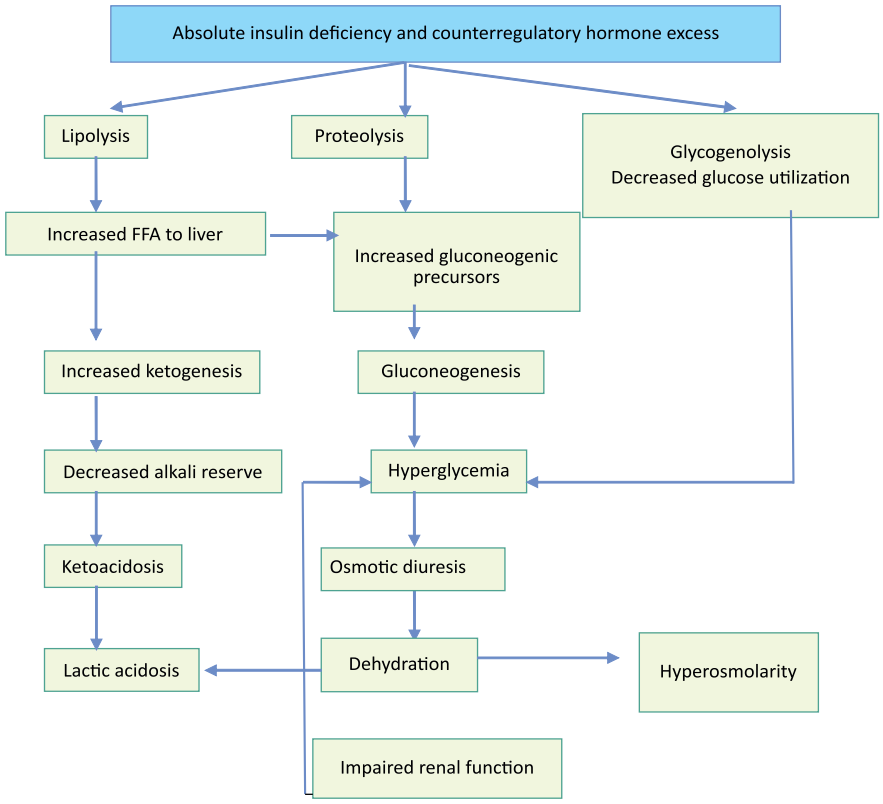
glycolysis and stimulation of gluconeogenesis. Additionally, elevated secretion of other counterregulatory hormones (such as catecholamines, cortisol, and growth hormone) oppose the actions of insulin and contribute to the development of hyperglycemia and ketosis. Since inhibition of lipolysis and ketogenesis is more sensitive to insulin rather than the inhibition of gluconeogenesis, the residual insulin secretion and its systemic action in HHS is enough to prevent the development of significant ketoacidosis but not hyperglycemia[21]. In patients with absolute or relative insulin deficiency, DKA and HHS are usually precipitated by stressful conditions that act in part by increasing the secretion of counterregulatory hormones.

The plasma glucose concentration in HHS is often > 1000 mg/dl, whereas in DKA, it is by and large <800 mg/dl and frequently in the range of 350-450 mg/dl[22]. There are two factors responsible for the lesser degree of hyperglycemia in DKA. Firstly, in DKA, patients present relatively early with symptoms of acute ketoacidosis like dyspnea, abdominal pain, and nausea and vomiting, whereas patients with HHS present late with symptoms of hyperosmolality. Secondly, patients with DKA are relatively young and have a high glomerular filtration rate (GFR), resulting in greater glucosuria than older patients with HHS. The pathogenesis of DKA has been illustrated in figure 1.

Figure 1: Pathophysiology of diabetic ketoacidosis and hyperglycemic hyperosmolar state



FFA: Free fatty acid

Clinical presentation and precipitating factors

Signs and Symptoms

A history of classical triad of hyperglycemia (polyuria, polydipsia and polyphagia), nocturia, generalized weakness, weight loss despite a good appetite, recurrent vaginal candidiasis

and a history of ants collecting around the child's urine may be present in the days-months prior to the acute episode. As ketoacidosis sets in, nausea and vomiting, abdominal pain, acidotic breathing with peculiar fruity odor and signs of dehydration appear. The patient is often drowsy at the time of presentation, though coma is rare. Infants tend to present with decreased energy and activity, irritability, weight loss, and physical signs of dehydration. A severe diaper dermatitis due to candidal infection is common in infants presenting with DKA.

Physical examination may disclose the following:

- Altered sensorium
- Tachycardia, tachypnea or hyperventilation (Kussmaul's breathing)
- Hypotension, very rarely hypertension
- Increased capillary refill time, poor perfusion
- Acetone odor of the breath reflecting ketosis

Precipitating Factors

A precipitating event can generally be discovered in patients with DKA. Most common precipitating factors are omission of insulin and acute infection. Omission of insulin usually occurs during an inter current illness in patients with poor awareness of sick day guidelines. Intentional omission of insulin is also possible, especially to try non-injectable "alternate systems of medicine". This may also be done with suicidal intent, as an attention seeking measure or as a manifestation of an eating disorder, especially in adolescents with T1DM. In patients using continuous subcutaneous insulin infusion (CSII), mechanical pump failure may be an important cause of DKA, especially in patients using the pump without adequate training and information.

Diagnosis and baseline assessment

DKA is defined by the presence of following[3]:

- Hyperglycemia – blood glucose of ≥ 200 mg/dl and
- Metabolic acidosis – venous pH < 7.3 or plasma bicarbonate < 15 mmol/L AND
- *Ketonemia (blood β-hydroxybutyrate ≥ 3 mmol/L) and ketonuria (typically urine ketones ≥ 2+)

  *A blood ketone (β-hydroxybutyrate) level between 0.6 and 1.5 mmol/L indicates mild elevation, while a level between 1.5 and 3 mmol/L suggests high risk for ketosis. Blood ketone level more than 3 mmol/L is usually associated with acidosis and warrants emergency admission and management for DKA.

