

DIABETES MELLITUS



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BCPS

- Diagnosis of GH Excess. While the diagnosis of acromegaly should be suspected in patients with the appropriate symptoms and signs, confirmation requires the demonstration of increased circulating GH or IGF-1. The gold standard diagnostic test for acromegaly is the oral glucose tolerance test. While normal subjects suppress their GH level to <1 ng/ml in response to a 75-g glucose challenge (the absolute value may vary depending on the sensitivity of the assay), patients with acromegaly either fail to suppress

Overview

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans (β -cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin).

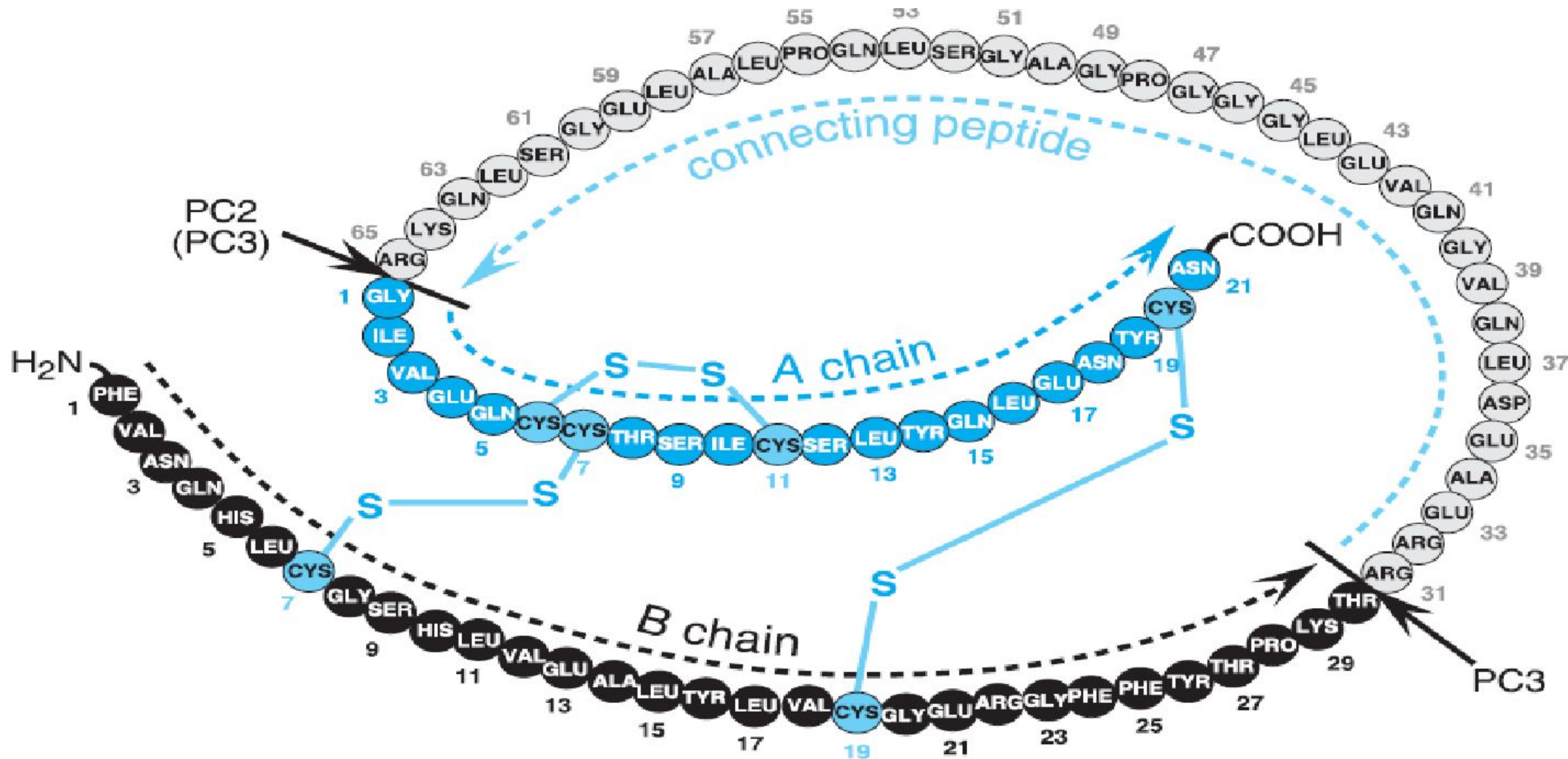
These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result.

Administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes.

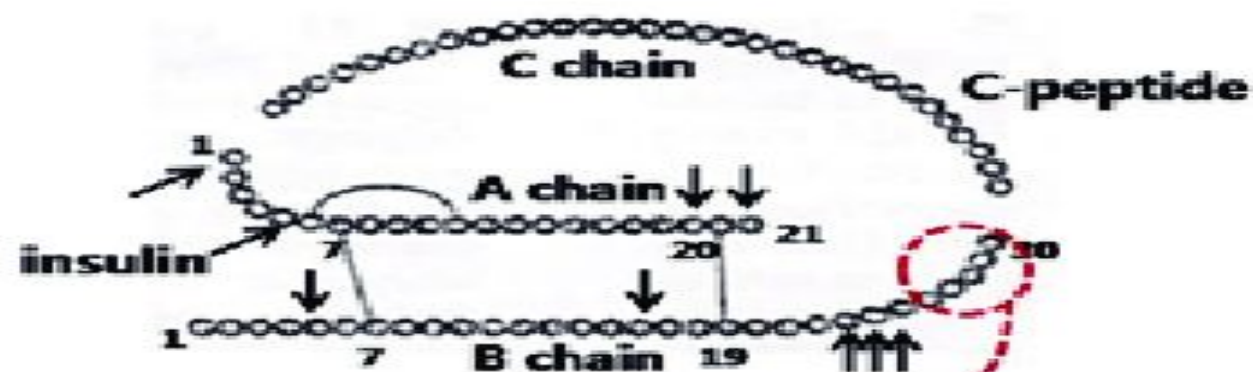
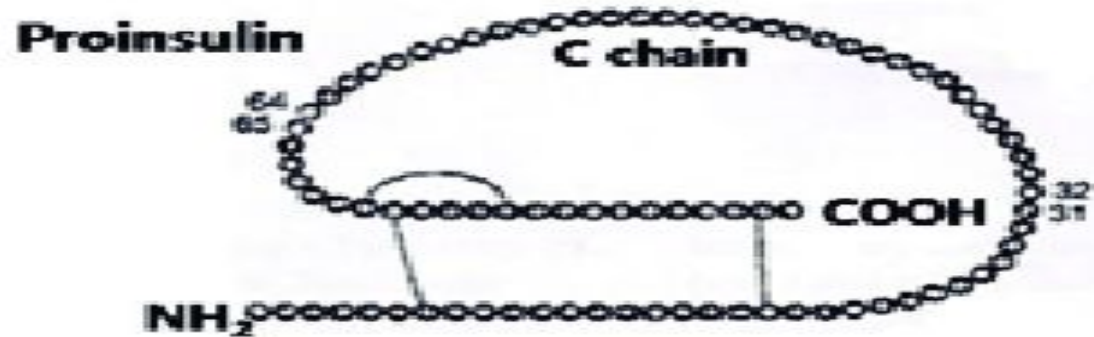
INSULIN	ORAL AGENTS	GLP-1 RECEPTOR AGONISTS
<i>Inhaled insulin</i> AFREZZA	<i>Acarbose</i> PRECOSE	<i>Albiglutide</i> TANZEUM
<i>Insulin aspart</i> NOVOLOG	<i>Alogliptin</i> NESINA	<i>Dulaglutide</i> TRULICITY
<i>Insulin degludec</i> TRESIBA	<i>Bromocriptine</i> CYCLOSET	<i>Exenatide</i> BYETTA, BYDUREON
<i>Insulin detemir</i> LEVEMIR	<i>Canagliflozin</i> INVOKANA	<i>Liraglutide</i> VICTOZA
<i>Insulin glargine</i> BASAGLAR, LANTUS, TOUJEO	<i>Colesevelam</i> WELCHOL	<i>Lixisenatide</i> ADLYXIN
<i>Insulin glulisine</i> APIDRA	<i>Dapagliflozin</i> FARXIGA	<i>Semaglutide</i> OZEMPIC
<i>Insulin lispro</i> HUMALOG	<i>Empagliflozin</i> JARDIANCE	
<i>NPH insulin suspension</i> HUMULIN N, NOVOLIN N	<i>Ertugliflozin</i> STEGLATRO	
<i>Regular insulin</i> HUMULIN R, NOVOLIN R	<i>Glimepiride</i> AMARYL	
AMYLIN ANALOG	<i>Glipizide</i> GLUCOTROL	
<i>Pramlintide</i> SYMLIN	<i>Glyburide</i> DIABETA, GLYNASE PRESTAB	
	<i>Linagliptin</i> TRADJENTA	
	<i>Metformin</i> FORTAMET, GLUCOPHAGE	
	<i>Miglitol</i> GLYSET	
	<i>Nateglinide</i> STARLIX	
	<i>Pioglitazone</i> ACTOS	
	<i>Repaglinide</i> PRANDIN	
	<i>Rosiglitazone</i> AVANDIA	
	<i>Saxagliptin</i> ONGLYZA	
	<i>Sitagliptin</i> JANUVIA	
	<i>Tolbutamide</i> GENERIC ONLY	

