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Acute complications of diabetes mellitus: current insights into pathophysiology and clinical management

NA Nyane,[1] M Balmith,[1] M Ravhengani,[1] BT Flepisi[2]

[1] Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa

[2] Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, South Africa

Corresponding author, email: ntsoaki.nyane@up.ac.za

Abstract

Diabetes mellitus is a chronic metabolic disorder with rising global prevalence and significant morbidity and mortality due to its complications. Among these, acute complications such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), hypoglycaemia, and lactic acidosis represent urgent and life-threatening conditions requiring immediate medical intervention. DKA and HHS share common pathophysiological pathways involving insulin deficiency and counter-regulatory hormone excess, leading to profound metabolic disturbances. Although DKA is more common in type 1 diabetes (T1D) and HHS in type 2 diabetes (T2D), both demand prompt diagnosis and structured therapeutic strategies to restore fluid and electrolyte balance and normalise blood glucose levels. Hypoglycaemia is often due to drug-induced insulin overdosing, and is associated with neuroglycopenic symptoms, while lactic acidosis involves derangements in lactate metabolism and may be triggered by conditions such as sepsis or metformin use. This review explores the pathophysiology, clinical presentation, diagnostic features, and management protocols for these acute complications. It further highlights the importance of preventive strategies, patient education, and the potential role of digital health and personalised medicine in reducing the risk of complications and improving diabetes outcomes.

Keywords: diabetes; diabetic ketoacidosis; hyperosmolar hyperglycaemic state; lactic acidosis; hypoglycaemia

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Introduction

Globally, the prevalence of diabetes continues to rise at an alarming rate.[1] According to the International Diabetes Federation (IDF), an estimated 589 million adults (aged 20–79 years) were living with diabetes in 2024, and this number is projected to increase to 853 million by 2050.[2] In sub-Saharan Africa, approximately 25 million adults had diabetes in 2024, with projections indicating a rise to 33 million by 2030 and 55 million by 2045.[2,3] The African region also has the highest proportion of undiagnosed diabetes globally, with nearly 53.6% of individuals unaware of their condition. In South Africa, recent IDF estimates suggest that approximately 4.2 million adults (approximately 12% of the population aged 20–79 years) are living with diabetes.[3]

Diabetes mellitus is a heterogeneous group of disorders characterised by persistent hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The two primary types are type 1 diabetes (T1D) and type 2 diabetes (T2D). T2D accounts for approximately 90–95% of all diabetes cases in the general population, while T1D, which typically presents in childhood, represents about 5–10% of cases.[4,5] However, other rare forms of diabetes include Maturity Onset Diabetes of the Young (MODY), Gestational Diabetes Mellitus (GDM) and idiopathic diabetes.[6] Clinical symptoms associated with diabetes are due to chronic hyperglycaemia and endocrine maladaptation. Glycosuria accompanied by polyuria is common in diabetic patients leading to dehydration that triggers compensatory polydipsia.[7,8] Diabetes may be diagnosed by glycated haemoglobin (HbA1c) or blood glucose concentrations where the latter is either the Fasting Blood Glucose (FBG), Random Blood Glucose (RBG) or Impaired Glucose Tolerance (IGT) with a 75 g glucose challenge.[1]

According to the American Diabetes Association (ADA), HbA1c is a marker of chronic glycaemia reflecting average blood glucose levels over a two to three-month period with the cut-off point of ≥ 6.5% for confirming diabetes as an alternative to FPG ≥ 6.0 mmol/L and RBG of > 11.0 mmol/L.[1] Glucose intolerance is defined as the inability of blood glucose levels to return to baseline two hours post 75 g oral glucose challenge. Patients must have fasted for more than eight hours before the Oral Glucose Tolerance Test (OGTT) interpretation. The normal FBG blood glucose concentrations range from 3.1 mmol/L–7.8 mmol/L depending on the fed or fasted state of the person.[9,10]

Diabetes is associated with several complications such as ketoacidosis, neuropathy, retinopathy, nephropathy and cardiovascular diseases that significantly contribute to increased morbidity and mortality.[11] The two most common life-threatening complications of uncontrolled diabetes mellitus include diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS). DKA usually occurs in patients with T1D but HHS is mostly diagnosed in patients with T2D and they both require prompt recognition and aggressive therapy to optimise clinical outcomes.[12] This review specifically focuses on the acute complications associated with diabetes.

Acute diabetes complications

Diabetic ketoacidosis, hyperglycaemic hyperosmolar state, lactic acidosis, and hypoglycaemia represent acute, severe metabolic disturbances associated with uncontrolled diabetes.[13] DKA and severe hypoglycaemia are more common in T1D, whereas HHS without ketoacidosis is more frequently associated with T2D. DKA and HHS require prompt recognition and aggressive therapy to optimise clinical outcomes.[14] Although there are important differences in their pathogenesis, the basic underlying mechanism for both disorders is the reduction in the effective concentrations of circulating insulin leading to hyperglycaemia and severe dehydration.[14]

Diabetic ketoacidosis (DKA)

DKA is an acute but major life-threatening complication of diabetes that mainly occurs in patients with T1D, even though uniquely frequent among some patients with T2D.[15] It is defined by blood glucose concentrations > 11.0 mM, venous blood pH < 7.3, bicarbonate < 15 mM, glycosuria, ketonaemia and ketonuria.[16] DKA is a consequence of absolute lack of insulin with a concomitant increase in plasma levels of insulin counter-regulatory hormones such as catecholamines, glucagon, cortisol and growth hormone leading to hyperglycaemia and ketosis (Figure 1). Ketosis is a metabolic state in which the body uses fat-derived ketone bodies for energy instead of glucose. It occurs when carbohydrate intake is low, or when insulin is insufficient, leading the body to break down fat for fuel. The lack of insulin combined with hyperglycaemia lowers the amount of fructose-2,6-phosphate in the liver. This alters the activity of phosphofructokinase and fructose-1,6-bisphosphatase, leading to increased glucose production in the liver and a reduction in glycolysis.[17] Insulin deficiency also reduces levels of GLUT4, which impairs glucose uptake into skeletal muscles and adipose tissues thus reducing intracellular glucose metabolism.[18] Insulin deficiency and increased counterregulatory hormones also lead to the release of free fatty acids (FFA) into circulation from adipose tissue (lipolysis), which undergo hepatic fatty acid oxidation to ketone bodies (beta-hydroxybutyrate and acetoacetate), resulting in ketonaemia and metabolic acidosis.[19] However, hyperglycaemia develops as a result of increased gluconeogenesis in the liver, accelerated glycogenolysis and impaired glucose utilisation by peripheral tissues.[15]

Precipitating factors of DKA

A precipitating factor for the development of DKA is infection, with urinary tract infections and pneumonia being the most common causes.[20] Additionally, newly onset T1D, inadequate insulin doses, or insulin pump malfunction can lead to the development of DKA.[21] Poor adherence to insulin therapy is a frequently observed cause of DKA, particularly in younger individuals. Other precipitating factors include myocardial infarction, cerebrovascular accident, acute pancreatitis, trauma, severe burns and alcohol abuse. Myocardial infarction and stroke can trigger diabetic ketoacidosis by increasing the release of stress hormones that raise blood glucose and ketone levels. These acute events lead to insulin resistance and elevated metabolic demand, worsening glucose metabolism. In patients with insufficient insulin, this can rapidly progress to severe hyperglycaemia and ketoacidosis.[22] In addition, medications such as glucocorticoids, atypical antipsychotics, and diazoxide can contribute to precipitation of DKA in individuals without a previous diabetes diagnosis.[21,22] Glucocorticoids and

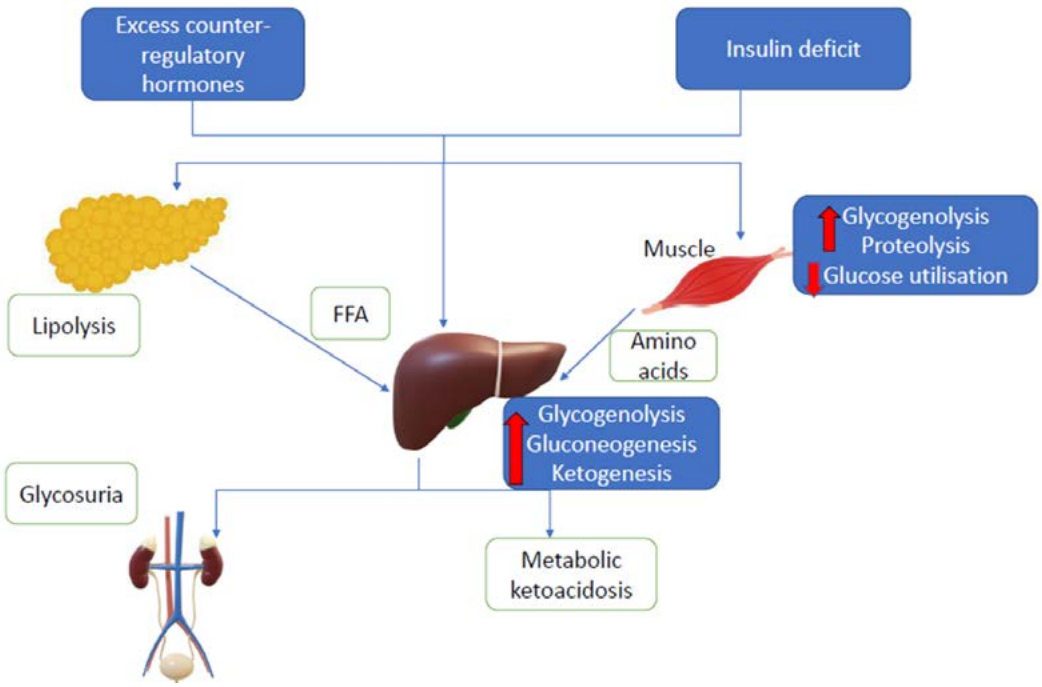


Figure 1: Pathophysiology of DKA. Insulin insufficiency promotes gluconeogenesis in the liver and ketogenesis in skeletal muscles. Increased production of insulin counter-regulatory hormones promotes lipolysis and proteolysis in the adipose tissue and the skeletal muscles. FFA: Free fatty acids; ↑: Increase: ↓: Decrease

atypical antipsychotics increase insulin resistance and promote hepatic glucose production, while diazoxide directly inhibits insulin secretion from pancreatic beta cells.[23]

Diagnosis and presentation of DKA

The clinical presentation of DKA usually develops rapidly, i.e. over a period of < 24 hours presenting with polyuria, polydipsia and weight loss.[15,24] With appropriate therapy the mortality in DKA is low (< 5%) and is closely related to underlying or precipitating events, such as infections or myocardial infarction.[25] The major non-metabolic complication of DKA therapy is cerebral oedema, which most often develops in children. Most individuals with DKA present with symptoms such as excessive urination (polyuria), excessive thirst (polydipsia), weight loss, vomiting, dehydration, general weakness, and altered mental status.[24] Physical examination may reveal signs such as poor skin turgor, deep and laboured breathing (Kussmaul respirations), rapid heart rate (tachycardia), and low blood pressure (hypotension).[22] Gastrointestinal manifestations may include nausea, vomiting, and generalised abdominal pain. Clinical signs of dehydration such as blood pressure, pulse rate, capillary refill, skin turgor, oral mucosal moisture, and degree of weight loss may not reliably reflect the hydration status in children. Therefore, regular monitoring of haemodynamic parameters is essential for accurate assessment.[21] The American Diabetes Association (ADA) classifies DKA into mild, moderate, and severe according to specific criteria (Table I).[15]

Management of DKA

Specific therapeutic goals for DKA require frequent monitoring of patients, correction of hypovolaemia and hyperglycaemia, replacement of electrolyte losses, and attention to precipitating factors. Treatment of DKA is initiated with intravenous (IV) fluids, normal saline (0.9% NaCl) at the rate of 15–20 mL/kg body weight during first hour unless the patient has cardiac dysfunction, and then followed by 0.45% normal saline at a rate of 4–14 mL/kg/h (Table II).[26] Hypotonic saline (0.45%) helps correct hyperosmolarity and reduces the risk of cerebral oedema, especially in children or those with severe dehydration. Once blood glucose reaches 11.1 mmol/l, IV fluids should be changed to 5% dextrose with 0.45% NaCl at 150–250 mL/hr.[19]

Insulin treatment is the cornerstone in the management of DKA. Continuous insulin infusion should be administered at a bolus dose of 0.1 unit/kg IV and a maintenance dose of 0.1 unit/kg/hr IV. Adequate renal function should be established (urine output ~50 mL/h). If potassium (K) is < 3.3 mEq/L, insulin can be stopped and 20–40 mEq/hr of K should be administered until K > 3.3 mEq/L. If K is > 5.5 mEq/L, it should not be given, but if K is between > 3.3 and < 5.3 mEq/L, K at 20–30 mEq should be given in each litre IV fluid to maintain K between 4–5 mEq/L.[15,27]

Occasionally, patients with DKA may present with significant hypokalaemia as a result of correction of volume or metabolic acidosis and/or insulin therapy.[26,27] Hypokalaemia can cause life-threatening arrhythmias and respiratory muscle weakness.[26] In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to > 3.3 mEq/L because insulin drives potassium into cells, further lowering serum potassium levels.[28] Generally, the administration of 20–30 mEq potassium in each litre of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range of 4–5 mEq/L. Bicarbonate therapy should be considered in patients with severe acidosis.[29,30] Careful attention should be paid to potential complications, such as cerebral oedema due to rapid osmotic shifts particularly in paediatric patients.

Hyperglycaemic hyperosmolar state (HHS)

HHS is a serious complication of diabetes mellitus, most commonly seen in individuals with T2D.[31] Although it can develop in those with T1D, such cases are uncommon. It is characterised by extreme hyperglycaemia, hyperosmolality, and severe dehydration but notably occurs without significant ketoacidosis.[32] HHS is marked by a relative deficiency of insulin concentrations to maintain normoglycaemia due to insulin resistance but adequate levels to prevent lipolysis and ketogenesis as indicated by residual C-peptide.[28] Insulin deficiency leads to hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilisation in the skeletal muscles.[17] Hyperglycaemia induces osmotic diuresis leading to intravascular volume depletion, which is exacerbated by inadequate fluid replacement. Most people with T2D still produce some insulin, unlike in T1D where insulin production is minimal or absent due to autoimmune destruction of beta cells.[28]

Although the fundamental difference between HHS and DKA is small, HHS is characterised by a greater severity of blood glucose elevation (> 33.3 mmol/L), marked increase of plasma osmolality

Table I: Diagnostic criteria and deficits of electrolytes in different stages of diabetic ketoacidosis (DKA)[15]

	Mild DKA (glu > 250)	Moderate DKA (glu > 250)	Severe DKA (glu > 250)
Arterial PH	7.25–7.30	7.00 to < 7.24	< 7.00
Serum bicarbonate	15–18	10 to < 15	< 10
Urine ketone	Positive	Positive	Positive
Serum ketones	Positive	Positive	Positive
Serum osmolality	Variable	Variable	Variable
Anion gap	> 10	> 12	> 12
Mental status	Alert	Alert/drowsy	Stupor/coma

(> 320 mOsm/kg), absence of or mild ketosis, and altered mental status.[24] It is associated with glycosuria, leading to osmotic diuresis and loss of water, sodium, potassium, and other electrolytes. General treatment of DKA and HHS requires frequent monitoring of blood glucose, electrolytes, renal function, acid-base status, and fluid balance. Continuous assessment helps guide insulin therapy, fluid replacement, correction of electrolyte imbalances and attention to precipitating factors.[28]

Precipitating factors of HHS

Infections may precipitate HHS by increasing insulin resistance and stimulating the release of counter-regulatory hormones, leading to severe hyperglycaemia.[33] HHS may also be triggered by certain medications, non-adherence to therapy, undiagnosed diabetes, substance abuse, and underlying comorbidities. It is frequently characterised by an altered mental state (confusion) and neurological symptoms.[26] While infections are the most common trigger for HHS, other precipitating factors include cerebrovascular accidents and trauma, myocardial infarction, and pancreatitis.[34] In addition, certain medications associated with metabolic decomposition and HHS include glucocorticoids thiazide diuretics, phenytoin, β-blockers, and more recently, atypical antipsychotics especially second-generation antipsychotics.[34] HHS occurs most commonly in elderly patients with T2D and early diagnosis and intervention are essential to prevent the onset of serious complications.[35]

Diagnosis and presentation of HHS

Patients with HHS present with profound dehydration, poor tissue turgor, dry buccal mucosa, soft, sunken eyeballs, cool extremities, and a rapid weak pulse.[33] Excessive urination (polyuria) and increased thirst (polydipsia) are the most frequent early signs of HHS. Furthermore, adults may present with a low-grade fever, while children may exhibit non-specific symptoms such as headache, weakness, and vomiting, which may occur with or without abdominal pain.[35] Seizures which may be resistant to anticonvulsives and phenytoin may worsen HHS. Acute focal or global neurological changes, such as drowsiness, delirium, seizures (focal or generalised), coma, visual disturbances, hemiparesis, and sensory deficits are considered late manifestations of HHS.[15]

Management of HHS

The goal of treatment is guided by several key principles aimed at i) normalising osmolality, ii) restoring fluid and electrolyte losses, and iii) normalising blood glucose.[26] Management and treatment of HHS begins with aggressive fluid replacement, initially with intravenous (IV) isotonic saline (0.9% sodium chloride [NaCl]) to replenish circulating volume and reverse dehydration, followed by insulin infusion (IV) (Table II), which should be carefully titrated based on serum sodium and osmolality levels.[36] Electrolytes, such as potassium must also be closely monitored and corrected as necessary.[26] Preventive strategies are essential in the management of HHS, including the use of thromboprophylaxis in high-risk individuals to mitigate the risk of thromboembolic events.[36] Additionally, close monitoring for potential neurological complications, such as cerebral oedema is critical.[33,36,37] It is also important to educate patients to support long-term diabetes management and prevent recurrence.

Hypoglycaemia

Hypoglycaemia is a common and potentially serious complication in individuals with diabetes. The primary cause is overdose of diabetes medications in particular, those which raise insulin levels independently of blood glucose, such as sulphonylureas and exogenous insulin.[38] It is defined as a blood glucose concentration of below 4 mmol (70 mg/dL), with severe episodes involving neuroglycopenic symptoms such as confusion, seizures, or loss of consciousness that require external assistance.[39] Common risk factors include the use of insulin or sulfonylureas, insufficient intake of exogenous glucose, such as during prolonged fasting or consumption of very low-carbohydrate meals, alcohol consumption, increased glucose utilisation during or after intense physical activity, renal or hepatic dysfunction, and advanced age.[40,41] These factors either enhance insulin action or weaken counter-regulatory hormonal responses, thereby predisposing individuals to low glucose levels.[40]

Diagnosis and presentation of hypoglycaemia

Hypoglycaemia is diagnosed when blood glucose levels fall below 4 mmol/L, often accompanied by symptoms such as sweating, trembling, confusion, irritability, or dizziness.[41] It may present suddenly and can range from mild to severe, with severe cases leading to seizures or loss of consciousness if not treated promptly. Blood glucose concentrations should be measured with a glucometer to confirm hypoglycaemia.[42]

Management of hypoglycaemia

In cases of confirmed or strongly suspected hypoglycaemia, intravenous dextrose 10% at 2–5 mL/kg is administered. After treatment, blood glucose should be reassessed within 10–15 minutes.[39] If hypoglycaemia persists, give an additional bolus of dextrose 10% at 2 mL/kg and initiate a continuous infusion of dextrose 5% or 10% at 3–5 mL/kg/hour to maintain glucose levels. Excessive fluid volumes should be avoided and continuous monitoring is essential until clinical recovery is evident. Hypoglycaemia can also be managed with either oral or intravenous glucose and/or intramuscular glucagon (Table II).[43]

Lactic acidosis

Lactic acidosis is a serious metabolic condition characterised by excessive accumulation of lactic acid in the bloodstream (> 5 mmol/L), leading to a decrease in blood pH (< 7.35) accompanied by low plasma bicarbonate levels (< 20 mmol/L).[44] This condition occurs due to an elevated rate of L-lactate production and/or a reduced rate of its metabolic clearance typically due to tissue hypoperfusion, mitochondrial dysfunction, or the effects of certain medications.[44] Lactic acidosis is classified into type A (hypoperfusion-related) and type B (non-hypoperfusion-related)

Table II: Management of diabetic complications[47]

Diabetes complication		Management strategy
Diabetic ketoacidosis	Type I diabetes	Intravenous (IV) fluids
		Insulin
		Electrolyte replacement
		Monitor pH
Hyperosmolar hyperglycaemic state	Type II diabetes	Aggressive IV fluids
		IV insulin
		Electrolyte replacement
Hypoglycaemia	Mild to moderate	Oral glucose
	Severe	Glucagon injection (IM or SC)
		IV dextrose (D50)
Lactic acidosis		Stop metformin
		Treat underlying causes
		Provide intensive care unit (ICU) care
		Monitor lactate, pH, renal function
		Dialysis or renal replacement therapy

forms. Septic shock remains a frequent cause of type A lactic acidosis.

Diagnosis and presentation of lactic acidosis

Lactic acidosis typically presents with symptoms such as rapid breathing, nausea, vomiting, abdominal pain, confusion, and fatigue. Diagnosis involves measuring serum lactate, performing corrected anion gap calculations (especially in cases of hypoalbuminaemia), and analysing arterial blood gases.[45]

Management of lactic acidosis

Treatment typically involves fluid resuscitation to improve circulation and oxygen delivery to the tissues.[44,46] Vasopressors may be necessary to maintain adequate blood pressure and organ perfusion in these patients.[44] Mechanical ventilation may be required to ensure proper oxygenation and ventilation. In severe cases, renal replacement therapy may be considered to help clear lactate and correct acidosis.[46] Sodium bicarbonate administration remains controversial and is generally reserved for extreme cases only due to the risk of mortality.[44] Continuous monitoring of lactate levels, acid-base status, and haemodynamic parameters is critical for informing therapy and assessing the response to treatment (Table II).

Preventative measures

It is well established that diabetes is associated with a significant number of life-threatening complications. These complications are responsible for burdens associated with diabetes, both on the individual and on healthcare systems.[48] Thus, preventative measures are required to prevent or delay the occurrence of these diabetes complications. The most effective measure for preventing complications is to prevent the onset of diabetes by modifying lifestyle-related factors such as diet, physical activity, and alcohol consumption.[49] However, these modifications may not be applicable to patients with T1D. The current diabetes management aims to prevent complications, which are a major cause of morbidity and mortality.[48] The current preventative measures of diabetes complications include appropriate education, adequate treatment, and frequent glucose monitoring.[50] In addition, it has been reported that the most effective preventative measures of diabetes complications include the long-term maintenance of normoglycaemia, regular blood glucose monitoring, patient education, and lifestyle modifications.[51] It has been suggested that the risk of diabetes complications could be limited through patient empowerment such as education, and diabetes self-monitoring and management training.[52] This promotes a partnership between clinicians and patients, and helps prevent both acute and chronic diabetes complications.

Conclusion

Although current therapies for the prevention and management of diabetes have been effective in optimising glycaemic control, complications persist leading to high morbidity and mortality. New multifactorial therapies with minimal adverse effects that can prevent these complications and reduce the burden of diabetes are thus required. In addition, future diabetes therapies should focus on personalised medicine where treatments are optimised based on patient-specific factors including genetic profiles, comorbid conditions, and risk of complications.[53,54] Furthermore, future directions should focus on improving self-monitoring of glucose and management by patients to promote adherence. The integration of digital health technologies and artificial intelligence in personalised medicine may offer promising avenues for monitoring and managing diabetes complications enabling more precise and timely interventions.[54] Future directions also involve the incorporation of wearable computers (digital devices), personal digital assistants, and mobile phones in monitoring and managing diabetes.[55,56]

References

1. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care 2014;38:S8-S16. https://doi.org/10.2337/dc15-S005.
2. IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes. 2025. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://idf.org/media/uploads/2025/04/IDF_Rec_2025.pdf.
3. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Science Reports. 2024;7(3). https://doi.org/10.1002/hsr2.2004.
4. Daneman D. Type 1 diabetes. Lancet 2006;367:847-58. https://doi.org/10.1016/S0140-6736(06)68341-4.
5. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414:782-7. https://doi.org/10.1038/414782a.
6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32:S62-S67. https://doi.org/10.2337/dc09-S062.
7. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. World J Clin Cases. 2014;2:488. https://doi.org/10.12998/wjcc.v2.i10.488.
8. Lee JW. Fluid and electrolyte disturbances in critically ill patients. Electrolytes & Blood Pressure. 2010;8:72. https://doi.org/10.5049/EBP.2010.8.2.72.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:S62-S69. https://doi.org/10.2337/dc10-S062.
10. Nathan DM. International Expert Committee Report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327-34. https://doi.org/10.2337/dc09-9033.
11. Chentli F, Azzoug S, Mahgoun S. Diabetes mellitus in elderly. Indian J Endocrinol Metab. 2015;19:744. https://doi.org/10.4103/2230-8210.167553.

12. Nyane NA, Tlaila TB, Malefane TG, Ndwandwe DE, Owira PMO. Metformin-like antidiabetic, cardio-protective and non-glycemic effects of naringenin: Molecular and pharmacological insights. Eur J Pharmacol. 2017;803:103-11. https://doi.org/10.1016/j.ejphar.2017.03.042.
13. Maletkovic J, Drexler A. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am. 2013;42:677-95. https://doi.org/10.1016/j.ecl.2013.07.001.
14. Hassan EM, Mushtaq H, Mahmoud EE, et al. Overlap of diabetic ketoacidosis and hyperosmolar hyperglycemic state. World J Clin Cases. 2022;10:11702-11711. https://doi.org/10.12998/wjcc.v10.i32.11702.
15. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;3:1335-43. https://doi.org/10.2337/dc09-9032.
16. Siddiqui AA, Siddiqui SA, Ahmad S, et al. Diabetes: mechanism, pathophysiology and management - a review. Int J Drug Dev. 2013;5:1-23.
17. Hatting M, Tavares CDJ, Sharabi K, Rines AK, Puigserver P. Insulin regulation of gluconeogenesis. Ann N Y Acad Sci. 2018;1411:21-35. https://doi.org/10.1111/nyas.13435.
18. Huang S, Czech MP. The GLUT4 Glucose Transporter. Cell Metab. 2007;5:237-52. https://doi.org/10.1016/j.cmet.2007.03.006.
19. El-Remessy A. Diabetic ketoacidosis management: updates and challenges for specific patient population. Endocrines. 2022;3:801-12. https://doi.org/10.3390/endocrines3040066.
20. Ahmad R, Narwaria M, Singh A, Kumar S, Haque M. Detecting diabetic ketoacidosis with infection: combating a life-threatening emergency with practical diagnostic tools. Diagnostics. 2023;13:24-41. https://doi.org/10.3390/diagnostics13142441.
21. Eledrisi MS, Alshanti MS, Faiq Shah M, Brolosy B, Jaha N. Overview of the diagnosis and management of diabetic ketoacidosis. Am J Med Sci. 2006;5:243-51. https://doi.org/10.1097/00000441-200605000-00002.
22. Chukwuka C, Johnson D, Abasi U, et al. Comprehensive review of diabetic ketoacidosis: an update. Annals of Medicine & Surgery. 2023;85:2802-7. https://doi.org/10.1097/MS9.0000000000000894.
23. Hall R, Keeble L, Sünram-Lea S-I, To M. A review of risk factors associated with insulin omission for weight loss in type 1 diabetes. Clin Child Psychol Psychiatry. 2021;26:606-16. https://doi.org/10.1177/13591045211026142.
24. English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. Postgrad Med J. 2004;80:253-61. https://doi.org/10.1136/pgmj.2002.004291.
25. Murunga AN, Owira PMO. Diabetic ketoacidosis: an overlooked child killer in subtropical. Medicine & International Health. 2013;18:1357-64. https://doi.org/10.1111/tmi.12195.
26. Dhatariya KK, Vellanki P. Treatment of diabetic ketoacidosis (DKA)/Hyperglycemic Hyperosmolar State (HHS): novel advances in the management of hyperglycemic crises (UK Versus USA). Curr Diab Rep. 2017;17:33. https://doi.org/10.1007/s11892-017-0857-4.
27. Kichloo A, El-amir Z, Wani F, Shaka H. Hospitalizations for ketoacidosis in type 1 diabetes mellitus, 2008 to 2018. Baylor University Medical Center Proceedings. 2022;35:1-5. https://doi.org/10.1080/08998280.2021.1978741.
28. Sibai BM, Viteri OA. Diabetic ketoacidosis in pregnancy. Obstetrics & Gynecology. 2014;123:167-78. https://doi.org/10.1097/AOG.0000000000000060.
29. Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises. Medical Clinics of North America. 2017;101:587-606. https://doi.org/10.1016/j.mcna.2016.12.011.
30. Ghauri SK, Javaeed A, Mustafa KJ, Podlasek A, Khan AS. Bicarbonate therapy for critically ill patients with metabolic acidosis: a systematic review. Cureus. 2019. https://doi.org/10.7759/cureus.4297.
31. Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A. Sodium bicarbonate therapy in patients with metabolic acidosis. Scientific World Journal. 2014:1-13. https://doi.org/10.1155/2014/627673.
32. Jellinger PS. Metabolic consequences of hyperglycemia and insulin resistance. Clin Cornerstone. 2007;8:S30-S42. https://doi.org/10.1016/S1098-3597(07)80019-6.
33. Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes. Diabetes Care. 2009;32:381-6. https://doi.org/10.2337/dc08-1671.
34. Muneer M, Akbar I. Acute metabolic emergencies in diabetes: DKA, HHS and EDKA. Diabetes: from Research to Clinical Practice. 2020:85-114. https://doi.org/10.1007/5584_2020_545.
35. Pasquel F, Umpierrez GE. Hyperosmolar hyperglycemic state: A historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014;37:3124-31. https://doi.org/10.2337/dc14-0984.
36. Umpierrez GE, Davis GM, ElSayed NS, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care. 2024;47:1257-75. https://doi.org/10.2337/dci24-0032.
37. Mustafa OG, Haq M, Dashora U, Castro E, Dhatariya KK. Management of Hyperosmolar Hyperglycaemic State (HHS) in adults: An updated guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care Group. Diabetic Medicine. 2023;40:e15005. https://doi.org/10.1111/dme.15005.
38. Dhatariya K, Mustafa O, Stathi D. Hyperglycemic crises [Internet]. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2000–[updated 2025 Jun 10; cited 2025 Jun 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279052/
39. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. J Clin Endocrinol Metab. 2013;98:1845-59. https://doi.org/10.1210/jc.2012-4127.
40. Lowe RN, Williams B, Claus L. Diabetes: how to manage patients experiencing hypoglycaemia. Drugs Context. 2022;11:1-12. https://doi.org/10.7573/dic.2021-9-11.
41. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol. 2014;10:711-22. https://doi.org/10.1038/nrendo.2014.170.
42. Cryer PE. Minimizing hypoglycemia in diabetes. Diabetes Care. 2015;38:1583-91. https://doi.org/10.2337/dc15-0279.
43. Prasad N, Bhadauria D. Renal phosphate handling: Physiology. Indian J Endocrinol Metab. 2013;17:620. https://doi.org/10.4103/2230-8210.113752.
44. Harding JE, Alsweiler JM, Edwards TE, McKinlay CJ. Neonatal hypoglycaemia. BMJ Medicine. 2024:3. https://doi.org/10.1136/bmjmed-2023-000544.
45. Kamel KS, Oh MS, Halperin ML. L-lactic acidosis: pathophysiology, classification, and causes; emphasis on biochemical and metabolic basis. Kidney Int. 2020;97:75-88. https://doi.org/10.1016/j.kint.2019.08.023.
46. Baddam S, Muttineni S. Recognising and managing albuterol-induced lactic acidosis. BMJ Case Rep. 2025:4. https://doi.org/10.1136/bcr-2024-263495.
47. Kraut JA, Madias NE. Lactic acidosis: current treatments and future directions. American Journal of Kidney Diseases. 2026;68:473-82. https://doi.org/10.1053/j.ajkd.2016.04.020.
48. Bae JH, Kim SG. Management of acute complications of diabetes mellitus. 2021:217-27. https://doi.org/10.1007/978-981-16-5123-6_19.
49. Templer S, Abdo S, Wong T. Preventing diabetes complications. Intern Med J. 52024;4:1264-1274. https://doi.org/10.1111/imj.16455.
50. Galaviz KI, Narayan KMV, Lobelo F, Weber MB. lifestyle and the prevention of type 2 diabetes: a status report. Am J Lifestyle Med. 2018;12:4-20. https://doi.org/10.1177/1559827615619159.
51. Ernawati U, Wihastuti TA, Utami YW. Effectiveness of diabetes self-management education (DSME) in type 2 diabetes mellitus (T2Dm) patients: systematic literature review. J Public Health Res. 2021:10. https://doi.org/10.4081/jphr.2021.2240.
52. Ładyżyński P, Wójcicki JM, Foltyński P. Preventive systems for the late complications of diabetes. Biocybern Biomed Eng. 2011;31:3-21. https://doi.org/10.1016/S0208-5216(11)70007-9.
53. Ezenwaka C, Eckel J. Prevention of diabetes complications in developing countries: time to intensify self-management education. Arch Physiol Biochem. 2011;117:251-53. https://doi.org/10.3109/13813455.2011.602692.
54. Asif HM, Nawaz A, Daniyal M. Editorial: Changing trends of precision medicine in diabetes. Front Med (Lausanne). 2025:12. https://doi.org/10.3389/fmed.2025.1499934.
55. Alanezi AA. The role of pharmacological interventions in optimizing glycaemic control and reducing complications in diabetes mellitus: Current insights and future directions. Ibero-American Journal of Exercise and Sports Psychology. 2025;20(1):98-106.
56. Bellazzi R. Telemedicine and diabetes management: current challenges and future research directions. Journal of Diabetes Science and Technology. 2008:2. https://doi.org/10.1177/193229680800200114.