

Diabetic Metabolic Emergencies



INTRODUCTION

Diabetes mellitus is a common group of metabolic disorders characterized by chronic hyperglycaemia resulting from relative insulin deficiency, insulin resistance or both. Diabetes is usually primary but may be secondary to other conditions, which include pancreatic (e.g. total pancreatectomy, chronic pancreatitis, haemochromatosis) and endocrine diseases (e.g. acromegaly and Cushing's syndrome). It may be drug induced, most commonly by thiazide diuretics and corticosteroids.

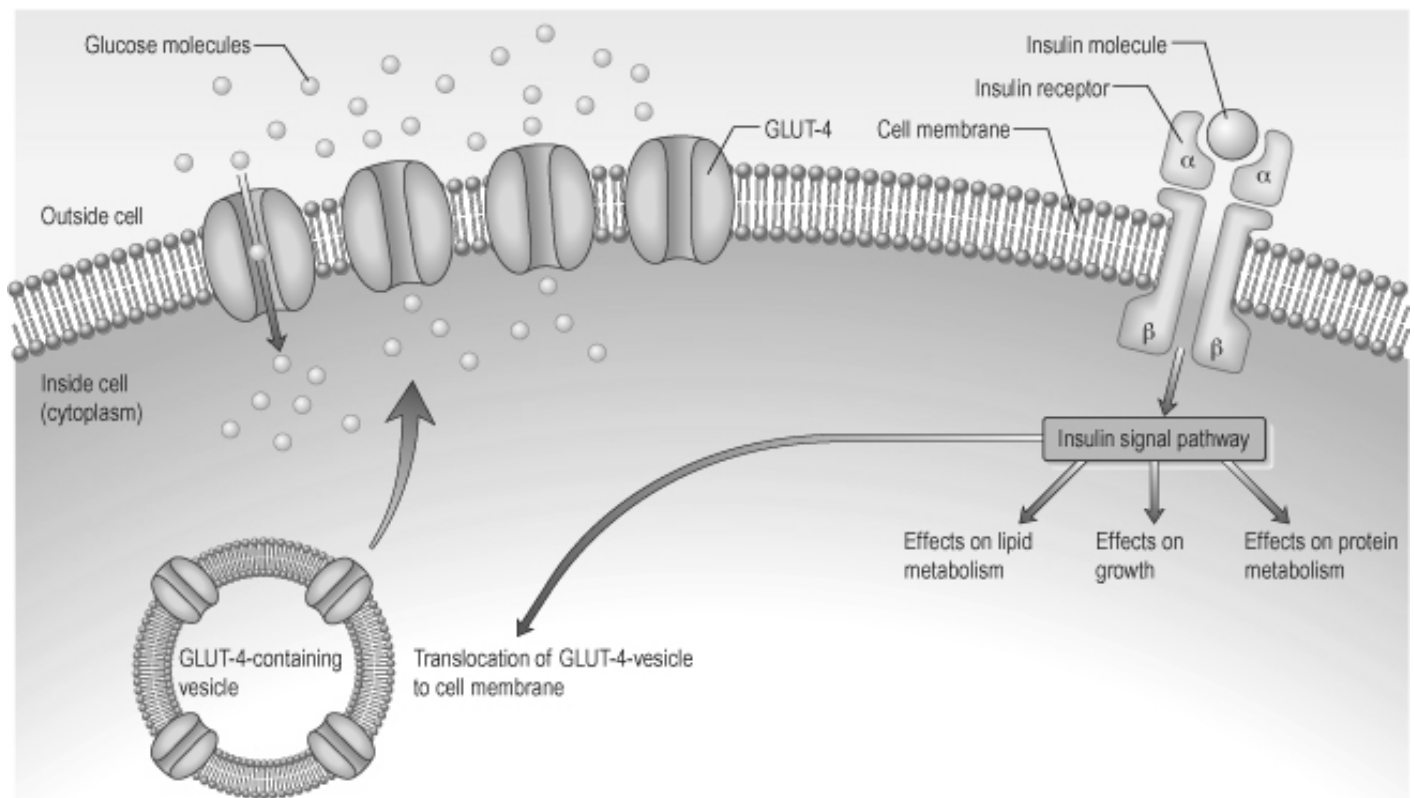
Primary diabetes is divided into 2 types of diabetes:

- Diabetes Type 1 (insulin Dependent Diabetes).
- Diabetes Type 2 (non-insulin Dependent Diabetes).