• Insulin and Insulin Analogs

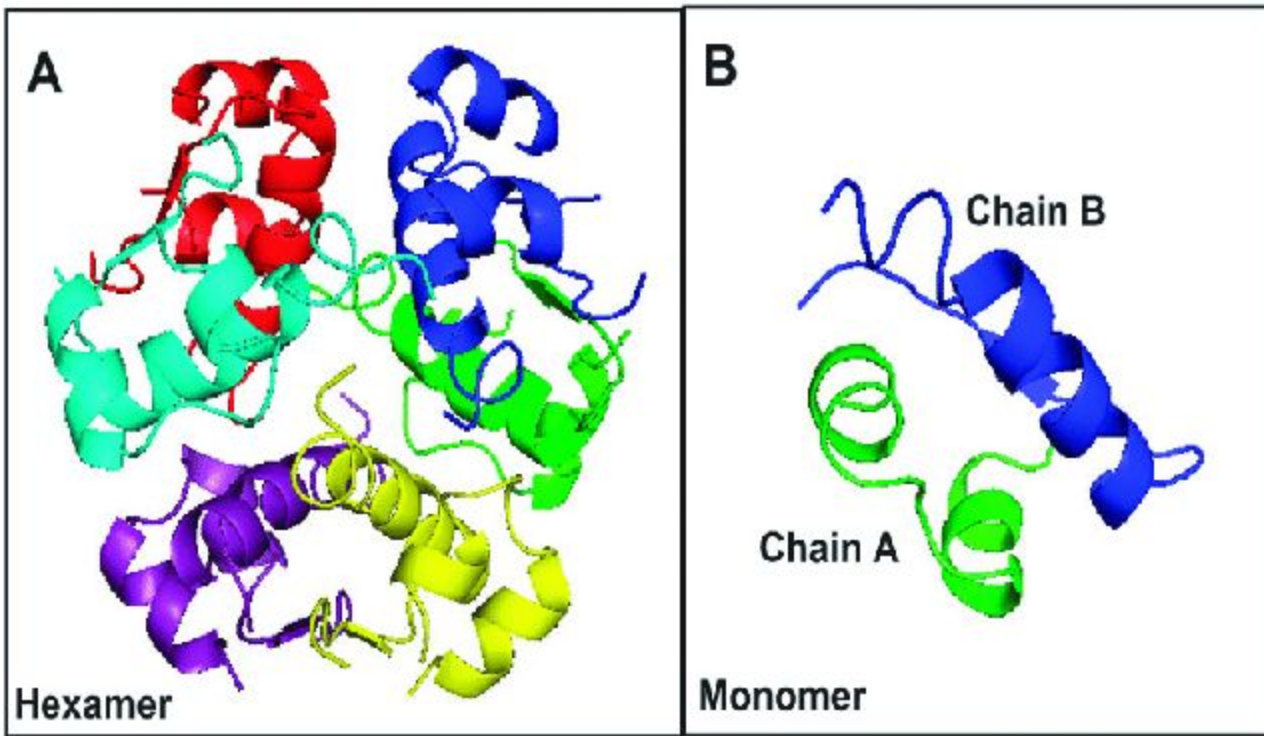
Insulin [it is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both IN-su-lin] is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. of which are secreted by the β cells of the pancreas. [Note: Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, measurement of C-peptide other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and provides a better index of insulin levels.] Insulin secretion is regulated by blood glucose levels, certain amino acids, generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K^+ channels, leading to membrane depolarization and an influx of Ca^{2+} . The increase in intracellular Ca^{2+} causes pulsatile insulin exocytosis.