Initial laboratory investigations should include plasma glucose, serum electrolytes, blood urea nitrogen, serum creatinine, venous blood gas analysis, and hematocrit. Measurement of blood β-hydroxybutyrate (BHB) should be performed, if possible. Point-of-care blood ketone test meter could also be used for this purpose. Several biochemical parameters may have fallacious readings in the setting of DKA. Plasma glucose may not be elevated in patients with repeated episodes of vomiting, reduced carbohydrate intake or those who have already received some treatment before presentation. Serum sodium can be falsely low due to dilutional hyponatremia resulting from hyperglycemia induced fluid shift from cells. An elevation of serum amylase and rarely, serum lipase may be present, unrelated to acute pancreatitis. Leucocytosis is common in DKA and does not always indicate infection.

Anion Gap (AG) is a very useful measure in calculating the severity of ketosis, and normalization of the anion gap is an indirect measure of the resolution of ketoacidosis. However, it cannot be used as a surrogate for blood pH since it fails to reveal the state of normal anion gap hyperchloremic metabolic acidosis, which may develop during treatment of DKA as a result of administration of chloride containing fluids and loss of potential bicarbonate precursors as ketoanions in urine.

AG is calculated as: AG (mmol/L) = Serum sodium (mmol/L) – [Serum chloride (mmol/L) + serum bicarbonate (mmol/L)] (normal value is 12 ± 2 mmol/L).

The severity of DKA is categorized by the degree of acidosis and is outlined below[3]:

- Mild: pH 7.20-7.29; serum bicarbonate 10-15 mmol/L
- Moderate: pH 7.10 -7.19; serum bicarbonate 5-10 mmol/L
- Severe: pH < 7.1; serum bicarbonate < 5 mmol/L

Differential diagnosis

The differential diagnoses of high anion gap metabolic acidosis have been outlined in Table I.

Table I: Differential diagnosis of high anion gap metabolic acidosis

Diabetic ketoacidosis
Uremia
Lactic acidosis
Methanol, ethylene glycol, ethanol ingestion
Salicylate toxicity

Management of DKA

Management of DKA broadly involves administration of intravenous fluids, intravenous insulin infusion and good supportive management (Table II)

Table II: Broad principles of DKA management

A (airway), B (breathing), C (circulation) of resuscitation
Intravenous fluids (normal saline)
Intravenous regular insulin infusion (after confirming normal serum potassium)
*Intravenous potassium supplementation (after confirming normal urine output) Serum potassium: < 3.3 mmol/L: correct potassium before starting intravenous insulin Serum potassium: 3.3-5.3 mmol/L: potassium supplementation along with intravenous insulin
Serum potassium: > 5.3 mmol/L: potassium supplementation not needed; monitor at regular intervals
Look for and treat the acute precipitating factor (such as infection)
Monitor vitals, hydration status, intake-output, neurological status at regular intervals Monitor blood glucose 1-2 hourly; urea, creatinine, sodium, potassium, bicarbonate, venous pH, urine or blood ketones every 4-6 hourly
Intravenous insulin infusion needed for both hyperglycemia and ketosis once BG <200-250 mg/dl, continue intravenous insulin infusion and replace intravenous normal saline with dextrose based intravenous fluid (DNS or D5W)
Once DKA resolved, and patient accepting orally, shift to subcutaneous insulin with adequate overlap

*Electrocardiography can be used as a surrogate for assessment of tissue potassium levels

Abbreviation: DNS: Dextrose normal saline, D5W: 5% dextrose

These measures are aimed at correction of ketoacidosis, hyperglycemia, hyperosmolality, hypovolemia and electrolyte disturbances. Like any other emergency, the first principle of resuscitation i.e. the ABCs (airway, breathing, circulation) apply to DKA as well. A decreased level of consciousness may lead to an unprotected airway and compromised breathing. Osmotic diuresis can cause a significant loss of fluid, leading to severe dehydration and circulatory collapse. Furthermore, severe electrolyte derangements significantly increase the risk of life threatening cardiac arrhythmias. Clinical assessment of degree of dehydration and level of consciousness is important and reader is directed to excellent reviews on these topics[23-25].

Fluid management

Fluid management in DKA involves the use of isotonic saline infusion to restore and expand extracellular volume and stabilize cardiovascular status. It should precede administration of intravenous insulin infusion. The use of fluids in the first hour before insulin administration has many advantages: a) it provides an opportunity to check potassium value, b) it prevents worsening of hypotension in a dehydrated patient (due to insulin-mediated shift of fluid from intravascular compartment) c) it decreases serum osmolality, reduces the counterregulatory hormone concentration, and improves hyperglycemia.

A bolus dose of isotonic (0.9%) normal saline is administered at a rate of 10 ml/kg intravenously over an hour or less, and may be repeated if necessary. A simple way of calculating total fluid requirement is outlined here. The sum of maintenance requirement (1500 ml/m2/day) + fluid deficit (calculated as 3%, 6% and 9% of body weight according to severity of dehydration) should be given evenly over 24-48 hours. Isotonic saline is recommended for the first 5-6 hours after which 0.45% saline can be used, provided serum sodium is rising. When the blood glucose falls below 200-250 mg/dl, 5% dextrose is added and at blood glucose levels below 150 mg/dl, 10% dextrose can be added. Addition of 5% dextrose to normal saline may be considered earlier (i.e., after the initial two hours of treatment), if blood glucose drops at a rate exceeding 90-100 mg/ dl/ hour.

