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Insulin
in Clinical Practice

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Chapter

1

Diagnosis of Diabetes Mellitus

Diabetes mellitus is a major disease which is increasing in the world day-by-day. Uncontrolled diabetes can lead to blindness, limb amputation, kidney failure, and vascular and heart disease. It is a silent disease and can cause lot of complications mentioned above if not diagnosed early. To diagnose diabetes mellitus early, all adults without risk factors should be screened with a test for prediabetes and type 2 diabetes starting at age 35. All women who are planning to become pregnant should be screened for diabetes by doing a fasting glucose test, especially if they have risk factors. For unplanned pregnancies, women should be screened at the first prenatal visit. Screening for gestational diabetes should be done again between 24 and 28 weeks.

ADA (American Diabetes Association) Criteria to Diagnose Diabetes Mellitus:

Diabetes is diagnosed with any one of the following criteria:	
1.	FBS ≥ 126 mg/dL, fasting is defined as no caloric intake for at least 8 hours OR
2.	2 hours post load glucose ≥ 200 mg/dL during an OGTT(oral glucose tolerance test). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water OR
3.	A1C ≥ 6.5% OR
4.	Random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. Random is defined as anytime of the day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydypsia, and unexplained weight loss

The above tests should be repeated once more to confirm the presence of diabetes mellitus unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL). Second test should be done as early as possible without much delay.

OGTT should be performed under controlled conditions to ensure its accuracy. Factors that decrease the value of OGTT include:

1. Carbohydrate restriction (<150 gm for 3 days)
2. Bed rest or severe inactivity
3. Medical or surgical stress
4. Drugs (e.g. Thiazides, steroids, β-blockers, phenytoin)
5. Smoking
6. Anxiety from repeated needle sticks.

Hence, OGTT should not be performed in acutely ill patients. Patients should ideally stop smoking and consume a liberal carbohydrate meal for at least 3 days prior to testing.

CRITERIA TO DIAGNOSE PREDIABETES STATES

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but have glucose levels more than the cut-off for normal individuals. These people have abnormal carbohydrate metabolism and are at risk of developing diabetes in future. Prediabetes is diagnosed by the presence of any one of the following criteria.

Impaired fasting glucose (IFG)
Fasting plasma glucose (FPG) 100 mg/dL to 125 mg/dL OR
Impaired glucose tolerance (IGT)
2 h plasma glucoe during 75 g OGTT 140 mg/dL to 199 mg/dL OR
A1C 5.7–6.4%

All patients with prediabetes states should be treated with diet and exercise and should be followed up yearly for the progression to diabetes.

Classification of Diabetes Mellitus

The ADA classification of diabetes includes four clinical classes:

- Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency).
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance).
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical induced (such as in the treatment of AIDS or after organ transplantation).
- Gestational diabetes mellitus (GDM) (diagnosed during pregnancy).

How to Know the Type of Diabetes

Understanding the type of diabetes is important from treatment point of view. However, many people do not fit exactly into one type. For example, some people with type 1 diabetes may become obese and develop insulin resistance which is a feature of type 2 diabetes. On the other hand most type 2 diabetics in advanced stages have little or no endogenous insulin secretion and such people have the characteristics of type 1 diabetes. Blurring of the lines between type 1 and type 2 diabetes is increasingly becoming common.

Clinical Clues

Type 1 diabetes usually begins in childhood, but can occur at any age. Approximately 50% of the adults develop type 1 diabetes before the age 40 years. The remainders develop it as older adults. Presence of other autoimmune diseases like celiac disease, Graves' disease, hypothyroidism, Addisons disease, pernicious anemia, etc. suggests type 1 diabetes. Family history of type 1 diabetes again suggests type 1 diabetes in the patient. Persons with type 1 diabetes are usually thin and have very high blood sugars at presentation. They often present with diabetic ketoacidosis. A type 2 diabetic is usually obese, presents after 35 years of age and may satisfy the criteria of metabolic syndrome. If the person is on oral antidiabetic agents

and is controlled with it, then he has type 2 diabetes because obviously oral agents do not work in type 1 diabetes.

Laboratory Clues

Ketone bodies: Presence of a large amount of ketone bodies goes in favour of type 1 diabetes, though type 2 also can have ketone bodies. If insulin is injected before testing for ketone bodies, the opportunity to find a large amounts of ketone bodies may be missed.

C- peptide levels: C-peptide is half of the precursor molecule to insulin that is split off when insulin is produced from the body. C-peptide levels can reveal how much insulin a person is producing. If c-peptide level is normal or high, type 2 diabetes is likely. If significantly low type 1 diabetes is likely. If the level is low normal, the person may have early type 1 or longstanding type 2 DM. When external insulin is being used it may suppress endogenous insulin production and hence c-peptide levels may be low. C-peptide levels should be measured after insulin has been reduced or discontinued, and the blood sugar has risen to 200 mg/dL or more.

Antibodies: Type 1 diabetes is an autoimmune disease, hence anti-islet anti-bodies and anti-GAD 65 (glutamic acid decorboxylase) antibodies can be found in 80 – 90% of patients with type 1 diabetes. Anti-GAD 65 antibodies can be found in only 3% of normal population. When both islet cell and GAD 65 antibodies are detected they increase the autoimmune disease detection to >90%. Blood tests can be done to detect the presence of these antibodies. If the person does not already have diabetes, presence of these antibodies predicts development of type 1 diabetes in such persons.

High triglyceride, low HDL, high uric acid: All these are markers of metabolic syndrome and suggest type 2 diabetes.

Glucose clamp procedure to detect insulin resistance: This is the gold standard to detect insulin resistance. Insulin resistance suggests type 2 diabetes. However, this is a time consuming procedure and is used only in research settings.

All the above lab tests especially C-peptide levels and auto antibodies need not be done routinely. Use them only when

Chapter

2

Insulin Basics

Discovery of insulin was one of the greatest milestones in medicine. It was discovered in 1921 by Banting and Best and they tried this on a patient in 1922. They received Nobel Prize in medicine for this remarkable discovery. The structure of insulin was subsequently fully worked out by Sanger in 1956.

DISULFIDE BONDS

Insulin is a two-chain polypeptide having 51 amino acids and molecular wt of 6000. These two polypeptide chains have been named as A and B chains **(Fig. 2.1)**. A chain contains 21 amino acids and B chain contains 30 amino acids. The A and B chains are held together by disulfide bonds. Insulin from different species differs only by a few amino acids. There are only minor differences between human, pork and beef insulins **(Table 2.1)**.

Note that the pork insulin resembles human insulin more than beef insulin. Pork insulin differs from human insulin by only one amino acid, whereas beef insulin differs by three amino acids.

Insulins of bovine or porcine origin were the only commercially available preparations for the first half century

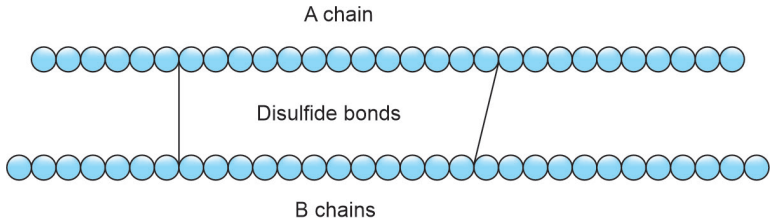

Fig. 2.1: Structure of insulin

Table 2.1: Differences in the amino acid composition of human, pork and beef insulin

Species	*A chain*	*B chain*	
	8th AA	10th AA	30th AA
Human	THR	ILEU	THR
Pork (porcine)	THR	ILEU	ALA
Beef (bovine)	ALA	VAL	ALA

of the insulin era. Though animal insulins differ slightly from human insulin as explained above, they are reliably absorbed into the human systemic circulation after subcutaneous injection and provide good control of plasma glucose. Limitations are mainly due to allergic reactions to impurities present in the formulations or the insulin molecule itself.

The first commercially available beef and pork insulins were amorphous solutions produced by alcohol extraction and acid precipitation. The addition of trace amounts of zinc to this process resulted in the formation of insulin crystals and production of the first short acting (crystalline zinc) insulin. This was called regular insulin or plain insulin. This had a short duration of action (5 – 8 hr).

The duration of action of subcutaneously injected insulin was further prolonged by complexing with protamine, a protein of fish origin. The protamine insulin complex is poorly soluble at physiologic pH and thus slowly absorbed from the subcutaneous tissue. Addition of trace amounts of zinc and further improvement in the molecule resulted in neutral protamine hagedron (NPH or isophane) insulin, which is intermediate acting. Hagedron is the name of the scientist who first formulated this preparation.

A second class of extended action insulins, the lente insulins, was developed in the 1950s by crystallizing insulin and zinc in acetate buffer without using protamine. These crystalline complexes dissolve slowly in body fluids and thus exhibit a prolonged duration of action after subcutaneous injection. Two types of insulins resulted by this method, semilente and

ultralente. Semilente has a peak and duration of action slightly longer than regular insulin. Ultralente has the greatest stability, lowest peak and long duration of action. Combining semilente and ultralente in the ratio of 30% and 70% gives lente insulin, which has a time action profile similar to NPH. Semilente is not used now except for producing lente.

So now we have NPH, lente and ultralente insulins. NPH and lente are intermediate acting and ultralente is long-acting. However, lente, semilente, and ultralente insulins are not available now.

HUMAN INSULIN

Refinement of microbiologic techniques led to the production of biosynthetic human insulin in 1980s. The first commercially available preparations of human insulin were sold from 1982 onwards. Recombinant human insulin is produced predominantly using *E. coli* and *Saccharomyces cerevisiae* for therapeutic use in human. In future, plant-based expression system hold tremendous potential for high-capacity production of insulin in very cost-effective manner. Very high level of expression of biologically active proinsulin in seeds or leaves with long-term stability, offers a low-cost technology for both injectable as well as oral delivery of proinsulin.

How to Measure Insulin Levels

1 mg of the international standard of insulin is 24 units. Insulin can be bioassayed by measuring blood sugar in rabbits or by its potency to induce hypoglycemic convulsions in mice. As pure preparations are now available, it can be assayed chemically also. Plasma insulin can be measured by radio immunoassay or enzyme immunoassay.

Regulation of Insulin Secretion

Insulin is secreted by beta-cells of pancreas. Under basal conditions, 1 unit insulin is secreted per hour by human pancreas. A larger quantity than this is secreted after every meal. Insulin secretion from beta-cells is regulated by chemical, hormonal, and neural mechanisms.

Chemical Control

Glucose, amino acids, fatty acids, and ketone bodies can stimulate insulin release, but glucose is the most powerful stimulus among these. Glucose and other nutrients are more effective in stimulating insulin release when given orally than intravenously because of generation of chemical signals (incretins) from the gut, which act on beta cells to cause anticipatory release of insulin. The incretins involved are gut-glucagon, secretin, gastrin, gastric inhibitory polypeptide, VIP, cholecystokinin – pancreozymin, etc.

Hormonal Control

GH, corticosteroids, thyroxine, prostaglandins, etc. have influence on insulin secretion. Different Islet cells of pancreas (alpha, beta, and delta) have influence on each other (paracrine effect).

Somatostatin (from delta cells), inhibits the release of both insulin and glucagon **(Fig. 2.2)**.

Glucagon (from alpha cells) evokes release of insulin as well as somatostatin.

Insulin (from beta cells) inhibits glucagon secretion.

Neural Control

The islets are richly supplied by sympathetic and parasympathetic (vagus) nerves.

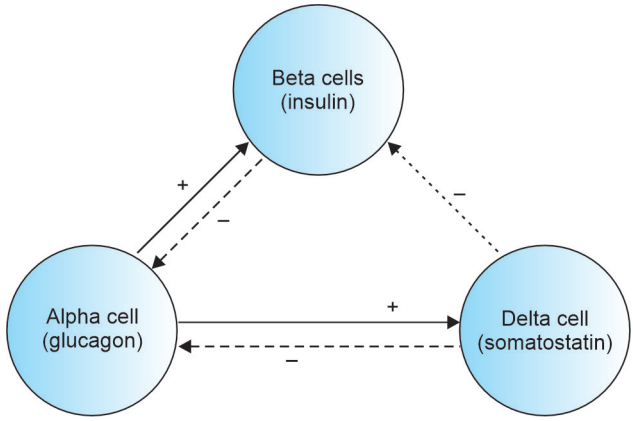

Fig. 2.2: Hormonal control of insulin secretion

Sympathetic

Adrenergic alpha-2 receptor activation inhibits insulin release by inhibiting beta-cell adenyl cyclase (prominent action). Adrenergic beta-2 stimulation increases insulin release by stimulating beta cell adenyl cyclase (less prominent action).

Parasympathetic

Muscarinic activation by acetylcholine or vagal stimulation causes increased insulin secretion.

Hypothalamus

Stimulation of ventrolateral nucleus in hypothalamus evokes insulin release, whereas stimulation of ventromedial nuclei inhibits insulin release.

Actions of Insulin

The ultimate goal of insulin is to favour storage of fuel:

- It facilitates glucose transport across cell membranes. Skeletal muscle and fat are highly sensitive to this action. However, glucose entry into liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Muscular activity induces glucose entry into muscle cells without the need for insulin, hence exercise has insulin sparing effect.
- It inhibits glycogenolysis in liver and facilitates glycogen synthesis (by stimulating glycogen synthetase) in liver, muscle, and fat.
- It inhibits gluconeogenesis (from protein) in liver and thus has protein sparing effect.
- It inhibits lipolysis in adipose tissue and favors triglyceride synthesis
- It stimulates transcription of vascular endothelial lipoprotein lipase and thus increases clearance of VLDL and chylomicrons.
- It facilitates amino acid entry and their synthesis into proteins in muscle cells and possibly other cells. Insulin deficiency leads to protein breakdown. In the absence of insulin, catabolism takes the upper hand over anabolism and this is what happens in diabetes.

of insulin pens are **HumaPen Ergo, Glaritus Pen Royale, INSUPen, and AllStar**.

Pen devices can deliver insulin from 0.5 to 70 units. The NovoPen-4 delivers a dose of 1 to 60 units. The BD pen has a maximum dose of 30 units.

Second-generation pen devices or "smart pens" with a memory function have been on the scene since 2007. The memory feature allows these devices to store the date, time, and amount of the previous doses. These devices are integrated with USB or Bluetooth features for efficient monitoring and data management. **HumaPen MEMOIR** is the world's first digital insulin pen with memory launched in 2007 by Eli Lilly followed by **HumaPen LUXURA HD**, a reusable pen for people who need insulin dosing in half-unit increments from 0.5 to 30 units. **NovoPen Echo**, the first insulin pen with memory and half-unit dosing features, was launched by Novo Nordisk in 2010. This device has several child-friendly attributes and displays time elapsed since the last dose.

Next generation insulin pens called connected pens (or smart pens use blue tooth and NFC (near field communication) to get connected to smart phones and other devices. **InPen System**, launched by Companion Medical, Novo Nordisk's **NovoPen 6 (Fig. 2.3) and NovoPen Echo Plus** fall into this category of pens. NovoPen 6 and NovoPen Echo Plus are reusable insulin pens equipped with NFC (near field communication) technology—meaning that they must be scanned in close proximity to move the data off the pen and to another device. The pens have an 800-injection dose memory and a remarkable five-year battery

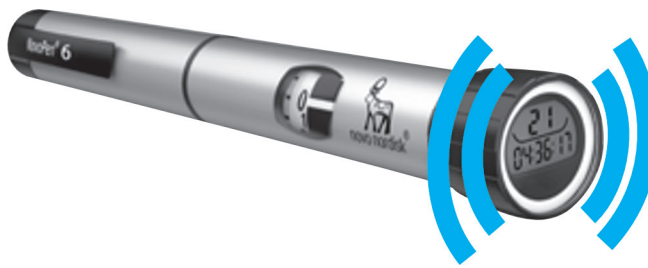

Fig. 2.3: NovoPen-6

Chapter

3

Different Types of Insulin Preparations

Two useful clinical classifications of insulin preparations are as follows.

Based on duration of Action

Rapid acting Lispro, aspart, glulisine
Short acting Regular insulin
Intermediate acting NPH insulin (neutral protamine hagedorn, also called isophane insulin)
Long acting Glargine, detemir, degludec

Based on Whether the Insulin Provides Prandial Coverage or Basal Coverage

Bolus or prandial insulins Regular or plain insulin, lispro, aspart, glulisine
Basal insulins NPH insulin, glargine, detemir, degludec

Regular and NPH insulins are also known as conventional (standard) preparations. They can be derived from beef, pork or recombinant-DNA technology (human insulin),

Lispro, aspart, glulisine, glargine, detemir and degludec are also called insulin analogues or designer insulins. They overcome some of the limitations of conventional insulin preparations. Insulin analogues are molecules that differ from human insulin in amino acid sequence but bind to same insulin receptors and function similarly as human insulin. Advantage

of new insulin analogues is that they have better time–action profiles than conventional insulins.

Time–Action Profiles of Different Insulin Preparations after Subcutaneous Injection

Normal physiologic insulin secretion includes both a continuous basal (low-level) insulin secretion and an incremental postprandial secretion associated with meals. However, subcutaneously injected insulin takes sometime to get absorbed into blood stream and start its action. Following is the time–action profiles different insulin preparations after subcutaneous injection **(Fig. 3.1 and Table 3.1)**.

Table 3.1: Time–action profiles of different insulin preparations

Insulin formulation	*Onset of action*	*Peak action*	Duration of action
Lispro, Aspart, Glulisine	< 15 min	1 h	3–5 h
Regular (plain)	30 – 60 min	2–4 h	6–8 h
NPH	2–4 h	4–12 h	10–18 h
Glargine	2–4 h	No peak	24 h
Detemir	Slow	No peak	Up to 24 h
Degludec	1–2 h	No peak	Up to 42 h

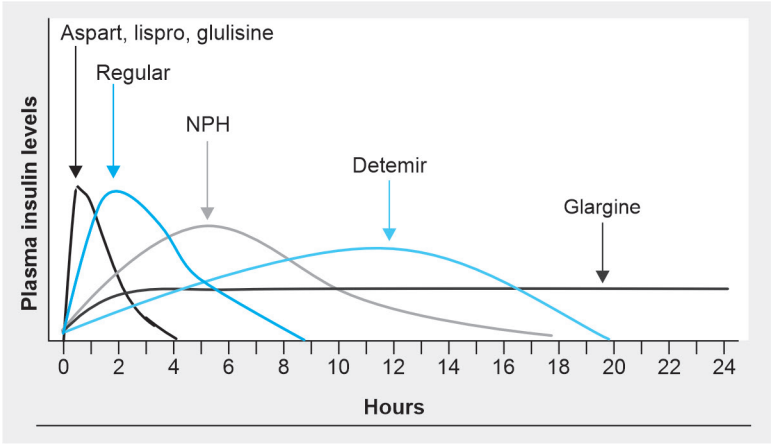

Fig. 3.1: Time–action profiles of different insulins

SHORT ACTING INSULINS

REGULAR INSULIN OR PLAIN INSULIN

Regular insulin has served the prototype of rapidly acting insulin for nearly the entire history of insulin therapy. It was earlier called rapid insulin. Now with the synthesis of newer insulin analogues which are rapid acting like insulin lispro and aspart, the term 'rapid acting' should not be used for regular insulin and instead should be used for lispro, aspart, and glulisine.

In nondiabetic person serum level of insulin rises rapidly after meal ingestion from basal levels of 5–20 μU/ml to peak levels of 80–120 μU/ml in 30–60 minutes after a high carbohydrate meal. Insulin secreted from pancreas enters portal circulation first and hence portal insulin concentrations are 2–3 fold higher than systemic insulin levels as the blood has to pass through liver first. This high concentration of insulin inhibits hepatic glucose output and hence helps in maintaining euglycemia. Because of all these, a non-diabetic person shows only a mild increase in blood glucose level after a meal.

Subcutaneously injected regular insulin cannot mimic the physiologic pattern of endogenous insulin secretion after eating. Subcutaneously injected regular insulin has a delayed onset and prolonged duration of action after administration making reproduction of physiologic insulin secretion impossible. Exogenously given insulin enters the systemic circulation directly. Long-term use of insulin can also lead to the production of antibodies against it with the possible development of insulin resistance.

Time–Action Profile of Regular Insulin (Fig. 3.1)

Regular insulin has an onset of action in 30–60 minutes after subcutaneous injection, a peak effect 2–4 hr after injection and duration of action of 6–8 hr. Hence, regular insulin has to be injected 30 to 40 minutes before meals in order to optimize the postprandial hyperglycemia.

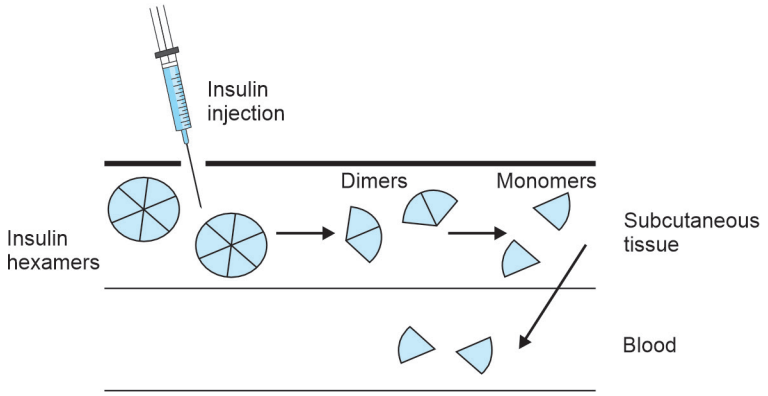

Fig. 3.2: Regular insulin absorption after subcutaneous injection

Insulin molecules are stored as hexamer form in beta cells of pancreas. The formation of hexamers is due to the presence of zinc. When secreted from the beta cells, the zinc gets released and hexamers dissociate into monomers which is the active form of insulin. Same thing happens with regular insulin preparation. Zinc is added to regular insulin and there is formation of insulin hexamers. When insulin is injected into subcutaneous tissue, zinc is released due to dilution, and insulin hexamers dissociate into dimers and then into monomers **(Fig. 3.2)**. Monomers are then absorbed into blood stream. This dissociation of insulin hexamers into monomers takes sometime leading to delayed onset of action of regular insulin.

INSULIN LISPRO

Insulin lispro was introduced in 1996. Lispro insulin is produced by interchanging two amino acids on beta chain, i.e. proline at B-28, and lysine at B-29. The first three letters of lysine and proline were combined to name it as Lyspro. Subsequently Lyspro was changed to Lispro since it was planned to release this all over the world and as some languages donot contain the letter "Y". Lispro insulin is at least twice as fast acting as regular human insulin.

In contrast to regular insulin where insulin monomers aggregate to form hexamers, lispro insulin molecules do not aggregate to form hexamers and remain in monomeric form. Hence, lispro insulin gets absorbed fast and has rapid onset of action. This property of insulin lispro is because of the interchange of 2 amino acids on β-chain, i.e. proline at B28 position and lysine at B29. Proline residue in the 28th position of β-chain has a crucial role in the formation of insulin dimers. Changing its position reduces the formation of dimers without changing the biological activity of the molecule.

Time–Action Profile of Insulin Lispro (Fig. 3.1)

After SC administration lispro begins acting within 15 mins, reaches peak concentrations between 30 and 60 minutes, peaks in activity in 60 to 90 minutes and has a duration of action of 3–5 hr. Peak insulin action occurs approximately twice as fast with the lispro as with regular insulin. Because of its fast onset of action, lispro can be given within 15 minutes before meals. It can also be given immediately before or after meals. After taking injection, there is no need to wait for 30 mins to take meals like regular insulin, hence lispro is also called no wait insulin.

The formation of antibodies to lispro is similar to that of human insulin. These antibodies usually decrease over time.

Advantages of Insulin Lispro Over Regular (Plain) Insulin

- Lispro is as effective as regular (plain) insulin and its peak concentrations are 2–3 times higher than regular insulin. It has better ability to mimic physiological pattern of insulin secretion than regular insulin. Because of its more rapid onset and peak action, insulin lispro more effectively controls postprandial blood sugar at 1 and 2 hr than regular insulin.
- Lispro is more effective in suppressing hepatic glucose output than regular insulin, because of higher concentrations attained in liver.
- The onset of action of lispro does not vary much with the site of injection as compared to regular insulin but when injected

Chapter

11

Acute Complications of Diabetes Requiring Insulin Therapy

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most serious complications of diabetes, which can occur in both type 1 and type 2 diabetes. DKA is more common in type 1 DM and HHS is more common in type 2 DM. Mortality rate for DKA in experienced centers is less than 5% and for HHS around 15%.

Basic underlying mechanism of pathogenesis in both is relative or absolute deficiency of insulin and increase in counter regulatory hormones, which leads to increased hepatic and renal glucose production and decreased peripheral utilization, giving rise to hyperglycemia and increasing osmolality of ECF. In DKA, there is also increased release of free fatty acids into the circulation due to the same mechanisms as above and there is unrestrained hepatic fatty acid oxidation giving rise to ketone bodies (β-hydroxy butyric acid and acetoacetate) with resulting ketonemia and metabolic acidosis. This fatty acid breakdown is not seen in HHS.

The most common precipitating factor in the development of DKA or HHS is infection. Other causes include CVA, alcohol abuse, myocardial infarction, trauma, drugs, pancreatitis, discontinuation of insulin, etc. Intake of drugs that affect the carbohydrate metabolism, such as corticosterioids, thiazides and sympathomimetic drugs (e.g. dobutamine and terbutaline) may precipitate the development of HHS and DKA. Psychological disorders complicated by eating disorders like bulimia nervosa may also be a precipitating factor.

CLINICAL FEATURES

DKA can develop in less than 24 hours whereas HHS evolves more slowly over days or weeks. In both cases patient may give history of polyuria, polydypsia, polyphagia, weight loss, and vomiting. Nausea and vomiting are present in 50–80% of patients with DKA. History of pain abdomen may be there in DKA which may be due to DKA itself or a precipitating factor like appendicitis, pancreatitis, etc. Examination may reveal signs of dehydration like dry mucous membranes, loss of skin turgor, sunken eyes, tachycardia, hypotension, etc. in both DKA and HHS. Acidotic breathing (kussmal respirations) may be noted in DKA. Altered mental status may be present in both which may range from stupor to coma. Coma is more frequent in HHS. 25% of DKA patients may have coffee ground vomitus because of hemorrhagic gastritis. Even though infection may be the precipitating factor, patients may not have fever. Presence of hypothermia is a poor prognostic indicator.

Diagnostic Criteria for DKA and HHS (Table 11.1)

Table 11.1: DKA and HHS

Plasma Glucose (mg/dL)	350 to 500 (usually <800)	Frequently exceeds 1000 mg/dL
Fluid deficit	6 Litres	9 Litres
Arterial pH	<7.30	>7.30
Serum bicarbonate (mEq/L)	Usually <15	>15
Urine ketones	Positive	Absent or small
Serum ketones	Positive	Absent or small
Effective serum osmolality (mosm/kg)	Variable	>320
Anion gap	>10	Variable
Alteration in sensorium or mental obtundation	Alert (coma in severe cases)	Stupor/coma

Urine and serum ketones are measured by nitroroprusside reaction method
Effective serum osmolality = 2 [measured Na(mEq/l)] + glucose (mg/dL)/18
Anion gap (mEq/l) = (Na) – (Cl^- + HCO_3)

Differential Diagnosis

- *Starvation and alcoholic ketoacidosis* can be distinguished by clinical history and blood glucose values, which ranges from mildly elevated to rarely >250 mg/dL to hypoglycemia. The serum bicarbonate in starvation ketosis is usually not lower than 18 mEq/L.
- *Lactic acidosis*, history of metformin intake should be sought. Measurement of blood lactate levels will help.
- *CKD*: Clinical history will help. There is hyperchloremic acidosis rather than high anion gap acidosis.
- *Ingestion of salicylate, methanol, ethylene glycol and paraldelyde* can cause similar picture like DKA. Clinical history and measurement of serum salicylate, methanol will help. Presence of calcium oxalate and hippurate crystals in urine suggests ethylene glycol ingestion. Paraldehyde ingestion is suggested by strong odor in breath (characteristic odor).

MANAGEMENT OF ADULT PATIENTS WITH DKA

Principles of Treatment

- Correction of dehydration, hyperglycemia, and electrolyte imbalance.
- Identification and treatment of precipitating events.
- Frequent patient monitoring.

Quick Initial Assessment

Check airway and breathing first especially in patients with altered sensorium. Take focused history and do brief physical examination. Obtain arterial blood gases, TC, DC, ESR, urinalysis, blood glucose, blood urea, serum creatinine, serum electrolytes, chemistry profile, and an ECG. Order chest X-ray and cultures if necessary.

Inpatient vs Outpatient Treatment

Patients with mild DKA who are alert and taking fluids orally can be treated on OPD basis under observation. The ADA guidelines for admission are a plasma glucose concentration greater than 250 mg per dL with an arterial pH level below 7.30, a serum

bicarbonate level of less than 15 mEq per L, and a moderate or greater level of ketones in the serum or urine. Patients with severe DKA require admission in the intensive care unit.

Fluid Replacement

Fluid replacement is the first priority while managing DKA and HHS. Fluid deficits are typically 100 mL per kg of body weight. Fluid replacement alone will lower blood glucose. Many studies have shown that during the first four hours of therapy for DKA, up to 80 percent of the decline in glucose concentration may be caused by fluid replacement. The effective serum osmolality ideally should not change more than three mOsm per hour during fluid replacement. The rate of initial isotonic saline infusion depends on the clinical state of the patient as follows.

- In patients with hypovolemic shock, isotonic saline should be infused as quickly as possible.
- In hypovolemic patients without shock (and without heart failure), isotonic saline is infused at a rate of 15 to 20 mL/kg lean body weight per hour (approximately 1000 mL/hour in an average-sized person) for the first couple of hours, with a maximum of <50 mL/kg in the first four hours.
- In euvolemic patients, isotonic saline is infused at a lower rate, guided by clinical assessment.

After the second or third hour, further fluid replacement should also take into account the sodium level. The "corrected" sodium concentration is calculated by adding 2 mEq/L to the plasma sodium concentration for each 100 mg increase in glucose level above normal. If the "corrected" serum sodium concentration is less than 135 mEq/L, isotonic saline should be continued at a rate of approximately 250 to 500 mL/hour. If sodium is normal or elevated, the IV fluid is generally switched to one-half isotonic saline at a rate of 250 to 500 mL/hour in order to provide more of electrolyte-free water.

When blood glucose approaches 200 mg/dL in DKA or 250 to 300 mg/dL in HHS, IV fluid is switched to dextrose in saline (DNS) and attempt is made to decrease the insulin infusion rate to 0.02 to 0.05 units/kg per hour. If possible, do not allow

the serum glucose at this time to fall below 200 mg/dL in DKA or 250 to 300 mg/dL in HHS, because this may promote the development of cerebral edema.

Insulin Therapy

Unless the episode of DKA is mild, intravenous insulin infusion is the treatment of choice. In adult patients, once hypokalemia (K^+<3.3 mEq/L) is excluded, an intravenous bolus of regular insulin at 0.1 units/kg body wt, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h (5 to 7 units/hr in adults), should be started. This initial insulin bolus is not recommended in pediatric patients as they may be very sensitive to insulin, instead a continuous insulin infusion of regular insulin at a dose of 0.1 unit/kg/h, may be started in these patients. Rapid acting insulin analogues (lispro, aspart, and glulisine) do not have any advantages over regular insulin when used as IV infusion. Any long-acting insulin should be withheld during DKA treatment. If the patient is on subcutaneous or intraperitoneal insulin pump, it should be stopped and the patient should be switched to an intravenous infusion. Aim for a decrease of plasma glucose concentration by 50–75 mg/dL/hour. If plasma glucose does not fall by 50 mg/dL from the initial value in the 1st hour, check hydration status; if necessary, the insulin infusion may be doubled every hour until a steady glucose decline between 50 and 75 mg/h is achieved **(Fig. 11.1)**.

If infusion pump is not available, SC route may be used. Then the initial bolus is 0.4 units/kg (out of this half is given IV and half is given as SC).

Direct measurement of β-hydroxy butyrate (β-OHB) in the blood is the preferred method for monitoring DKA. The nitroprusside method only measures acetoacetic acid and acetone. However, β-OHB, the strongest and most prevalent acid in DKA is not measured by the nitroprusside method. During therapy, β-OHB is converted to acetoacetic acid, which may lead the clinician to believe that ketosis has worsened. Therefore, assessments of urinary or serum ketone levels by the nitroprusside method should not be used as an indicator of response to therapy. During therapy for DKA or HHS,