Human proinsulin and its conversion to insulin. The amino acid sequence of human proinsulin is shown. By proteolytic cleavage, four basic amino acids (residues 31, 32, 64, and 65) and the connecting peptide are removed, converting proinsulin to insulin. The sites of action of the endopeptidases PC2 and PC3 are shown



Human Insulin
 Insulin Lispro
 Insulin Aspart
 Insulin glargine
 Insulin glulisine



Insulin is a member of a family of related peptides termed *insulinlike growth factors* (IGFs). The two IGFs (IGF-1 and IGF-2) have molecular masses of about 7500 daltons and structures that are homologous to that of proinsulin. However, the short equivalents of the C peptide in proinsulin are not removed from the IGFs. In contrast with insulin, the IGFs are produced in many tissues, and they may serve a more important function in the regulation of growth than in the regulation of metabolism. These peptides, particularly IGF-1, are the presumed mediators of the action of growth hormone, and they originally were called *somatomedins*. The uterine hormone *relaxin* also may be a distant relative of this family of polypeptides, although the relaxin receptor clearly is distinct from those for insulin and IGF-1. The receptors for insulin and IGF-1 are also closely related. Thus, insulin can bind to the receptor for IGF-1 with low affinity and *vice versa*. The growth-promoting actions of insulin appear to be mediated in part through the IGF-1 receptor, and there may be discordance between the metabolic potency of an insulin analog and its ability to promote growth. For example, proinsulin has only 2% of the metabolic potency of insulin *in vitro*, but it is half as potent as insulin in stimulating mitogenesis.

The islets of Langerhans are richly innervated by both adrenergic and cholinergic nerves. Stimulation of α_2 adrenergic receptors inhibits insulin secretion, whereas β_2 adrenergic receptor agonists and vagal nerve stimulation enhance release. In general, any condition that activates the sympathetic branch of the autonomic nervous system (such as hypoxia, hypoglycemia, exercise, hypothermia, surgery, or severe burns) suppresses the secretion of insulin by stimulation of α_2 adrenergic receptors. Predictably, α_2 adrenergic receptor antagonists increase basal concentrations of insulin in plasma, and β_2 adrenergic receptor antagonists decrease them. Glucose is the principal stimulus to insulin secretion in human beings and is an essential permissive factor for the actions of many other secretagogues. The sugar is more effective in provoking insulin secretion when taken orally than when administered intravenously because the ingestion of glucose (or food) induces the release of gastrointestinal hormones and stimulates vagal activity. Several gastrointestinal hormones promote the secretion of insulin. The most potent of these are gastrointestinal inhibitory peptide (GIP) and glucagonlike peptide 1 (GLP-1). Insulin release also is stimulated by gastrin, secretin, cholecystikinin, vasoactive intestinal peptide, gastrin-releasing peptide, and enteroglucagon.