Diabetic metabolic Emergencies:

Diabetic emergencies can be divided into the following:

- Diabetic Ketoacidosis (DKA).
- Diabetic Non-Ketotic Hyperosmolar state (D-NKHOS).
- Lactic acidosis
- Hypoglycemia.



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DIABETIC KETOACIDOSIS (DKA):

DKA is the hallmark of type 1 diabetes. It does not usually occur in non-insulin-dependent diabetes, however recently DKA is being increasingly recognized in some type II diabetics, esp. Afro-Caribbean's.

Remember, patients may be prescribed insulin for poor diabetic control, and yet have non-insulin dependent diabetes.

DKA usually occurs in the following circumstances:

- Stress of intercurrent illness (e.g. sepsis) – 30 - 40%
- interruption of insulin therapy – 20 - 25%
- Previously undiagnosed diabetes - 25%

Definition of DKA:

Diabetic ketoacidosis is defined as:

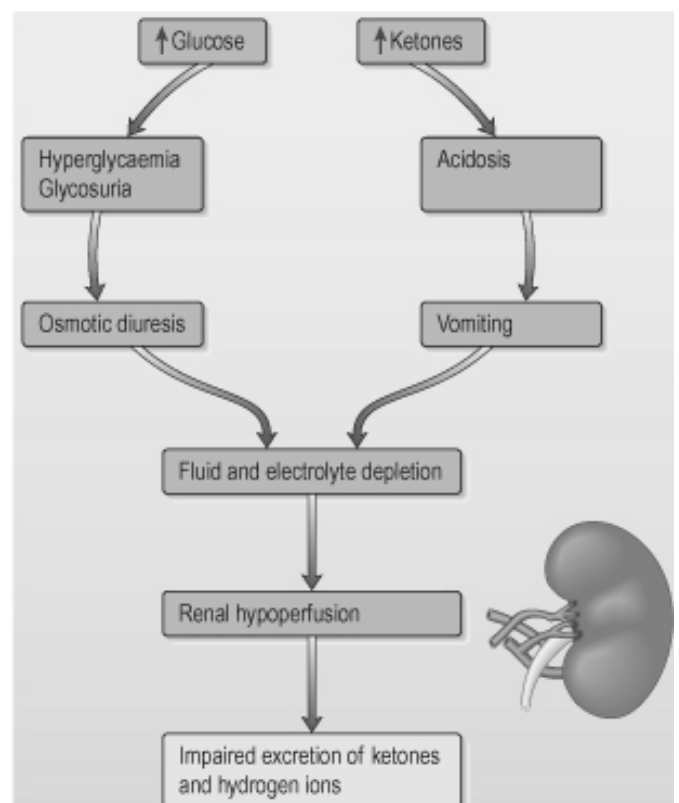
- Hyperglycaemia (> 14 mmol/l = mg/dl).
- Metabolic acidosis (pH < 7.35 or bicarbonate < 15 mmol/l)
- High anion gap.
- Ketonaemia.

DID YOU KNOW??

- 8.9% of patients with diabetes have an episode of DKA in 1 year.
- 42% of patients with DKA have another episode.
- 14% of patients with a blood glucose > 11 mmol/l and any complaint have DKA.
- 25% of patients with DKA have new-onset diabetes
- DKA may have no underlying cause.

Pathophysiology

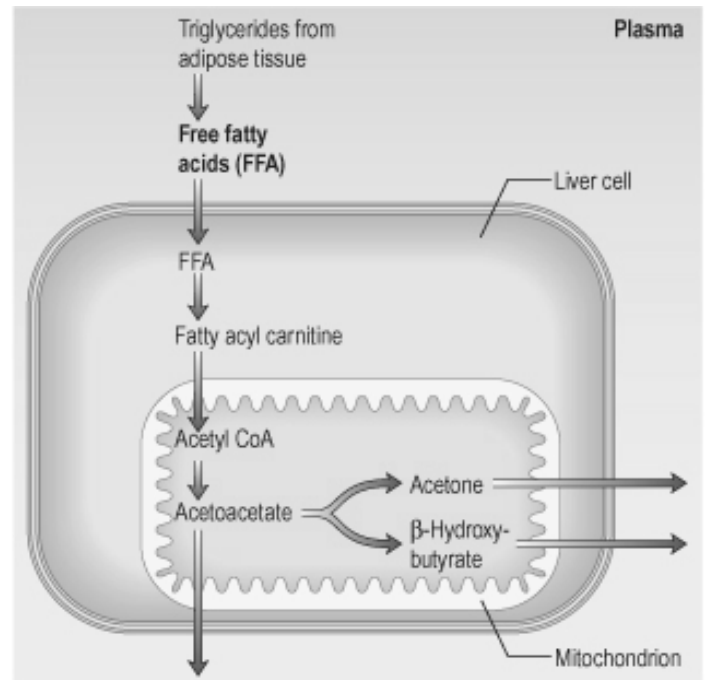
- Ketoacidosis is a state of uncontrolled catabolism associated with insulin deficiency. Insulin deficiency is a necessary precondition since only a modest elevation in insulin levels is sufficient to inhibit hepatic ketogenesis, and stable patients do not readily develop ketoacidosis when insulin is withdrawn.
- Other factors include counter-regulatory hormone excess and fluid depletion.
- In the absence of insulin, hepatic glucose production accelerates, and peripheral uptake by tissues such as muscle is reduced. Rising glucose levels lead to an osmotic diuresis, loss of fluid and electrolytes, and dehydration.
- Plasma osmolality rises and renal perfusion falls.



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- In parallel, rapid lipolysis occurs, leading to elevated circulating free fatty-acid levels. The free fatty acids are broken down to fatty acyl-CoA within the liver cells, and this in turn is converted to ketone bodies within the mitochondria. Accumulation of ketone bodies produces a metabolic acidosis.
- Vomiting leads to further loss of fluid and electrolytes.
- The excess ketones are excreted in the urine but also appear in the breath, producing a distinctive smell similar to that of acetone.
- Respiratory compensation for the acidosis leads to hyperventilation, graphically described as 'air hunger'. Progressive dehydration impairs renal excretion of hydrogen ions and ketones, aggravating the acidosis.
- As the pH falls below 7.0 ($[H^+] > 100$ nmol/L), pH-dependent enzyme systems in many cells function less effectively. Untreated, severe ketoacidosis is invariably fatal



Clinical Features

- Symptoms of uncontrolled diabetes (*polyuria, weight loss*)
- Symptoms of acidosis (*hyperventilation, Kussmaul's breathing, vomiting*)
- Abdominal pain mimicking acute abdomen (*exclude MI, and think of intra-abdominal conditions triggering DKA for example pancreatitis!*)
- Symptoms of altered mental state (*confusion & stupor are common, coma may be seen in up to 5% of cases*)
- Hypovolemic shock and death may ensue in extreme cases.
- On examination assess state of hydration, ventilation rate and smell for ketones, temperature (hypothermia)

Diagnosis:

- Demonstrate Hyperglycemia + acidosis + Ketonaemia + Ketonuria

DID YOU KNOW??

- In DKA, there might be hypothermia even in the presence of underlying infection, so don't rely on body temperature to diagnose infection.
- The Skin is usually dry (unlike hypoglycemia), the eye balls is lax to pressure in sever dehydration.

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Levels of Severity of DKA

Severity	HCO ₃	pH	Volume Depletion	Vomiting
Ketosis	≥20 mEq/L	>7.35	None to mild	No
Mild DKA	15-20 mEq/L	7.30-7.35	Mild; compensated	Usually No
Moderate DKA	10-15 mEq/L	7.2-7.3	Moderate; clinical apparent	Common
Severe DKA	<10 mEq/L	<7.2	Usually >7%-10%	Frequent

Investigations

Blood Glucose:

- Is usually high, but not always, values are usually above 17 mmol/l (300 mg/dl). RBG should be measured at arrival of patient, and hourly for the acute phases of treatment. After the patient is out of the DKA it should be monitored continually every 8 hours. Other investigations include:
- Urea & Electrolytes
- Full Blood count
- Blood Gases
- Blood and Urine culture
- Chest x-ray
- ECG & cardiac enzymes
- Serum Amylase

Management

PRINCIPLES OF MANAGEMENT:

- Replace Fluid.
- Replace electrolytes loss.
- Restore acid base balance.
- Replace the deficit insulin.
- Monitor blood Glucose.
- Replaces energy loss.
- Seek the underlying cause.

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Replace Fluid:

- This is the most important step in management, restoring the fluid loss will help correct the dehydration, the metabolic acidosis and minimize electrolytes loss as result of adjustment of the two former parameters.
- Replace the fluid losses with normal saline (0.9% saline).
- **Rate of correction:** there is no ultimate guidelines for fluid therapy, as it is guided by the clinical setting and the particular patient (i.e. pulse, BP, urinary output, decreasing symptoms, JVP, and co-morbid conditions), but generally, An average regimen would be 1 L in 30 minutes, then 1 L in 1 hour, then 1 L in 2 hours, then 1 L in 4 hours, then 1 L in 6 hours.
- Once plasma glucose falls below 250 mg/dl and ketons disappear from the serum, change to 5% dextrose.

PRACTICAL TIP

- In DKA, the patient may undergo pre-renal failure, or may have pre-existing renal impairment. giving potassium in this setting may be harmful, so it is advisable to give the first liter of saline and measure the urinary output, if its adequate (1-2ml/kg/h) then potassium can be started safely with the 2nd liter as the healthy kidney can get rid of excess potassium easily. Otherwise use little or no potassium.

Replace electrolytes loss:

Potassium (K⁺):

- Potassium levels need to be monitored with great care, as patients have a total body potassium deficit (up to 1000mmol may be lost) although initial plasma levels may not be low (i.e. pseudohyperkalemia). This in fact due to vomiting that accompanies DKA.
- When Insulin therapy is started, this leads to uptake of potassium by the cells with a consequent further fall in plasma K⁺ levels, Potassium is therefore given as soon as insulin is started.
- An average regime would be 20mmol Potassium Chloride (KCL) with each liter of fluid given; this may be increased or decreased depending on the 2-hourly serum K⁺ level.
- Potassium Sliding scale may be used to guide K⁺ replacement:

Serum K ⁺	Amount of KCL to be added to each liter of saline.
• < 3.0 mmol/l	• 40 mmol/l
• < 4.0 mmol/l	• 30 mmol/l
• < 5.0 mmol/l	• 20 mmol/ l
• > 6.5 mmol/l	• Withheld potassium until subsequent measurement.

Sodium (Na⁺):

- Patient with DKA usually have hyponatremia, in many cases this is a pseudohyponatremia as hyperglycemia causes an artifact in measuring Na⁺ levels, causing it to appear falsely lower than their actual concentration (for every 100mg/dl increase in glucose above the normal level, there is 1.6 MEq/L drop in serum sodium).
- To correct this use the following formula = **Corrected Na⁺ = "Na + (Glucose -5) / 3.5"**.

For example if the B.Glucose was 400mg/dl and the Na⁺ was 130mmol/l:

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Then the corrected $\text{Na}^+ = 130 + (400-5)/3.5 = 135\text{mmol/l}$.

- **Note that** a patient whose serum sodium concentration falls or fails to rise during rehydration is at increased risk of developing cerebral oedema. A failure to rise suggests rehydration with excess free water.

Restore acid base balance:

- A patient with healthy kidneys will rapidly compensate for the metabolic acidosis once the circulating volume is restored.
- Bicarbonate is seldom necessary and is only considered if the pH is below 7.0 ($[\text{H}^+] > 100 \text{ nmol/L}$), and is best given as an isotonic (1.26%) solution.
- Calculate the anion gap = $[(\text{Na}^+ + \text{K}^+) - \text{HCO}_3^-]$. The normal anion gap is about 8-17 mmol/l, a high anion gap is caused by unmeasured anions (e.g. DKA, drugs, uremia)

Replace the deficit insulin:

- Modern treatment is with relatively modest doses of insulin, which lower blood glucose by suppressing hepatic glucose output rather than by stimulating peripheral uptake, and are therefore much less likely to produce hypoglycemia.
- Soluble insulin is given as an intravenous infusion where facilities for adequate supervision exist, or as hourly intramuscular injections.
- The subcutaneous route is avoided because subcutaneous blood flow is reduced in shocked patients.
- Insulin is given as an infusion

Monitor blood Glucose:

- Hourly measurement is needed in the initial phases of treatment.
- Aim for a fall of blood glucose not more than 5 mmol/hour (about 90mg/dl).
- Keep the blood glucose $> 10\text{-}14 \text{ mmol/l}$ (180-250 mg/dl), until the ketoacidosis resolves.

Replaces energy loss:

- When plasma glucose falls to near-normal values (12 mmol/L), saline infusion should be replaced with 5% dextrose containing 20 mmol/L of potassium chloride. The insulin infusion rate is reduced and adjusted according to blood glucose.

Seek the underlying cause:

Physical examination may reveal a source of infection (e.g. a perianal abscess). Two common markers of infection are misleading:

- Fever is unusual even when infection is present, and polymorpholeucocytosis is present even in the absence of infection.
- Relevant investigations include a chest X-ray, urine and blood cultures, and an ECG (to exclude myocardial infarction).
- If infection is suspected, broad-spectrum antibiotics are started once the appropriate cultures have been taken.

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SUBSEQUENT MANAGEMENT

- Monitor glucose hourly for 8 hours.
- Monitor electrolytes 2-hourly for 8 hours.
- Adjust K replacement according to results

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NON-KETOTIC HYPEROSMOLAR STATE (D-NKHOS):

This condition, in which severe hyperglycaemia develops without significant ketosis, is the metabolic emergency characteristic of uncontrolled type 2 diabetes.

Pathophysiology

Patients present in middle or later life, often with previously undiagnosed diabetes. Common precipitating factors include:

- *Consumption of glucose-rich fluids (e.g. Lucozade).*
- *Concurrent medication such as thiazide diuretics or steroids.*
- *Intercurrent illness.*
- *Myocardial ischemia.*
- *Failure to comply with medications.*
- *Pancreatitis.*

Non-ketotic coma & ketoacidosis represent two ends of a spectrum rather than two distinct disorders, the biochemical differences may partly be explained by:

- *Age:* The extreme dehydration characteristic of non-ketotic coma may be related to age as old people are less likely to feel thirst, so they become dehydrated progressively without realizing that.
- *Renal Function:* there is usually mild renal impairment associated with age; this is further more aggravated by diabetes. This results in increased urinary losses of fluid and electrolytes.
- *Degree of Insulin deficiency:* is less severe in non-ketotic coma. Endogenous insulin levels are sufficient to inhibit hepatic ketogenesis, whereas glucose production is unrestrained.

DID YOU KNOW??

- In D-NKHOS, insulin deficiency is relative not absolute, and it is known that little amount of insulin is sufficient to inhibit ketone body synthesis. That's why they don't develop ketosis and acidosis!!!
- Symptoms of D-NKHOS are minimum, absence of acidosis abolishes features such as nausea, vomiting and abdominal pain. In addition the elderly patients of type 2 diabetes experience little symptoms and signs of dehydration.
- Cloudiness of consciousness may be the only presenting feature!!
- Abdominal pain in elderly patient with type 2 diabetes with D-NKHOS should raise the possibility of Myocardial infarction.

Clinical Features

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- Dehydration and stupor or coma (5%).
- Impairment of consciousness is directly related to the degree of hyper-osmolality.
- Evidence of underlying illness such as pneumonia or pyelonephritis may be present, and the hyperosmolar state may predispose to stroke, myocardial infarction or arterial insufficiency in the lower limb.



Management

The same principles of management of DKA are applied, yet there are some adjustments:

- The plasma osmolality is usually extremely high, It can be measured directly or calculated as $(2(\text{Na}^+ + \text{K}^+) + \text{glucose} + \text{urea})$ all in mmol/L.
- Many patients are extremely sensitive to insulin, and the glucose concentration may plummet. The resultant change in osmolality may cause cerebral damage.
- They need a lower dose of insulin as they are extremely sensitive; insulin is infused at a rate of 3 U per hour for the first 2-3 h, increasing to 6 U/h if glucose is falling too slowly.
- The standard fluid for replacement is 0.9% physiological saline; avoid 0.45% saline, since rapid dilution of the blood may cause more cerebral damage than a few hours of exposure to hypernatraemis in excess of 50%, however some authorities advocate the use of 0.45% saline if the serum sodium is extremely high.
- Some resources advocate prophylaxis against DVT with heparin.

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LACTIC ACIDOSIS:

Lactic acidosis is a rare complication of diabetic pharmacological therapy; its clinical significance lies in that it resembles ketoacidosis, and should be differentiated from it in order to give the correct treatment.



Pathophysiology

Lactic acidosis is divided into two types:

- **Type A:** with occurs in the setting of hypoxia, leading to impaired tissue oxygenation. Pyruvate generates lactate due to defective phosphorylation (*anaerobic metabolism*).
- **Type B:** this type is toxin generated, tissue oxygenation is normal.

Type B may occur in diabetic patients on biguanide therapy (*especially phenformin*). The risk in patients taking metformin is extremely low provided that the therapeutic dose is not exceeded and the drug is withheld in patients with advanced hepatic or renal dysfunction.

DID YOU KNOW??

- A Cochrane review showed little risk of lactic acidosis when metformin is used in standard therapeutic doses, most diabetologists would withdraw the drug when serum creatinine reaches 150 $\mu\text{mol/l}$



Clinical Features

- Patients present in severe metabolic acidosis with a large anion gap normally less than 17mmol/L).
- Usually they don't have significant hyperglycaemia or ketosis (in contrast to DKA).
- Diagnosis is confirmed by demonstrating the above features, plus measuring serum L-lactate levels which are elevated.



Management

Treatment is by:

- Stopping any offending drugs.
- Rehydration and intravenous support.
- Infusion of isotonic 1.26% bicarbonate in severe cases.
- The mortality is in excess of 50%.

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HYPOGLYCEMIA:

- This is the most common complication of insulin therapy and anti-diabetic medications, being more common in the former due to the fact that insulin-dependent patients need tighter glycemic control.
- It limits what can be achieved with insulin treatment, not to mention the anxiety it causes for patients & relatives.
- Virtually all patients experience intermittent symptoms and 33% will go into a coma at some stage in their lives.
- A small minority suffer attacks that are so frequent and severe as to be virtually disabling.

Pathophysiology

Hypoglycemia results from an imbalance between injected insulin and a patient's normal diet, activity and basal insulin requirement. The times of greatest risk are:

- *before meals*
- *During the night.*

Patients who are at increased risk include:

- *Those with Irregular eating habits.*
- *Those on long acting insulin (usually on a single dose).*
- *Those who are using artificial pumps or continuous infusion to deliver insulin.*
- *Elderly patients and those with long standing diabetes (sympathetic response is blunted by neuropathy)*
- *Behavioral factors: e.g. unusual exertion, alcohol excess.*
- *Patients with variation in insulin absorption.*

Hypoglycaemic unawareness:

People with diabetes have an impaired ability to counter-regulate glucose levels after hypoglycaemia. this is due to multiple factors:

1. **Autonomic failure.**
2. **Deficiency of glucagon response** *is invariably deficient, even though the alpha-cells are preserved and respond normally to other stimuli (found in type 1 diabetes)*
3. **Failure of epinephrine (adrenaline) response** *may also fail in patients with a long duration of diabetes, and this is associated with loss of warning symptoms.*
4. **Recurrent hypoglycaemia** *may itself induce a state of hypoglycaemia unawareness, and the ability to recognize the condition may sometimes be restored by relaxing control for a few weeks.*

Nocturnal hypoglycaemia

Basal insulin requirements fall during the night but increase again from about 4 a.m. onwards, at a time when levels of injected insulin are falling. Patients may sometimes increase the dose of insulin in response to the following:

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- “**Somogyi effect**”- in which nocturnal hypoglycemia leads to a surge of counter regulatory hormones to produce high blood glucose levels by 7 AM.
- “**Dawn phenomenon**”—reduced tissue sensitivity to insulin between 5 AM and 8 AM—is present in as many as 75% of type 1 patients and can aggravate the hyperglycemia

The problem may be helped by the following:

- checking that a bedtime snack is taken regularly
- for patients taking twice-daily mixed insulin to separate their evening dose and take the intermediate insulin at bedtime rather than before supper

Clinical Features

- Symptoms develop when the blood glucose level falls below 3 mmol/L (60 mg/dl) and typically develop over a few minutes, with most patients experiencing 'adrenergic' features of sweating, tremor and a pounding heartbeat.
- Physical signs include pallor and a cold sweat.
- Many patients with longstanding diabetes report loss of these warning symptoms and are at a greater risk of progressing to more severe hypoglycaemia. Such patients appear pale, drowsy or detached, signs that their relatives quickly learn to recognize. Behavior is clumsy or inappropriate, and some become irritable or even aggressive. Others slip rapidly into hypoglycaemic coma.
- Occasionally, patients develop convulsions during hypoglycaemic coma, especially at night. This must not be confused with idiopathic epilepsy, particularly as patients with frequent hypoglycaemia often have abnormalities on the electroencephalogram. Another presentation is with a hemiparesis that resolves within a few minutes when glucose is administered.
- B-blockers may diminish symptoms of hypoglycemia.

Management

Mild hypoglycemia:

- Oral sweets or glucose rich fluid (the patient should keep sweets in his pocket!!).

Severe hypoglycemia:

- intramuscular glucagon (0.5- 1 mg) or (may be i.v or s/c) or;
- Intravenous glucose (25-50 mL of 50% dextrose solution) followed by a flush of normal saline to preserve the vein (since 50% dextrose scleroses veins).
- Oral carbohydrate should then follow above management.

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REFERENCES & RESOURCES:

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6. Current medical diagnosis and treatment 2006, 45th edition.