Potassium replacement

Potassium deficit in children with DKA is around 3-6 mmol/kg of body weight. Despite the deficit, serum potassium may be elevated at presentation due to hypertonicity, insulin deficiency and metabolic acidosis. In most situations, potassium replacement should be started after initial fluid resuscitation and concurrent with insulin therapy. In case of hypokalemia, potassium replacement may be started after initial fluid resuscitation, but insulin therapy should not be initiated till serum potassium is >3.3 mmol/L. If immediate serum potassium measurements are not available, a bedside ECG may help determine the presence of significant hyperkalemia or hypokalemia at tissue level. Hypokalemia is indicated by the flattening/inversion of T waves, ST segment depression, wide QT interval, and presence of U waves. Tall and peaked symmetrical T waves, prolongation of PR interval, wide and flat/absent P wave, widened QRS complex and sine wave pattern are indicators of hyperkalemia. Initial potassium concentration in the infusate should be 40 mmol/L with subsequent potassium replacement rates based on serum potassium measurements (Table III).

Table III: Potassium replacement in diabetic ketoacidosis

Serum Potassium (mmol/L)	Potassium replacement (mmol/L)
< 3.3	40 - 60
3.3 - 4.3	30 - 40
4.3 - 5.3	20 - 30
> 5.3	0 - 20

Insulin therapy

Although fluid replacement by itself lowers blood glucose, insulin therapy is required to lower it further, and suppress lipolysis and ketogenesis. Intravenous insulin bolus at start of the therapy is not recommended, since it may increase the risk of cerebral edema[26,27]. Intravenous insulin infusion should be administered to all patients with moderate to severe DKA with serum potassium >3.3mmol/L. Regular insulin should be initiated at 0.05 to 0.1 U/kg/h intravenously by continuous infusion, at least 1 hour after starting intravenous fluids. To prepare the insulin drip, 50 units of regular insulin should be dissolved in 50 ml of normal saline. The usage of regular human insulin is recommended as short acting analogues offer no added advantage over regular insulin, when using the intravenous route for DKA management. The dose of insulin infusion should be titrated to achieve blood glucose reduction of 50-75 mg/dl/hour. The initial infusion rate may be kept at 0.05 units/kg/hr for patients with mild DKA, in infants or those with severe hypokalemia. Initial insulin infusion rate should be continued till resolution of diabetic ketoacidosis (BG <200 mg/dl, pH >7.3, bicarbonate>15 mmol/L and normalization of AG). It should be remembered that target of therapy is not merely normalization of hyperglycemia, but also resolution of ketoacidosis (which takes longer to correct than hyperglycemia).

Bicarbonate therapy

Acidosis in patients with DKA improves with insulin and fluid therapy, and the use of bicarbonate therapy for correction of acidosis remains controversial. Bicarbonate use in DKA is based on the theoretical assumption that severe acidosis could contribute to vital organ malfunction and prompt correction of acidosis may be beneficial. However, controlled trials have failed to show clinical benefit from bicarbonate therapy. On the other hand, therapy is associated with following risks:

a) A heightened risk of hypokalemia
b) Induction of paradoxical central nervous system acidosis
c) Worsening of intracellular acidosis owing to increased carbon dioxide production
d) Prolongation of ketoanion metabolism
e) Hyperosmolarity due to added sodium load

The only valid indications of administration of bicarbonate therapy are severe acidosis with arterial pH<6.9 and presence of life-threatening hyperkalemia[14].

Transition to subcutaneous insulin

The tapering of IV insulin infusion and initiation of a multiple-dose subcutaneous insulin regimen is recommended when the plasma glucose is <200 mg/dl (11.1 mmol/L), and at least two of the following parameters are achieved:

AG <12 mmol/L

Serum bicarbonate ≥15 mmol/L Venous pH >7.30

Beta-hydroxybutyrate < 1mmol/L

Insulin infusion should be continued for at least 1-2 hours after the initiation of subcutaneous regular insulin and 30-60 minutes after initiation of subcutaneous rapid acting insulin analog. The overlap is recommended because sudden discontinuation of intravenous insulin (before onset of effect of subcutaneous insulin) may result in recurrence of hyperglycemia and/ or ketoacidosis. If the patient is not able to eat, it is preferred to continue the intravenous insulin infusion.

Prevention of DKA

DKA can be prevented by better access to medical care, proper patient education, and effective communication with a health care provider during an inter current illness. Paramount in this effort is improved education regarding sick day management, which includes the following (also refer to the sick day guidelines in the chapter on "Education"):

1. Early contact with the health care provider.
2. Emphasizing the importance of insulin during an illness.
3. Review of blood glucose goals and the use of supplemental short or rapid acting insulin.
4. Having medications available to suppress a fever and treat an infection.
5. Initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated. Taking plenty of fluids along with salt should be encouraged as it helps to restore intravascular volume.
6. Education of family members on sick day management and record keeping including assessing and documenting body temperature, blood glucose, and urine/ blood ketone testing, insulin administration, and monitoring of oral intake and weight.
7. The use of home glucose-ketone meters may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home and, possibly, may prevent hospitalization for DKA.
8. The observation that stopping insulin for economic reasons is a common precipitant of DKA underscores the need for our health care delivery systems to address this problem, which is costly and clinically serious.
9. Emphatically counselling the family that insulin is the only effective treatment, and they should trynon-injectable alternative medications.

Complications of DKA

Cerebral edema

About 0.5-1% of DKA episodes in children may be complicated by cerebral edema. Clinical features include persistent headache, recurrent vomiting, irritability, drowsiness, incontinence inappropriate for age, focal neurological deficits and signs of raised intracranial tension (hypertension, bradycardia, and irregular respiration). The postulated risk factors for the

development of cerebral edema include overtly rapid fluid resuscitation with acute decline in serum osmolality, administration of bolus intravenous insulin or use of intravenous insulin in first hour of fluid resuscitation and administration of bicarbonate therapy[14]. Young children (<5 years of age) with severe acidosis and hypocapnia, elevated blood urea nitrogen and less than expected rise in serum sodium with declining plasma glucose are at highest risk of cerebral edema[14]. The treatment should be started immediately pending the results of neuroimaging studies and includes:

1. Head end elevation
2. Reviewing and adjusting the fluid administration rate so that excessive fluids are avoided
3. Intravenous mannitol (0.25 to 1 g/kg) over 20 minutes; the dose can be repeated in two hours, if there is no initial response
4. Hypertonic (3%) saline, at 2.5–5.0 ml/kg over 10–15 minutes may be used as an alternative to mannitol, especially in cases where there is no initial response to mannitol
5. Intubation and mechanical ventilation for airway protection and assisted ventilation

Infections

Apart from bacterial infections, rare fungal infections like rhinocerebral mucormycosis and pulmonary aspergilllosis are seen at an increased incidence in patients with DKA. A high index of suspicion coupled with appropriate investigations may help recognize and treat these potentially life threatening infections.

Acute kidney injury (AKI)

AKI with urine output < 0.5 ml/kg/hr is a poor prognostic marker and can predispose patients to cerebral edema and acute respiratory distress syndrome (ARDS).

Hyperchloremic acidosis

Hyperchloremic acidosis manifests as normal AG metabolic acidosis, usually at 8-12 hours after therapy, when ketosis has already resolved. It occurs as a result of administration of intravenous fluid containing excessive chloride (0.9% NS) and requires substitution to lesser chloride (0.45% NS) containing intravenous fluids.

Hypophosphatemia

Hypophosphatemia usually manifests after treatment initiation as a result of transcellular shift of phosphate from extracellular to intracellular compartment by insulin. Encouraging early oral intake (<24 hours), when possible, may help prevent this complication. Severe hypophosphatemia with serum phosphorous<1 mg/dl may manifest as muscle weakness and rhabdomyolysis, and should be treated regardless of the symptoms.

Deep venous thrombosis

DKA is considered to be a prothrombotic state, and therefore, to prevent venous thrombosis, central venous access should preferably be avoided. Heparin prophylaxis may be considered for children requiring central venous catheters placement and for those likely to remain immobile for more than 24–48 hours.

Other acute complications

These include hypoglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, aspiration pneumonia, acute gastric dilatation, acute pancreatitis, upper gastrointestinal bleeding, rhabdomyolysis, cortical venous thrombosis, basilar artery thrombosis and subarachnoid hemorrhage[28].

Section B-Hypoglycemia in T1DM

Definition and incidence of hypoglycemia

Hypoglycemia is the limiting factor in the glycemic management of patients with diabetes[29,30]. It causes recurrent morbidity in most people with T1DM, and is sometimes fatal. Hypoglycemia in a patient with diabetes is defined as all episodes of abnormally low plasma glucose concentration that exposes an individual to potential harm. Individuals with diabetes should become concerned about possibility of developing hypoglycemia at self-monitored plasma glucose concentration of 70 mg/dl or less[31]. Iatrogenic hypoglycemia is very common in patients with T1DM[32-34].

Physiological defenses against hypoglycemia and clinical manifestations of hypoglycemia

In normal individuals, the first defense against falling plasma glucose concentration is decrease in insulin secretion (at glycemic threshold of about 80-85 mg/dl). With further decline of plasma glucose, increased secretion of counter-regulatory hormones glucagon and epinephrine occurs (at glycemic threshold of about 60-65 mg/dl). Glucagon acts as the second line of defense, while epinephrine acts as third line of defense against hypoglycemia. Epinephrine defense becomes critical when glucagon is deficient. Cortisol and growth hormone are also released (at glycemic threshold of about 60-65 mg/ dl); however, they are not critical counter-regulatory hormones in the defense against hypoglycemia.

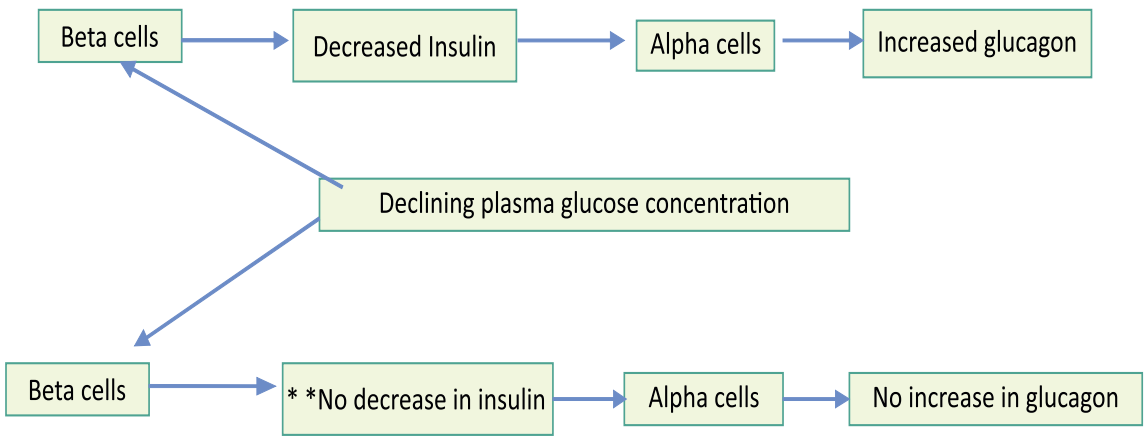
These defenses typically prevent an episode of symptomatic hypoglycemia; however, in case plasma glucose concentration continues to decline, neurogenic symptoms of hypoglycemia appear (at a glycemic threshold of about 50-55 mg/dl). These symptoms prompt behavioral defense against hypoglycemia (intake of oral carbohydrates). The symptoms are non-specific and glycemic threshold for appearance of the symptoms is rather dynamic. In patients with recurrent hypoglycemia, the glycemic threshold may shift to much lower concentration, while in those with poorly controlled diabetes, it may shift to much higher plasma glucose concentration[35]. The neurogenic symptoms are a result of sympathoadrenal discharge and include adrenergic symptoms (such as tremor, palpitations and anxiety/ arousal) and cholinergic symptoms (such as hunger, sweating and paresthesias). The symptoms are typically stereotypical for a given individual. At further lower plasma glucose concentration (at a glycemic threshold of <50 mg/dl), neuroglycopenic symptoms due to brain glucose deprivation appear. These include cognitive impairment, behavioral changes, psychomotor abnormalities, seizures and finally, coma. A patient with neuroglycopenic symptoms may not be able to manage the episode of hypoglycemia by self, requiring assistance of another person to deal with it. In most instances, neurological recovery is complete following correction of hypoglycemia, however permanent neurological damage may occur in case of prolonged insult to the brain. Unpredictable playing/activity pattern and fussy eating behavior may put children at higher risk of developing hypoglycemia.

Additionally, they (especially young children) may be at a higher risk of developing severe hypoglycemia due to their inability to communicate the symptoms and show appropriate behavioral eating response.

Pathophysiology of iatrogenic hypoglycemia in T1DM

Therapeutic insulin excess coupled with impaired glucose counter regulation is the chief pathophysiology behind recurrent hypoglycemia in patients with T1DM. As plasma glucose levels fall in response to iatrogenic hyperinsulinemia, insulin levels fail to decline (loss of first line of defense). Additionally, glucagon levels fail to increase in response to falling glucose concentrations, despite presence of functional alpha cells (loss of second line of defense) (Figure 2).

Figure 2: Response to decline plasma glucose concentration in a normal person (top panel) and individual with type 1 diabetes mellitus (bottom panel). The bottom panel shows how the first and second lines of defense against hypoglycemia are lost in patients with type 1 diabetes mellitus.

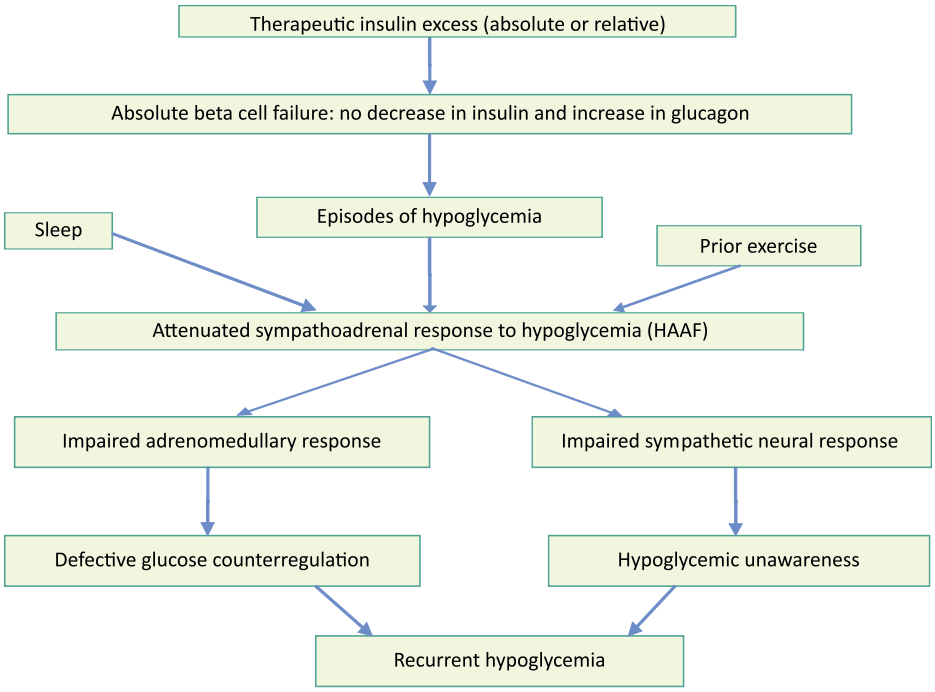


* There exists a state of absolute endogenous insulin deficiency and relative exogenous insulin excess.

The epinephrine response, which becomes critical in such situations, is typically attenuated as well, especially in patients with long-standing disease and those with recurrent antecedent hypoglycemia. The lack of effective physiological defense mechanisms against hypoglycemia constitute the syndrome of defective glucose counterregulation, which is associated with 25-fold higher risk of severe iatrogenic hypoglycemia[36,37].

The attenuated epinephrine response is also a marker for impaired sympathoadrenal discharge (sympathetic neural and adrenomedullary response). This implies that neurogenic symptoms of hypoglycemia may be blunted, resulting in clinical syndrome of hypoglycemia unawareness, which is associated with 6-fold higher risk of severe hypoglycemia. The impaired glucose counterregulation and hypoglycemia unawareness set the tone for vicious cycle of recurrent hypoglycemia in such patients. The attenuated sympathoadrenal discharge in response to hypoglycemia is known as hypoglycemia associated autonomic failure (HAAF). Risk factors for HAAF include history of recent antecedent hypoglycemia, prior exercise and sleep, and aggressive glycemic therapy for control of hyperglycemia[35]. HAAF is a functional form of autonomic failure, which can be reversed by scrupulous avoidance of hypoglycemia for 2-3 weeks. The pathophysiology of iatrogenic hypoglycemia in patients with T1DM has been elucidated in figure 3.

Figure 3: Pathogenesis of iatrogenic hypoglycemia in patients with type 1 diabetes mellitus. HAAF: Hypoglycemia associated autonomic failure



Risk Factors for hypoglycemia in T1DM

1. **Incorrect insulin therapy:** Syringe-vial mismatch, incorrect technique, incorrect timing, insulin stacking, higher insulin dose
2. **Decreased exogenous glucose delivery into blood:** Due to missed meals, delayed absorption or malabsorption
3. **Increased glucose utilization:** During or after exercise
4. **Impaired endogenous glucose production:** Due to alcohol ingestion, liver or renal disease
5. **Improved insulin sensitivity:** Late after exercise, in middle of the night or following improved fitness
6. **Decreased clearance of insulin:** Renal failure and uncontrolled hypothyroidism
7. **Others:** Concomitant adrenal insufficiency, use of high dose of insulin during the honeymoon phase of T1DM and infrequent self-monitoring of blood glucose (SMBG).

Prevention of iatrogenic hypoglycemia in T1DM

1. Patient education

Patients need to be educated about the action profile of different insulin preparations, importance of regular meal timings, avoidance of intramuscular administration and syringe-vial mismatch, symptoms of hypoglycemia, its recognition and appropriate management.

2. Frequent SMBG and CGMS

Frequent SMBG may help discover episodes of asymptomatic hypoglycemia, especially during the night. However, SMBG provides a snapshot of blood glucose values and not the longitudinal trend. CGMS provides an opportunity to capture the glucose data in a

longitudinal fashion as it records interstitial fluid glucose every 5-15 minutes. CGMS/ SMBG readings can be used to make meaningful decisions on adjustments in diet and insulin therapy to prevent future hypoglycemia episodes.

3. Insulin analogues

Use of relatively peakless long-acting insulin analogues (such as glargine, detemir or degludec) instead of intermediate acting insulin NPH (Neutral Protamine Hagedorn) may help reduce the incidence of nocturnal hypoglycemia in patients with T1DM[38-40]. Similarly, rapid acting insulin analogues (aspart, lispro, glulisine) may be preferred over regular insulin in patients having delayed pre-meal hypoglycemia with regular insulin. However, the extra cost of treatment associated with use of insulin analogues should be considered and substitution should only be done in cases where hypoglycemia persists despite best measures (such as ensuring a mid-meal snack).

4. Address the risk factors for HAAF

HAAF is associated with vicious cycle of recurrent hypoglycemia due to blunted sympathoadrenal flow. Temporary relaxation of glycemic control, and scrupulous avoidance of hypoglycemia for 2-3 weeks may help restore the awareness[41-42].

Management of hypoglycemia

Treatment is warranted for both symptomatic and asymptomatic episodes (detected by SMBG or CGMS). For most adults, oral intake of a concentrated and quickly absorbed simple carbohydrate source containing 15-20 g glucose (such as 3-4 teaspoon glucose powder dissolved in water or 4-5 glucose tablets) corrects hypoglycemia. In children, 0.3 g/kg body weight oral glucose is sufficient to correct hypoglycemia (approximately 5 g for a 15 kg child). Solution of simple sugar (sucrose) may be used in case glucose powder or tablet is not available. Glucose and sucrose are likely to be more efficacious than fructose in treating hypoglycemia[43]. Since the response to oral glucose is only transient, intake of oral glucose should be followed by a snack or a meal comprising of a mixed food source (proteins, fats etc.). The snack should be taken only after 15 minutes of intake of the simple carbohydrate to avoid interference with its absorption. Recheck the plasma glucose again in 15 minutes to affirm that glucose values have normalized and to decide if any further treatment is essential. In case repeat blood glucose is less than 70 mg/dl, above treatment should be repeated.

A small dose of subcutaneous glucagon has been used efficaciously to prevent approaching hypoglycemia or in the context of “sick day” management for a child with anorexia or with inadequate oral intake[44-45]. For patients with severe neuroglycopenic symptoms who may be unable to take glucose orally, parenteral administration of glucagon or dextrose is necessary. Glucagon can be administered either subcutaneously or intramuscularly and a close relative of the patient should be trained regarding the same. A 0.5 mg dose is used for body weight ≤20 kg, and a dose of 1 mg is administered when body weight is >20 kg. Glucagon may lead to nausea and vomiting within 45-60 minutes after injection and it is advisable to follow glucagon injection by oral consumption of concentrated carbohydrates, instantaneously upon recovering from the confused state. Since glucagon corrects hypoglycemia by stimulating glycogenolysis, in the rare scenario of hypoglycemia following alcohol binge in a patient with T1DM, glucagon will be ineffective. In scenarios permitting intravenous (IV) access and presence of a qualified medical personnel, dextrose

can be administered IV at a dose of 0.25 g/kg (maximum single dose 25 g). The intravenous bolus should be followed by a continuous IV dextrose infusion and when feasible, oral carbohydrate consumption.

It is recommended that every patient with T1DM should have a glucagon kit at home, at school/daycare, and during long journeys. Prescriptions of glucagon should be filled again before the date of expiration. Every patient with T1DM should wear a recognition band to ascertain proper intervention by emergency personnel, should such a situation arise.

Nocturnal hypoglycemia

Iatrogenic hypoglycemia often occurs at night, specifically during sleep, in patients with T1DM[46]. This is typically the longest inter-prandial interval and also the longest gap between two self monitored blood glucose measurements. Middle of night is also the time of maximum sensitivity to insulin[47]. The occurrence of hypoglycemia at night is particularly worrisome to children and adolescents with T1DM. This stems from the fear that nighttime hypoglycemia may not be treated in a timely fashion or that it may go entirely undetected and lead to irreparable brain damage or death. In addition, as discussed above, sympathoadrenal responses to hypoglycemia are reduced further during sleep[47,48] and probably because of their markedly reduced sympathoadrenal responses, patients with T1DM are substantially less likely to be awakened by hypoglycemia than non- diabetic individuals[48].

Therapeutic approaches to the prevention of nocturnal hypoglycemia in T1DM include the use of insulin analogs during the day in multiple daily injection (MDI) regimens, continuous subcutaneous insulin infusion (CSII) regimens[49,50] and a variety of bedtime treatments. Among the latter, bedtime snacks are the time- honored approach. Other measures intended to produce more sustained exogenous glucose delivery overnight include bedtime administration of the slowly digested complex carbohydrate (uncooked cornstarch)[51] and administration of an α-glucosidase inhibitor to delay the digestion of carbohydrates in the evening meal[52]. A possibility of midnight hypoglycemia causing high morning fasting blood glucose (Somogyi phenomenon) should always be considered before increasing the dose of intermediate or long acting insulin delivered at night.

Section C- Infections in T1DM

Introduction

Patients with diabetes are prone for a variety of infections which are also more likely to run a complicated course compared to the general population. In a prospective study from Denmark, patients with diabetes were found to have 1.5-3.0-fold higher risk for pneumonia, soft tissue infections and urinary tract infection (UTI) compared to the non-diabetic population. Among patients admitted with UTI, mortality at 28 days was 4-fold higher in those with diabetes. The authors also reported that each 1 mmol/L (18 mg/dl) increase in blood glucose increased the risk for pneumonia, soft tissue infection and UTI by 6-10% after adjustment for confounding factors[53].

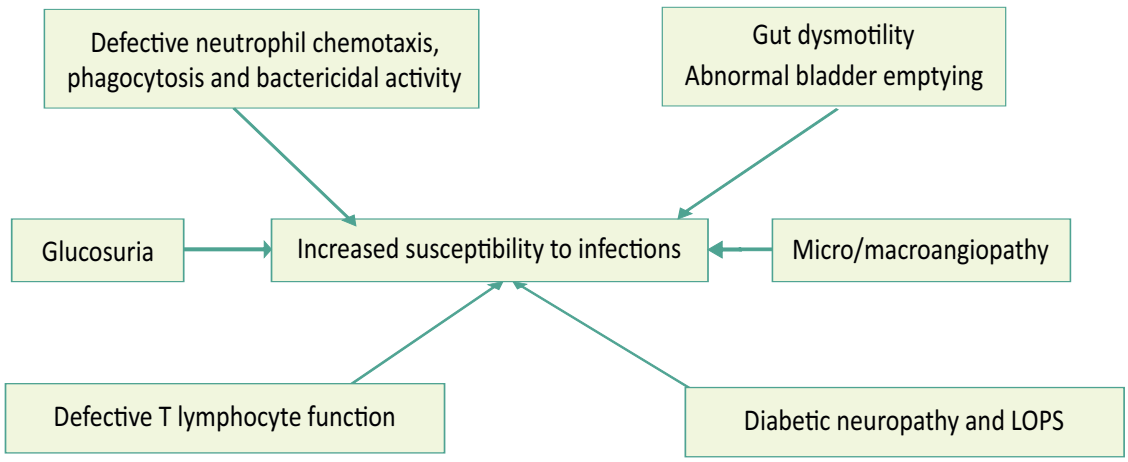
Apart from infections common to the general population, certain infections are more specific to patients with diabetes including rhino-orbital-cerebral mucormycosis, malignant otitis externa, necrotizing fasciitis, fournier gangrene, emphysematous cholecystitis, emphysematous pyelonephritis, and diabetic foot infections[54]. Any infection in a patient

with T1DM may increase risk for DKA and hence sick day education to tackle such an event should be imparted to all patients (refer to sick day guidelines in the chapter on "Education").

Pathophysiology for increased susceptibility to infections in diabetes

Increased susceptibility to infections in patients with diabetes could be due to various mechanisms including impaired immune function, micro/ macroangiopathy, glucosuria and diabetic sensory and autonomic neuropathy (Figure 4)[54-56].

Figure 4 : Pathophysiology of infections in patients with type 1 diabetes mellitus



LOPS: Loss of protective sensation.

Impaired immune function

Hyperglycemia is known to affect chemotaxis, phagocytosis and bactericidal activity of neutrophils and macrophages. In addition, reduced T lymphocyte function and defect in humoral innate immunity (reduced complement factor C4 and impaired cytokine response to stimulation) may contribute to increased risk of infection in these patients.

Micro/macroangiopathy

Micro/macroangiopathy due to diabetes may lead to increased risk of skin ulceration and secondary infection.

Glucosuria

Glucosuria due to uncontrolled hyperglycemia is associated with increased risk of urinary tract infections.

Diabetic sensory and autonomic neuropathy

Loss of protective sensation (LOPS) due to neuropathy is associated with increased risk of foot ulceration and diabetic foot infection. In addition, impaired bladder emptying and gastrointestinal dysmotility due to diabetic autonomic neuropathy may predispose to urinary tract infection and gastrointestinal infection, respectively.

In the following sections, major infections encountered in patients with T1DM will be discussed.

Head and neck infections

Rhino-orbital-cerebral mucormycosis (ROCM)

This potentially fatal angioinvasive infection is caused by fungi of class Zygomycetes and the order Mucorales. The most common genera implicated in causation of mucormycosis are Rhizopus, Mucor and Rhizomucor. Rhizopus oryzae is the most common reported species among microbiologically proven cases[57].

ROCM commonly occurs in patients with uncontrolled diabetes mellitus and DKA is present in 30-70% of cases at the time of presentation. Low serum pH is known to inhibit binding of iron to transferrin, making free iron available for utilization by the ferrophilic fungi. Also, both hyperglycemia and acidosis inhibit chemotaxis, phagocytosis and bactericidal activity of neutrophils and macrophages, impairing host defenses against invasion by Zygomycetes[54,58].

Clinical features include facial swelling (especially periorbital region), redness, pain, decreased visual acuity, proptosis, headache, nasal stuffiness, rhinorrhea, ophthalmopelagia, facial numbness and presence of black eschar in nasal cavity or on the palate. A high index of suspicion should be kept for patients with uncontrolled diabetes presenting with any of the above clinical features. Diagnosis depends on demonstration of fungal elements in the tissue specimen. However, in appropriate clinical setting, it may be prudent to initiate therapy even in absence of fungal elements on initial tissue sampling. Characteristic histopathological feature of mucormycosis is the presence of broad aseptate hyphae which branch at right angles. Imaging studies like computerized tomography (CT) and magnetic resonance imaging (MRI) help in quantifying the extent of disease at initial presentation and on follow-up.

Prompt and aggressive surgical debridement along with institution of systemic antifungal therapy (amphotericin B) is the mainstay of treatment. It should be emphasized that medical treatment alone (in absence of surgical debridement) is likely to be ineffective. This is due to the limited drug delivery to the infected site as a result of extensive vascular thrombosis. Conventional amphotericin B is administered at dose of 0.5-1.5 mg/kg/day while liposomal amphotericin B is administered at dose of 3-5 mg/kg/day. The liposomal formulation has the advantage of being less nephrotoxic; however, it is more expensive than the conventional preparation. Patients on amphotericin B should be monitored for hypokalemia and hypomagnesemia besides renal dysfunction. The cumulative dose of amphotericin B administered may vary from case to case basis depending on the treatment response. Typically, a cumulative dose of 2.5-3.0 g has been described for the conventional formulation. The oral azole posaconazole may be used in patients not able to tolerate amphotericin or as a step-down therapy.

The current advances in diagnosis and management have significantly improved the prognosis associated with ROCM. However, despite best measures, mortality rates vary from 30-70% across various studies. Presence of cerebral involvement, hemiparesis, altered sensorium, bilateral sinus involvement, facial necrosis and delayed presentation are factors associated with poorer outcomes in patients with ROCM[59]. Among survivors of ROCM, residual defects such as blindness and cranial nerve palsies are common. In a review of 179 cases of paranasal sinus mucormycosis by Blitzer et al, residual defects were reported in 62/90 (70%) survivors, the most common being blindness (39/62, 63%) and cranial nerve palsies (11/62, 18%)[60].

Malignant otitis externa (MOE)

MOE is a potentially fatal necrotizing infection, which begins in external auditory canal and rapidly spreads to the underlying deep tissue. Pseudomonas aeruginosa is the most commonly implicated microorganism; however Staphylococcus aureus, Staphylococcus epidermidis, Proteus mirabilis, Klebsiella oxytoca, Aspergillus niger, Aspergillus fumigatus, and Candida species have also been associated with MOE[61]. The infection begins in external auditory canal (at junction of cartilage and bone), and rapidly spreads to the underlying temporal bone, leading to osteitis and eventually skull base osteomyelitis. A common inciting event is trivial trauma following irrigation for impacted wax or ear picking. Patients present with throbbing otalgia and purulent ear discharge. Lower motor neuron facial palsy is a complication seen early in the disease course, while other cranial nerves (IX,X,XI,XII) may get involved as the infection invades further into skull base. The presence of cranial nerve palsy portends a poor prognosis[62].

Otoscopic examination reveals presence of granulation tissue in external auditory canal at the junction of bone and cartilage with intact tympanic membrane.

CT and MRI help in defining the extent of disease in terms of soft tissue and bony involvement as well as intracranial extension[62]. Nuclear imaging modalities like Technetium 99m bone scintigraphy and Gallium (Ga-67) scan are helpful in monitoring the disease progression[63,64].

Antimicrobial therapy is the mainstay of therapy and should be initiated empirically once the pus sample has been sent for bacterial/fungal cultures. The initial antimicrobial therapy could be an antipseudomonal penicillin/cephalosporin (piperacillin-tazobactam, cefoperazone-sulbactam or ceftazidime) in combination with a fluroquinolone (ciprofloxacin)[65]. Ciprofloxacin has the advantage of oral administration and good bone penetration; however emergence of resistance against this agent is of concern[66]. The antibiotic regimen may be modified according to the culture results, once available. The total duration of antibiotic therapy is generally 4-6 weeks. Apart from antimicrobial therapy, achieving good glycemic control and regular aural toileting is important. Surgical intervention may be needed for drainage of abscesses, debridement of deep lesion and to obtain tissue diagnosis in cases not responding to systemic treatment (to exclude malignancy or granulomatous disease). With the advances in diagnosis and treatment coupled with early detection, mortality rate due to this dreaded infection has reduced from 50% to 20%[62]. It has therefore been suggested that it is more appropriate to use the term “necrotising otitis externa” or “skull base osteomyelitis” instead of “malignant otitis externa”.

Skin and soft tissue infections (SSTIs)

Skin and soft tissue infections (SSTIs) include infection of skin, subcutaneous tissue, fascia, and muscle (Table IV). These may range from mild superficial infections to deep and rapidly spreading potentially fatal infections[67]. Gram positive cocci (Staphylococcus aureus and Streptococcus pyogenes) are the most common organisms implicated. However, in most cases of necrotizing fasciitis, etiology is polymicrobial (combination of gram positive cocci, gram negative bacilli and anaerobes).