Goals of Diabetes Management in Nonpregnant Adults

1. Primary goal: Prevent the onset of acute or chronic complications
2. Acute complications: Hypoglycemia, diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic syndrome
3. Chronic complications
 - a. Microvascular: Retinopathy, nephropathy, and neuropathy
 - b. Macrovascular: Cardiovascular, cerebrovascular, and peripheral vascular diseases
4. Glycemic therapy goals
 - a. A1C less than 7.0% (Note: The American College of Endocrinology/AACE guidelines recommend 6.5% or less.)
 - i. Obtain every 6 months in patients at goal A1C and every 3 months in those over goal.
 - ii. Less-stringent A1C targets may be appropriate in those with a short life expectancy (e.g., terminal cancer), advanced diabetic complications, longstanding diabetes that is difficult to control (e.g., frail older adults with a history of hypoglycemia at risk of falls), or extensive other comorbidities. (In such situations, a higher A1C [e.g., less than 8%] may be sufficient to limit the risk of acute complications of hyperglycemia such as dehydration and electrolyte deficiencies.)
 - b. FPG or premeal 80–130 mg/dL. Frequency of monitoring depends on regimen, type of DM, and current glycemic control.
 - c. Peak postprandial glucose (1–2 hours after a meal) less than 180 mg/dL

Pharmacokinetics

Human insulin is produced by **recombinant DNA** technology using strains of **Escherichia coli or yeast** that are genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties. Insulin preparations vary primarily in their onset and duration of activity. Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations. Because insulin is a polypeptide, it is degraded in the **gastrointestinal tract if taken orally**. Therefore, it is generally administered by **subcutaneous injection**, although an inhaled insulin formulation is also available. [Note: In a hyperglycemic emergency, *regular insulin* is administered **intravenously (IV)**.] Continuous subcutaneous insulin infusion (also called **the insulin pump**) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin. The pump is programmed to deliver a basal rate of insulin. In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose.

Insulin agents

a. Categorized on the basis of duration after injection

i. Rapid acting: Insulin aspart (two formulations), lispro, glulisine, and inhaled insulin

ii. Short acting: Regular human insulin

iii. Intermediate acting: Neutral protamine Hagedorn (NPH)

iv. Long acting: Insulin glargine, degludec and detemir

b. Combination insulin products (intermediate or long acting, regular or rapid acting): 70/30, 75/25, insulin degludec and glargine available in combination with GLP-1 agonist

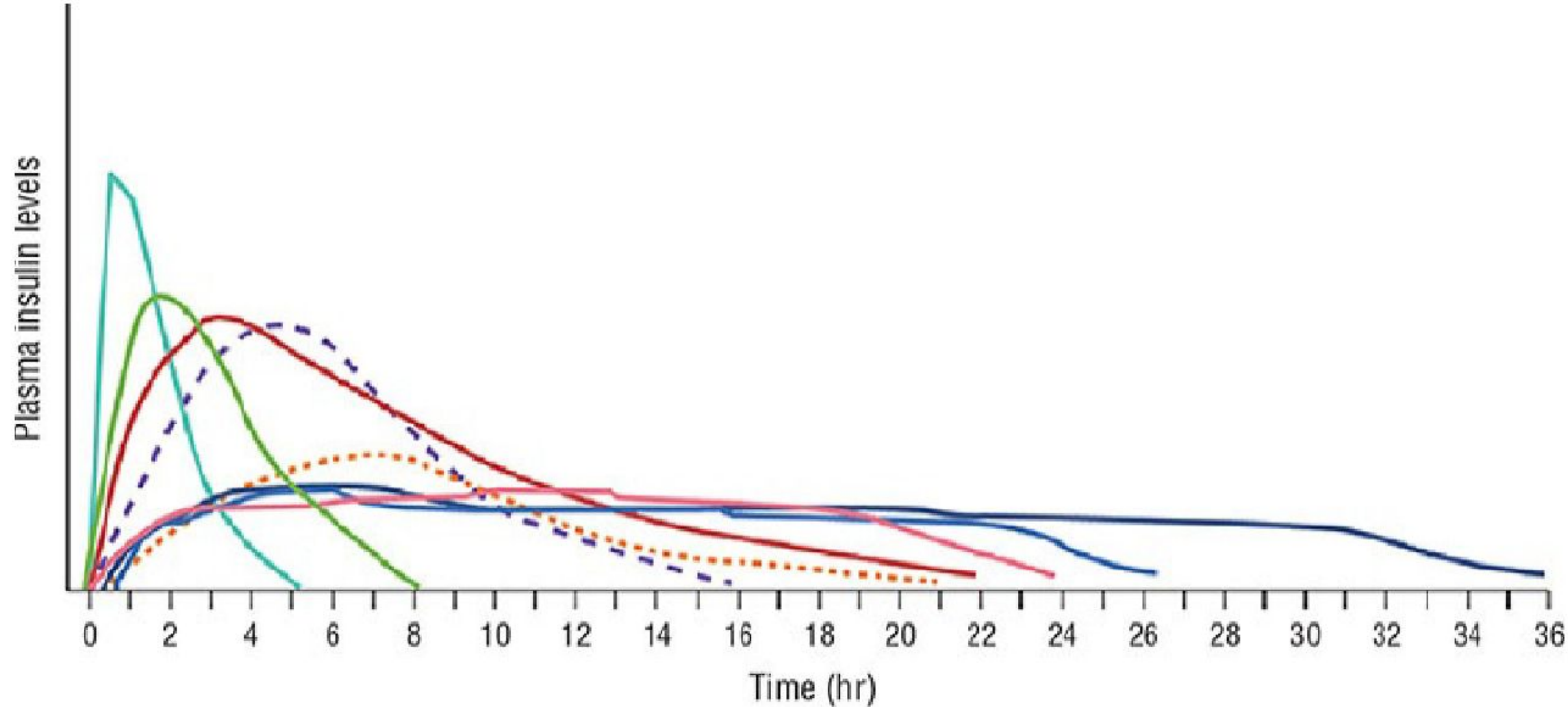
c. Higher-concentration insulin products

