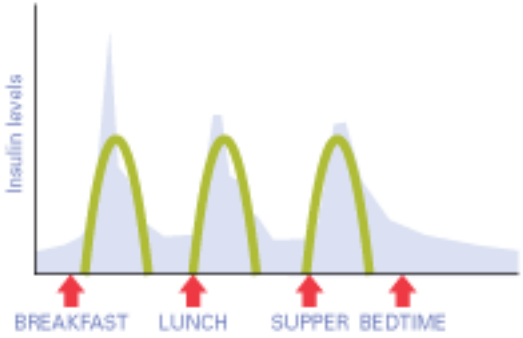


Onset
0.5-1 hours

Duration
10-16 hours

PRANDIAL

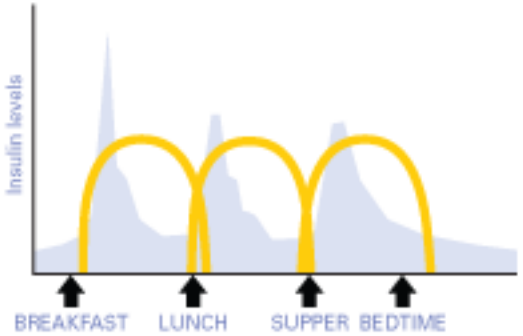
RAPID-ACTING INSULIN



Onset
~5 minutes

Duration
4-5 hours

SHORT-ACTING INSULIN (RHI)

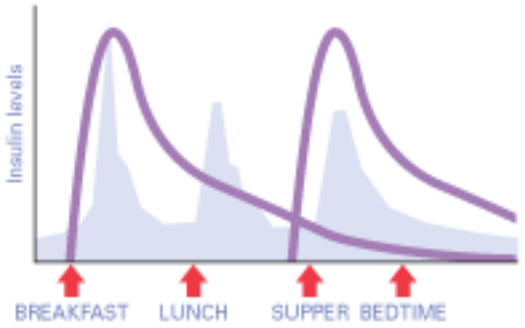


Onset
30 minutes

Duration
Up to 6 hours

PREMIX

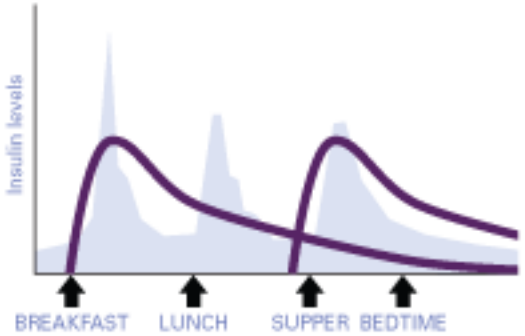
PREMIXED INSULIN (ANALOG)



Onset
5-15 minutes

Duration
10-16 hours

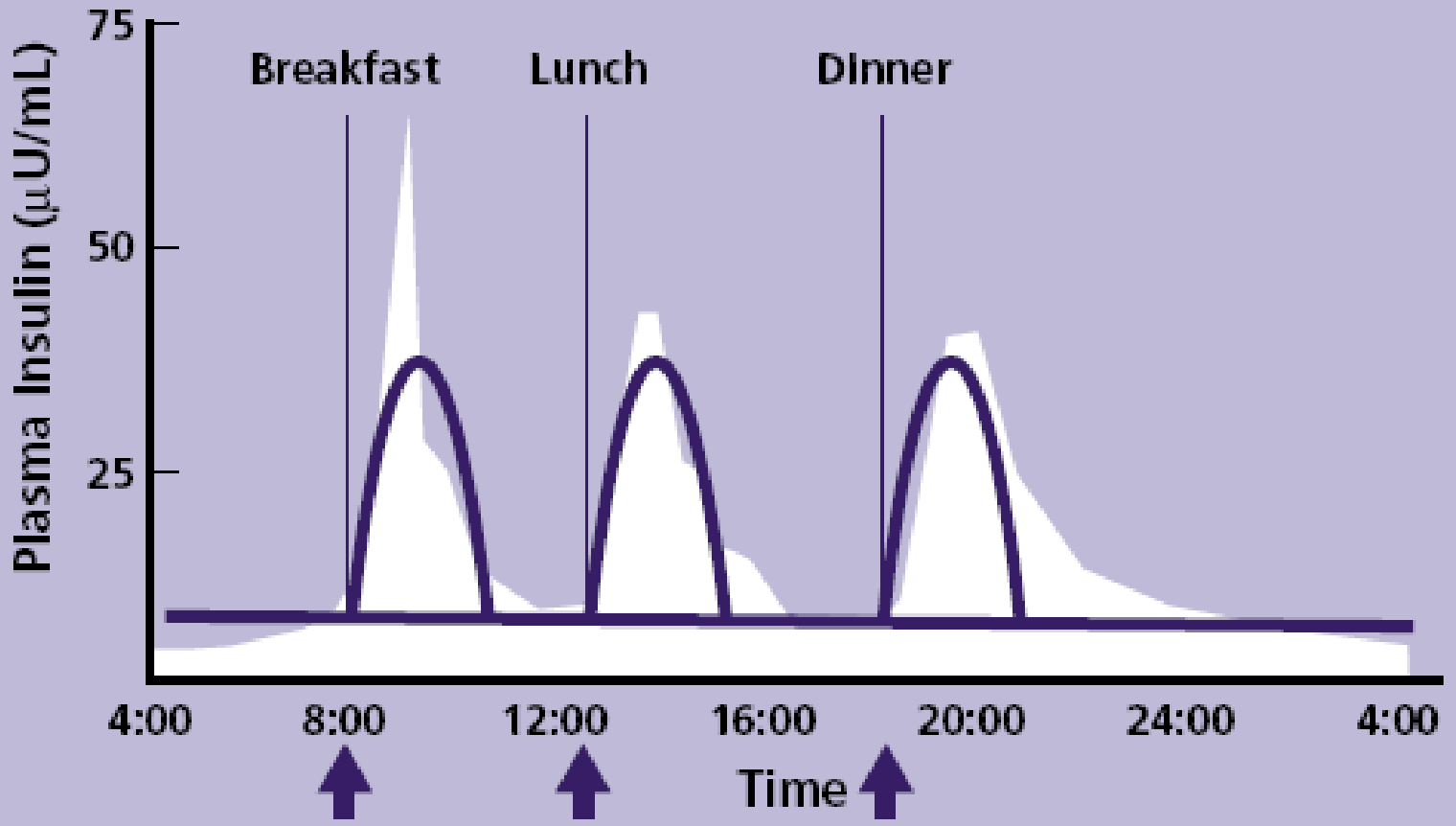
PREMIXED INSULIN (HUMAN)



Onset
5-15 minutes

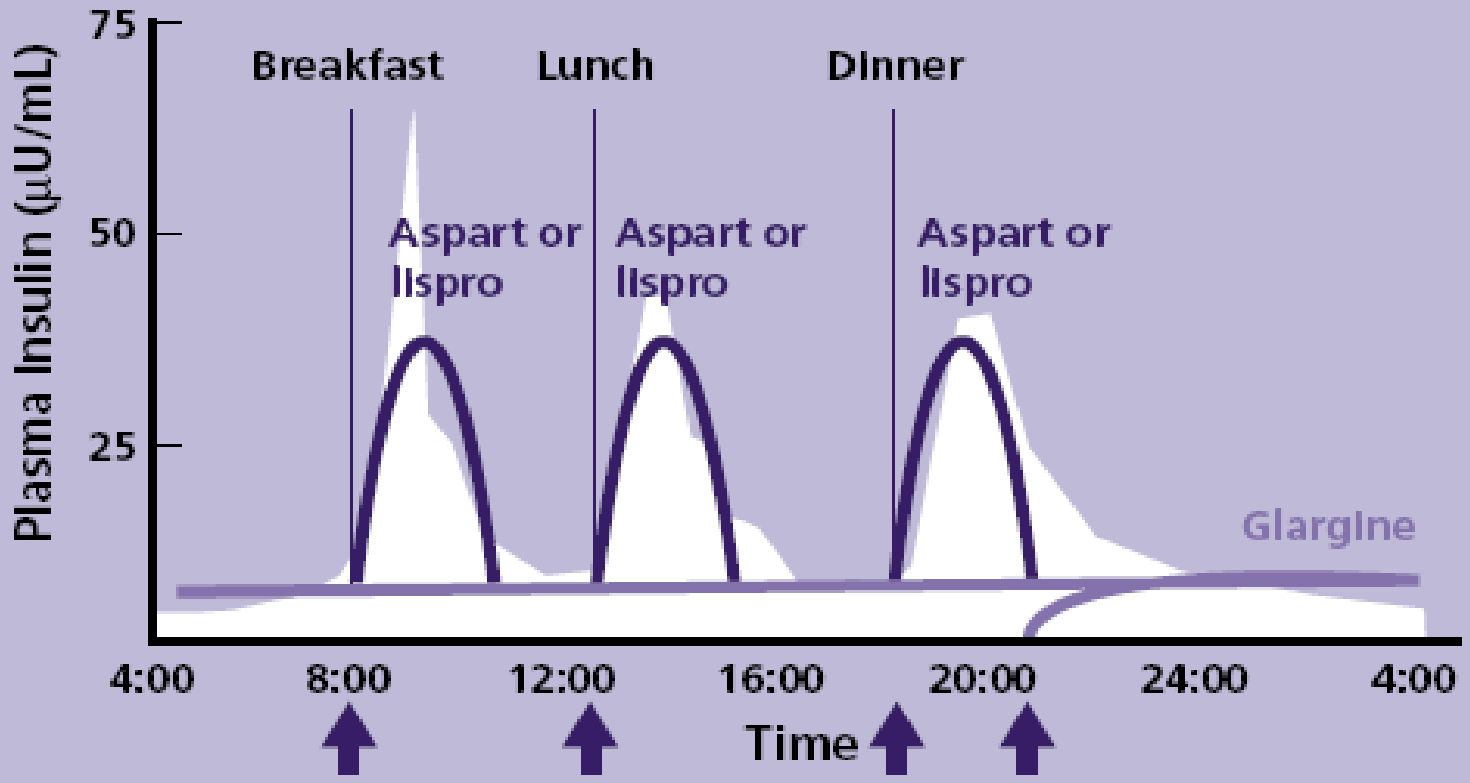
Duration
10-16 hours

Ideal Insulin Replacement Pattern



. Profile of ideal insulin replacement pattern.

Basal-Bolus Therapy Using Glargine and Aspart or Lispro



. Basal plus meal-related regimen using glargine plus aspart or lispro.

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin[2]

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)

If already on GLP-1 RA or dual GIP/GLP-1 RA, or if these are not appropriate, or if insulin is preferred

If A1C is above goal

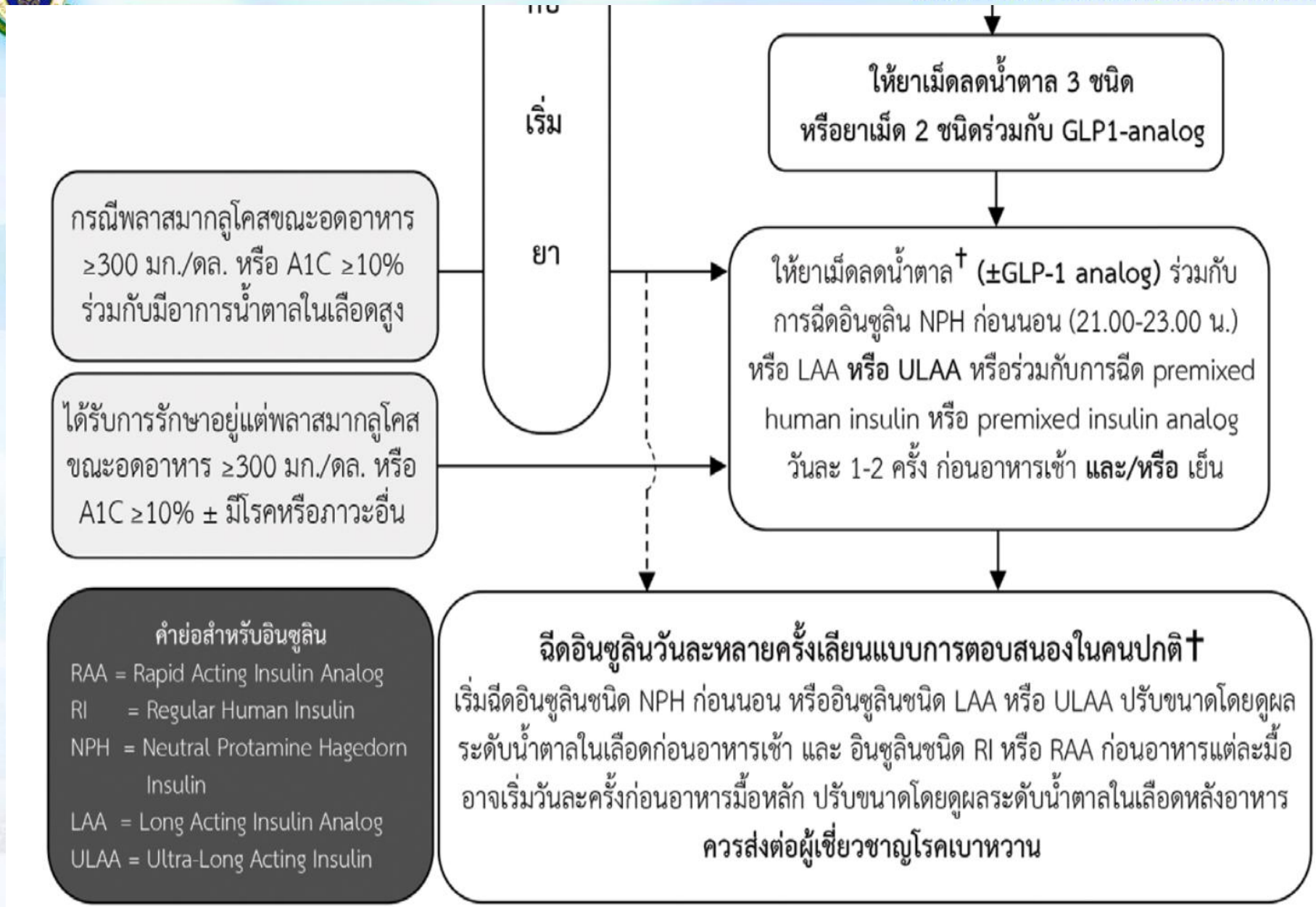
Considerations for adding basal insulin[3]

Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

Initiation and titration of basal analog or bedtime NPH insulin[4]

INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day
TITRATION:

- Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
- For hypoglycemia: determine cause; if no clear reason, lower dose by 10-20%


เริ่มยา
ให้ยาเม็ดลดน้ำตาล 3 ชนิด
หรือยาเม็ด 2 ชนิดร่วมกับ GLP1-analog
กรณีพลาสมากลูโคสขณะอดอาหาร ≥300 มก./ดล. หรือ A1C ≥10% ร่วมกับมีอาการน้ำตาลในเลือดสูง
ได้รับการรักษาอยู่แต่พลาสมากลูโคสขณะอดอาหาร ≥300 มก./ดล. หรือ A1C ≥10% ± มีโรคหรือภาวะอื่น
ให้ยาเม็ดลดน้ำตาล† (±GLP-1 analog) ร่วมกับการฉีดอินซูลิน NPH ก่อนนอน (21.00-23.00 น.) หรือ LAA หรือ ULAA หรือร่วมกับการฉีด premixed human insulin หรือ premixed insulin analog วันละ 1-2 ครั้ง ก่อนอาหารเช้า และ/หรือ เย็น
คำย่อสำหรับอินซูลิน
RAA = Rapid Acting Insulin Analog
RI = Regular Human Insulin
NPH = Neutral Protamine Hagedorn Insulin
LAA = Long Acting Insulin Analog
ULAA = Ultra-Long Acting Insulin
ฉีดอินซูลินวันละหลายครั้งเลียนแบบการตอบสนองในคนปกติ†
เริ่มฉีดอินซูลินชนิด NPH ก่อนนอน หรืออินซูลินชนิด LAA หรือ ULAA ปรับขนาดโดยดูผลระดับน้ำตาลในเลือดก่อนอาหารเช้า และ อินซูลินชนิด RI หรือ RAA ก่อนอาหารแต่ละมื้อ อาจเริ่มวันละครั้งก่อนอาหารมื้อหลัก ปรับขนาดโดยดูผลระดับน้ำตาลในเลือดหลังอาหาร
ควรส่งต่อผู้เชี่ยวชาญโรคเบาหวาน

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6.1.2 Oral antidiabetic drugs

1.	Glibenclamide	tab (เฉพาะ 2.5 และ 5 mg)	ก

คำเตือนและข้อควรระวัง

พึงระมัดระวังในผู้ป่วยสูงอายุหรือผู้ป่วยที่มีการทำงานของไตบกพร่อง

2.	Glipizide	tab	ก
3.	Metformin hydrochloride	tab	ก
4.	Pioglitazone hydrochloride	tab (เฉพาะ 15 และ 30 mg)	ข

เงื่อนไข

ใช้เป็นยาทางเลือก ภายหลังการใช้ยา Metformin หรือยากลุ่ม Sulfonylureas

คำเตือนและข้อควรระวัง

1. ห้ามใช้ยานี้ในผู้ที่มีหัวใจล้มเหลวในระดับที่รุนแรง (NYHA ในระดับ 3 และ 4) ยานี้อาจทำให้เกิดภาวะหัวใจล้มเหลว
2. ไม่ควรใช้ยานี้ในผู้ป่วยที่กำลังเป็นมะเร็งกระเพาะปัสสาวะ

5.	Repaglinide	tab (เฉพาะ 0.5, 1 และ 2 mg)	ง

เงื่อนไข

1. ใช้สำหรับลด postprandial hyperglycemia
2. ใช้ในผู้ป่วยที่มีความเสี่ยงต่อ hypoglycemia สูง

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6.1 Drugs used in diabetes

6.1.1 Insulins

1.	Biphasic isophane insulin (Soluble insulin + Isophane insulin)	sterile susp	ก

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2.	Isophane insulin (NPH; Isophane protamine insulin)	sterile susp	ก
3.	Soluble insulin (Neutral insulin; insulin injection)	sterile sol	ก
4	Insulin aspart	sterile sol	ง
	เงื่อนไข 1. ใช้เฉพาะผู้ป่วยที่เกิด hypoglycemia บ่อยเมื่อใช้ conventional insulin 2. ใช้สำหรับควบคุมภาวะ postprandial hyperglycemia		
5.	Insulin aspart + Insulin aspart protamine	sterile susp (เฉพาะ 30% + 70%)	ง
	เงื่อนไข เช่นเดียวกับ Insulin aspart		
6.	Insulin lispro	sterile sol	ง
	เงื่อนไข 1. ใช้เฉพาะผู้ป่วยที่เกิด hypoglycemia บ่อยเมื่อใช้ conventional insulin 2. ใช้สำหรับควบคุมภาวะ postprandial hyperglycemia		
7.	Insulin lispro + Insulin lispro protamine	sterile susp (เฉพาะ 25% + 75%)	ง
	เงื่อนไข เช่นเดียวกับ Insulin lispro		
8.	Insulin glargine	sterile sol (cartridge เฉพาะ 100 IU/ml) (3 mL), (pre-filled pen เฉพาะ 100 IU/ml) (3 mL)	ง

Inhaled Insulin

- A powdered form of insulin
- Delivered with a nebulizer into the lungs where it is absorbed
- In 2014, US FDA approved Afrezza for both Type I and Type II adult diabetics

New Type 2 DiabetesTreatments

- Nearly 100 new Type 2 diabetes medications are being studied in clinical trials
- Many of them work differently from current treatment options
- Providing heart, kidney, and body weight-related benefits

New Type 2 DiabetesTreatments

- Tirzepatide
- In early 2022, the FDA approved a new medication called tirzepatide (Mounjaro)
- Tirzepatide has been found to work better than semaglutide at lowering A1C. And people taking it lost more weight.

New Type 2 DiabetesTreatments

- Sotagliflozin:Dual SGLT1/2 inhibitors
- IcoSema:combines semaglutide with insulin icodec, a new once-weekly insulin
- CagriSema: combines semaglutide and cagrilintide into a once-weekly injection. Cagrilintide is a new long-acting amylin analogue

Questions???

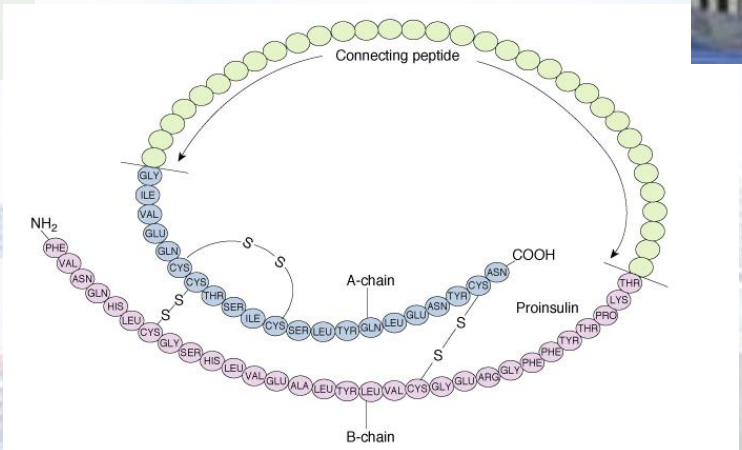

Figure 43-3 Structure of proinsulin. With removal of the connecting peptide (C-peptide), proinsulin is converted to insulin.