i. More commonly used in patients with T2D needing significant daily insulin doses

ii. U-300 glargine (300 units/mL), U-200 degludec (200 units/mL), U-200 lispro (200 units/mL), U-500 regular insulin (500 units/mL)

The pharmacokinetics and pharmacodynamics of insulin products are characterized by the onset, peak, and duration of appearance and action. Absorption of insulin from a subcutaneous depot is dependent on several factors, including source of insulin, concentration of insulin, additives to the insulin preparations (eg, zinc and protamine), blood flow to the area (rubbing of injection area, increased skin temperature, and exercise in muscles near the injection site may enhance absorption), and injection site. The abdomen provides the most consistent absorption for insulin.

Category	Drug Name	Clarity	Onset	Administration Time Before Meal (min)	Peak (hr)	Duration (hr)
Rapid acting	Aspart Lispro Glulisine Inhaled insulin	Clear	15–30 min	15 (inhaled insulin at beginning of meal)	1–3 (shorter with inhaled)	2–5 (shorter with inhaled)
Short acting	Regular	Clear	30–60 min	30	2–3	4–6
Intermediate acting	Neutral protamine Hagedorn	Cloudy	1–2 hr	N/A	4–8	10–20
Long acting	Detemir Glargine Degludec	Clear	2–4 hr 1–2 hr 1–2 hr	N/A	6–8 “Peakless” “Peakless”	6–24 ~24 24–42



- | | |
|--|--------------------------------------|
| — Rapid (aspart, lispro, glulisine, insulin human [inhaled]) | — Short (regular U-100) |
| — Mixed short/intermediate (regular U-500) | - - - Intermediate (NPH) |
| — Long (glargine U-100) | Long (detemir) |
| — Ultra-long (glargine U-300) | — Ultra-long (degludec U-100, U-200) |

Basal insulin, also called background insulin, refers to longer acting insulins that regulate BG levels in between meals by suppressing hepatic glucose production and maintaining near-normal glycemic levels in the fasting state.

Bolus insulin refers to short or rapid-acting insulins that cover meals (also called prandial insulin) or glycemic excursions (also called correction insulin).

Basal insulin is the preferred and most convenient initial insulin formulation in patients with type 2 DM while patients with type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control.

Basal insulin options include NPH, detemir, glargine U-100, glargine U-300, degludec U-100, or degludec U-200. From a pharmacokinetic/pharmacodynamics (PK/PD) perspective, NPH is the least ideal basal insulin as it has a distinct peak and a duration of action much less than 24 hours. While it can be given once daily in some patients with type 2 DM, it usually is dosed twice daily.

Detemir also has a peak and often lasts less than 24 hours, but has a more ideal profile compared to NPH. It can be given once daily in some patients but should be dosed twice daily at low doses (less than 0.3 units/kg). Insulin glargine

Insulin glargine U-100 offers a slightly better profile; it is considered to be peakless and can usually be given once daily. The longer acting agents (glargine U-300 and degludec) have no peak and a longer duration of action compared to glargine U- 100 and detemir. They are given once daily.

The effectiveness of insulin is highly dependent on its appropriate use. Product selection, education and training, and reinforcement is crucial. Counseling must include proper administration (including dose, injection technique, and timing of injection), glycemic targets, SMBG, dose titration or adjustment, storage, and prevention, detection, and treatment of hypoglycemia. Each insulin product is unique in the delivery device used. Some insulin products are available in vials, disposable pen devices, or pen cartridges, but many newer insulins are only available in pen devices. Each pen device product has different quantities, maximum injection doses, storage requirements and expirations. NPH insulin and all suspension-based insulin preparations should be inverted or rolled gently at least 20 times to fully suspend the insulin prior to each use. Improper mixing of the suspension prior to administration can lead to glycemic variability.

Management of insulin therapy

- a. First step is to estimate TDI requirements.
- b. Weight-based estimate if insulin naive
 - i. 0.3–0.6 unit/kg/day
 - ii. Requirements higher if treating DKA near initial diagnosis of DM
 - iii. Honeymoon phase shortly after treatment initiation often requires lower daily insulin needs.
- c. One common approach is to use older insulin formulations (NPH and regular insulin).
 - i. Two-thirds of TDI is given before the morning meal. Two-thirds of this is given as NPH, and one-third is given as regular insulin.
 - ii. One-third of TDI is given before the evening meal. Again, two-thirds of this is given as NPH, and one-third is given as regular insulin. Alternative is regular given before evening meal and NPH at bedtime.
 - iii. Advantages: Daily insulin injection frequency two or three times daily and less expensive than newer insulins
 - iv. Disadvantages: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events

- d. Basal-bolus insulin therapy (i.e., physiologic insulin therapy)
 - i. Use insulin analogs to better mimic natural insulin secretion patterns
 - ii. Use long-acting basal insulin to prevent ketosis and control FPG
 - iii. Use bolus insulin to control postprandial hyperglycemia
 - iv. Basal insulins: Insulin glargine or degludec once daily or insulin detemir once or twice daily
 - v. Bolus insulins: Rapid-acting insulin (can use short-acting insulin)
 - vi. Basal requirements are typically 50% of estimated TDI.
 - vii. Bolus requirements are typically 50% of estimated TDI split three ways before meals.
 - (a) Provides initial estimate of prandial insulin needs
 - (b) Typically, patients begin to estimate bolus requirements given the amount of carbohydrates to be ingested. Requires significant patient education in food carbohydrate estimates
 - (c) Alternative bolus requirement (Rule of 500): Dividing 500 by TDI will estimate the amount of carbohydrates (in grams) that 1 unit of a rapid-acting insulin will cover.

Advantages over NPH plus regular approach: More physiologic, less hypoglycemia, more flexible to patient mealtimes

Disadvantages: Cost and increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately). Note that the same process of basal-bolus insulin therapy can apply to a patient with T2D who is receiving intensive insulin therapy with or without oral DM medications.

Correctional insulin needs

“1800 rule”: $1800/\text{TDI}$ = milligrams per deciliter of glucose lowering per 1 unit of rapid-acting insulin

(a) For example, if TDI is 60 units, $1800/60 = 30$, suggesting that 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.

(b) Also called *insulin sensitivity factor*

“1500 rule” when using regular human insulin (i.e., $1500/\text{TDI}$)

More patient-specific than traditional sliding-scale insulin

EX.

Pt. on detemir 10 u/12hr, and 5 u every meal

6 AM breakfast	190 mg/dl
1 PM lunch	120 mg/dl
7 PM dinner	160 mgdl
10 PM bed time	140 mg/dl

Adverse effects

- Hypoglycemia is the most serious and common adverse reaction to insulin. Other adverse effects include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation