# A Comprehensive Review on Therapeutic Bridge In Between Diabetics Condition and Diabetics Ketoacidosis

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**Abstract**

Diabetes Mellitus (DM) is a chronic metabolic disorder that affects millions worldwide, with Type 1 and Type 2 diabetes being the most common forms. One of the most serious and potentially life-threatening complications of diabetes is Diabetic Ketoacidosis (DKA), which occurs when the body lacks insulin and starts breaking down fats for energy, leading to excessive ketone production. This condition is most frequently seen in individuals with Type 1 diabetes and requires immediate medical intervention. This presentation explores the intricate relationship between diabetes and DKA, shedding light on their pathophysiology, risk factors, prevalence, and management strategies. It delves into the epidemiology of diabetes, highlighting its rising global burden and the disproportionate impact on low- and middle-income countries. The discussion extends to the clinical diagnosis of diabetes and DKA, emphasizing early detection and differential diagnosis to prevent severe complications. Management strategies, including insulin therapy, fluid resuscitation, and electrolyte balance, are thoroughly examined, along with recent advancements in diabetes treatment, such as continuous glucose monitoring, artificial pancreas technology, and smart insulin solutions. The presentation also considers the psychological toll of diabetes, particularly the emotional distress, anxiety, and depression that many patients experience, especially after severe DKA episodes. As diabetes continues to be a major global health challenge, this review underscores the importance of technological advancements, accessible healthcare, and preventive policies to improve patient outcomes. By integrating innovative treatments, mental health support, and effective public health strategies, we can bridge the gap between diabetes care and the prevention of its life-threatening complications like DKA.

**Keywords**: Insulin deficiency, autoimmune response, Insulin resistance, Beta cells (pancreatic), Risk factors, Hyperglycemia

## 1. Introduction

Diabetes Mellitus (DM) is a metabolic condition characterized by the presence of persistent hyperglycaemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins(1). DM is arguably one of the oldest illnesses that humans have ever encountered. About 3,000 years ago, it was first mentioned in an Egyptian papyrus(2) . The distinction between type 1diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) was made explicit in 1936 (3). In 1988, T2DM was initially identified as a part of the metabolic syndrome . There are two major hyperglycaemic crises associated with diabetes(4). Diabetic ketoacidosis (DKA) and the hyperosmotic hyperglycaemic state. There are 120,000 admissions for DKA and hyperosmolar hyperglycaemic state (HHS) per year in the United States alone(5) . The most of frequent but avoidable consequence of T1DM is DKA .it is characterised as an acute metabolic complication of T1DM that include the biochemical trifecta of metabolic acidosis (PH <7.3), hyperglycaemia (plasma glucose >250 mg/dL), and ketosis (Urine acetoacetate +). DKA may also be the initial sign of T1DMin many persons(6) . DKA is the second most common presenting symptom of T1DM in patients with known DM, while hypoglycaemia is the first. Patients with T1DM typically use regular insulin to control their blood sugar, but if they miss a dose, they may present with DKA, with rate ranging from 15% to 67%(7) . This is true for patients less than six years of age, as up to 44% of children were found to have DKA upon presentation. DKA is almost always associated with T1D. The presence of DKA was assumed to suggest the underlying substantial and irreversible β-cells damage that characterises these diabetic patients as T1DM(7) .

### 1.1 Definition and type of diabetes

**Diabetes**

When blood sugar level (glucose) is too high, you develop diabetes(8). It appears when your body isn’t reacting appropriately to the effects of insulin or when your pancreas is not producing enough of it. People of all age is affected by diabetes(9). All types of diabetes can be controlled with medicine or lifestyle modification, although the majority are chronic.

#### 1.1.1 Types of Diabetes mellitus

| Type 1 diabetes Mellitus | Type 2 diabetes Mellitus | Gestational diabetes |
|---|---|---|
| T1DM is One of the disorders where the pancreas is unable to generate enough insulin for the body is type 1 diabetes mellitus. Insulin-dependent diabetes is the term for it. Insulin is injected through the skin during this procedure(10). | T2DM Also known as insulin-independent diabetes, this form of the disease occurs when the body produces some insulin through the pancreas. However, the cells are resistant to the insulin and the amount produced is insufficient to meet the body's needs. T2DM is the name given to this illness(11). | Gestational diabetes (GD) is a form of diabetes that typically manifests as elevated blood sugar levels in a pregnant woman who has never had diabetes before(12). |

### 1.2 Pathophysiology of diabetes and diabetic ketoacidosis

#### 1.2.1 Pathophysiology of diabetes

DM is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin production, action, or both. The pathophysiology varies between T1D and T2D.T1DM is an autoimmune condition in which the immune system attacks pancreatic β-cells, leading to a complete lack of insulin(13). As a result, glucose cannot enter cells, causing hyperglycaemia and symptoms like excessive thirst, frequent urination, unintended weight loss, and, in severe cases, DKA(14). In contrast, T2DM develops due to insulin resistance, where the body's cells fail to respond effectively to insulin. Initially, the pancreas compensates by producing more insulin, but over time, β-cell function declines, resulting in rising blood sugar levels. Additionally, the liver contributes by over producing glucose, further worsening hyperglycaemia. Chronic high blood sugar in T2DM increases the risk of complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease(15). Unlike T1DM, ketoacidosis is uncommon in T2DM, though severe cases may lead to a hyperosmolar hyperglycaemic state (HHS). Other forms of diabetes include gestational diabetes, which occurs due to hormonal changes during pregnancy, and secondary diabetes, which results from underlying medical conditions or certain medications. Effective management requires lifestyle modifications, medications, and sometimes insulin therapy to prevent complications and maintain blood sugar control(16).

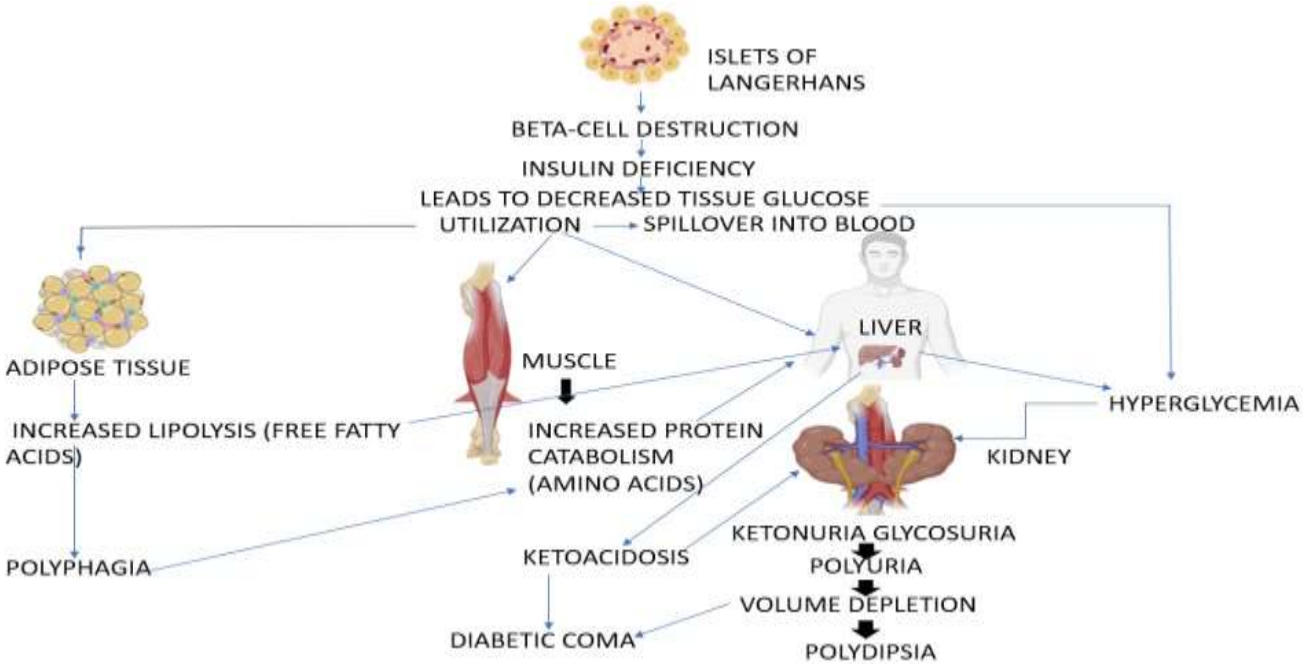



**Fig. Pathophysiology of DM**

#### 1.2.2 Pathophysiology of DKA

Diabetic patients with ketoacidosis experience aberrant physiology due to insulin inefficiency. This led to an increase in hormones that catabolise in the body, causing insulin resistance and hyperglycaemia, hyperketonaemia, hyper-osmolality, and electrolyte imbalance. These hormones are glucagon, growth hormone and catecholamine(17). Elevated blood glucose

concentration in interstitial space causes an osmotic gradient, leading to diuresis, hypovolemia and dehydration. This can exacerbate hyperglycaemia and acidosis by acting counter-regulatory stress hormone as growth hormone, cortisol, glucagon and catecholamine. These abundantly circulating free fatty acids (FFA) taken to the liver and transported to its mitochondria for oxidation; then ketone bodies are formed, including beta- Hydroxy butyrate (BOHB), acetone, and acetoacetate. Insulin checks the biochemical process, but excessive ketone production results from insufficient insulin. In the absence of insulin, potassium uptake decreases(18). There is other way to cause ketoacidosis such as: Starvation, Alcoholic Ketoacidosis, 0smotic diuresis.

| **Starvation** | **Alcoholic Ketoacidosis** | **Osmotic diuresis** |
|---|---|---|
| Starvation ketosis happen when a person consumes less than 500 kcal per day for an extended period. Low carbohydrate intake causes a decline in blood glucose levels and decreased insulin release, activating two mechanisms: lipolysis and ketogenesis(19). | Chronic alcohol misuse can lead to alcoholic ketoacidosis, which cause nausea, vomiting and severe hunger due to its unique aetiology. To distinguish between diuretic and alcohol-induced ketoacidosis blood glucose level should be measured. Acute alcohol withdrawal can trigger the release of counter-regulatory hormone, and starvation can lead to low insulin secretion, resulting in lipolysis and ketogenesis. Diabetic ketoacidosis is characterised by significant hyperglycaemia, while ketoacidosis without hyperglycaemia indicates alcoholic ketoacidosis (20). | Osmotic diuresis increases the risk of ketoacidosis by decreasing glomerular filtration rate and reducing glucose excretion. Hypovolemia leads to higher level of counter-regulatory hormones. Low circulation volume can produce hypo-perfusion, leading to a rise in lactic acid level at peripheral tissue switches to anaerobic respiration(21) . |

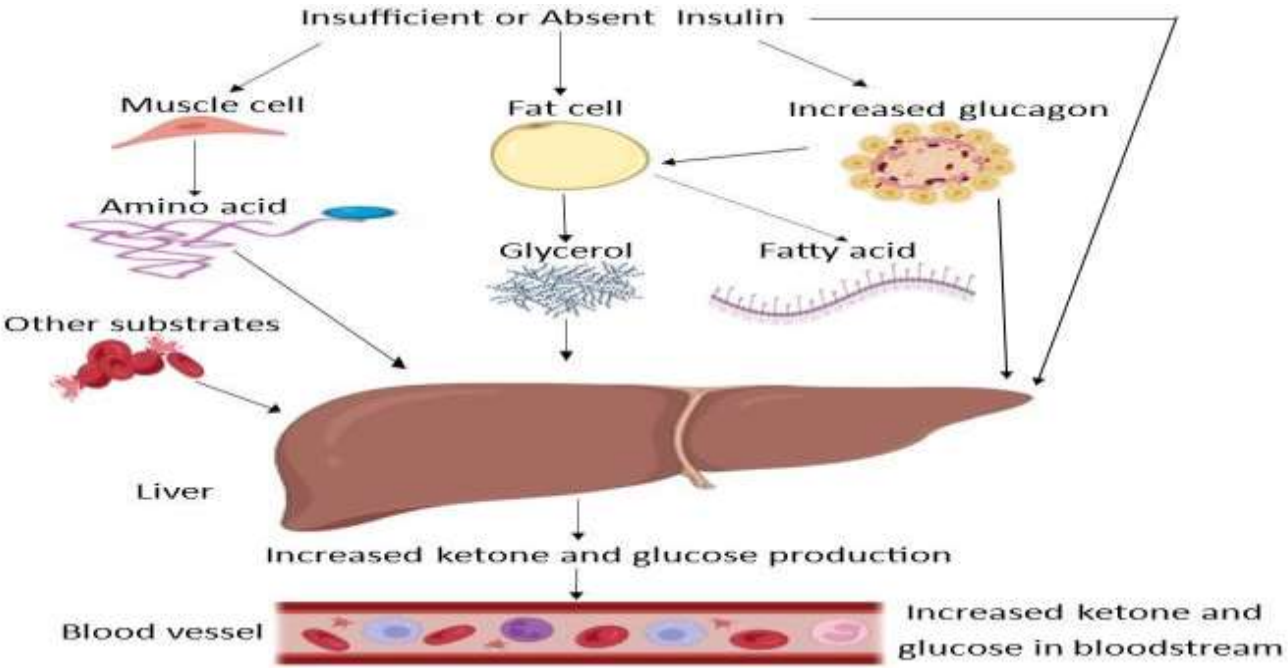



**Fig. pathophysiology of DKA**

## 2. Epidemiology and public health impact of diabetes and diabetic ketoacidosis

According to 2019, the International Diabetes Federation estimates that 537 million people globally have diabetes(22) . In 2020, diabetes ranked as the ninth leading cause of mortality globally, resulting in almost 2 million fatalities annually from both diabetes-related kidney disease and diabetes itself(23) . Although DM can occur anywhere in the world, it is more prevalent in industrialized nations, particularly type 2. However low-and middle-income nations notably those in Asia and Africa are seeing the biggest prevalence(24) . By 2030 the majority of patients will likely be found there. Numerous facets of DM, including its natural history, prevalence, incidence, morbidity, and mortality in various population worldwide, have better understood thanks to the application of epidemiology to the study of the condition. Determining the disease's source and potential preventive measures that may be implemented to stop or postpone the onset of this illness which has spread to epidemic proportions in both developed and developing countries(25) . DKA affects 4.6-8.0 per 1000 patients with diabetes each year. In the United Kingdom, approximately 4% of people with T1D gets DKA each year, but in Malaysia, approximately 25% develop the illness each year. T1DM is the initial diagnosis of DKA in paediatric patients under age of 18. Variations in both the population and the incidence rate. DKA mostly has an incidence rate between 13% & 80% and an estimated death rate between 4% & 10%(26). Although the proportion of adult with ketosis-probe T2M is unknown, the condition has become more common globally since the early 2000. A correlation between 135 developing the disease and full-length tyrosine phosphate 1A -2 antibody (1A-2FL) or its extracellular domain (1A-2EC) has been proposed by studies 134 examining autoimmunity in ketosis-prone T2D(27) . It is unknown how often DKA is in developing countries, but it might be higher than in industrialized ones. Individuals of Caucasian descent exhibit a higher prevalence of T1D which contributes to the increased incidence of DKA within this demographic(28). Females are somewhat more predisposed than males to acquire DKA for

unspecified reasons. Young women with T1D sometimes encounter recurrent DKA, usually due to inadequate insulin administration(29).

### 2.1 Global prevalence of diabetes

Diabetes is becoming an increasingly urgent global health issue, with the number of people affected rising at an alarming rate. By 2022, around 828 million adults worldwide were living with the condition-nearly double what the World Health Organization had previously estimated(30). This surge is especially pronounced in low- and middle-income countries, where many people struggle to access essential treatments like insulin and regular blood sugar monitoring. Without proper care, diabetes can drastically impact a person's quality of life and put immense strain on healthcare systems(30).

One of the most dangerous complications of DKA a life-threatening condition that mostly affects people with T1D. DKA happens when the body can't produce enough insulin, forcing it to break down fat for energy. This process releases acidic ketones into the bloodstream, which, if not controlled, can lead to severe dehydration, organ damage, and even death. Every year, an estimated 4.6 to 8 out of every 1,000 people with diabetes worldwide experience DKA(31). In the United States alone, DKA leads to about 135,000 hospital admissions annually, making up a significant portion of medical costs tied to T1D(31).

**Global Diabetes & DKA Prevalence**

| **Country** | **Diabetes Prevalence (%) (Adults 20-79)** | **Estimated Diabetes Cases (Millions)** | **DKA Incidence (per 1,000 people with diabetes annually)** | **Key Risk Factors** |
|---|---|---|---|---|
| Pakistan | 30.8% | 33.0 | High risk due to limited healthcare access | Poor diet, low insulin access, undiagnosed cases (32) |
| Kuwait | 24.9% | 1.5A | Rising cases among youth | Obesity, sedentary lifestyle (32) |
| Nauru | 24.9% | 0.01 (small population) | Data unavailable | High obesity rates, genetics (33) |
| Egypt | 20.9% | 20.1 | High, especially in children | Poor awareness, late diagnosis (34) |

| | | | | |
|---|---|---|---|---|
| Solomon Islands | 19.8% | 0.08 | Limited data | Poor healthcare infrastructure(35) |
| American Samoa | 20.3% | 0.02 (small population) | High, lack of proper care | Obesity, lack of diabetes education (36) |
| Sudan | 18.9% | 4.3 | High due to insulin shortages | Malnutrition, lack of healthcare(37) |
| Saudi Arabia | 18.7% | 7.5 | 7.2 per 1,000 | High obesity rates, genetic predisposition (38) |
| Tonga | 18.7% | 0.05 | Limited data | Processed food consumption (39) |
| Guam | 18.7% | 0.03 | Rising obesity and diabetes rates | Poor diet, lack of awareness(40) |
| Mexico | 16.9% | 14.1 | High, particularly among newly diagnosed patients | Processed foods, sugar intake(41) |
| India | 12.3% | 101.3 | ~6.8 per 1,000, increasing DKA cases in urban areas | High carb diet, genetic risk(42) |
| United States | 11.3% | 32.4 | 135,000 hospitalizations per year | Obesity, poor diet(43) |
| Brazil | 10.5% | 16.8 | ~5.3 per 1,000, rising DKA cases in youth | High sugar intake, low exercise (44) |
| China | 10.0% | 140.9 | ~3.6 per 1,000 | Urbanization, changing diet (45) |
| United Kingdom | 8.0% | 4.9 | 4.8 per 1,000 | Processed foods, sedentary jobs(46) |
| Germany | 7.5% | 6.1 | 3.9 per 1,000 | Aging population, obesity (47) |

| | | | | |
|---|---|---|---|---|
| Japan | 7.0% | 7.5 | 2.1 per 1,000 | Low obesity rates but aging risk (48) |
| Canada | 7.0% | 3.8 | 5.2 per 1,000, growing concern among young adults | Processed foods, genetics (49) |
| Australia | 6.8% | 2.1 | 4.5 per 1,000, DKA rates stable | High sugar diet, obesity (50) |

### 2.2 Morbidity and mortality of DKA

Hyperglycaemia metabolic acidosis and ketonemia are the hallmarks of DKA, a life-threatening acute emergency that can cause significant morbidity and death in diabetic patients. Both HHS and DKA are types of hyperglycaemic crisis that manifest as acute consequences of diabetes. With over 231,000 hospitalizations in 2019, these illnesses are a significant cause of morbidity and medical costs in the US (50). According to earlier studies, the death rate for these illnesses decreased between 1985 and 2002. Pattern of mortality from hyperglycaemic crises may have changed over time, given trends of declining diabetes management and rising diabetes related commodities starting in the early 2010s. If diabetes not addresses, DKA, a potentially lethal consequences, can occur. The country the patient's condition has an impact on the DKA fatality rate(51) . Between 0.2% and 2.5% of people in the developing nations die from DKA. Between 2% and 5% of individuals in industrialised nations succumb to diabetic ketoacidosis DKA (52). DKA is

still a frequent cause of hospitalization and is linked to significant morbidity and mortality, despite advancements in insulin therapy and patient education .

## 3. Clinical presentation and diagnosis of diabetes and DKA

### 3.1 Diagnosis of Diabetes

The identification of patients with diabetes or pre-diabetes by screening allows for earlier intervention, with potential reductions in future complication rates, although randomized trials are lacking to definitively show benefit. The patient described in the vignette has risk factors and should be screened. About 25% of patients with T2DM already have microvascular complications at the time of diagnosis suggesting that they have had the disease for more than 5 years at the time of diagnosis(53). As a result, there are different approaches to diagnose diabetes among individuals. The 1997 American Diabetes Association (ADA) recommendations for diagnosis of DM focus on Fasting Plasma Glucose (FPG), while we Oral Glucose Tolerance Test (OGTT)(54) .

### 3.1.1 Diagnosis of both Types 1 and Types 2 Diabetes

**Random plasma test:** The simplest test and doesn't require fasting before taking the test. If 200 or more than 200 mg/dl of blood glucose it probably indicates diabetes but has to be reconfirmed(55).

**Fasting plasma glucose test:** There should be eight hours fasting before taking this test. Blood glucose more than 126 mg/dl on two or more tests conducted on different days confirm a diabetes(56).

### 3.2 Diagnosis of Diabetic ketoacidosis

Mainly diagnosis of DKA is based on their three major signs which are hyperglycaemia, metabolic acidosis and ketosis(57) .

**Glucose:** The joint British diabetes societies advocate a glucose cut-off of 11mmol/L. The American diabetes association recommends a higher cut-off of >13.9mmol/L (58).

**Ketones:** Recent observational studies indicates that 3-hydroxybutyrate levels vary when evaluating diabetic ketoacidosis(59) .

**Bicarbonate: The** joint British societies recommend venous carbonate below 15mmol/ L(60)

**Venous pH:** The Venous joint British societies recommend a venous pH less than (7.3)(61) .

**A differential diagnosis**

Other frequent illnesses may mimic DKA because of its heterogeneous and complex presentation, which shares many characteristics with other common physiologies. Hyperglycaemia, ketonemia, and anion gap metabolic acidosis are the biochemical trinity that make up DKA, each of these elements can be observed in different metabolic disorders in Physical and laboratory testing is therefore necessary to rule out alternative causes of metabolic acidosis. For instance, total ketone bodies are significantly larger in alcoholic ketoacidosis (AKA) than in DKA, with a higher BOHB to acetoacetate ratio of 7:1 compared to 3:1 in DKA (62). Starvation ketoacidosis, pancreatitis, alcoholic ketoacidosis, lactic acidosis, uremia, hyperosmolar hyper-glycaemic nonketotic syndrome, and myocardial infarction are among the distinguishing factors(63) . DKA must be differentiated from advanced chronic renal failure, high anion gap acidosis, including lactic acidosis, and including drug consumption including salicylate, methanol and ethylene glycol. Though it tends to cause hypoglycaemia rather than hyperglycaemia, isopropyl alcohol which is frequently sold as rubbing alcohol can cause significant ketosis and a substantial osmolar gap without metallic acidosis(64) .

### 3.3 Sign and symptoms of diabetes

Sign and symptoms of diabetes are divided into main three categories mainly
Those related to expression of physical symptoms eg:

- Polydipsia (frequent urination)
- Glycosuria (glucose in urine)
- Polyphagia (extreme hunger or increased appetite)
- Decrease of skin turgor (very dry skin)
- Nocturia
- Tachycardia (fast heart rate)
- Dehydration (65)

- Dry mouth or hyposalivation(66)
  Those arising from specific long-term lesions of DM
- Retinopathy (sudden vision change)
- Nephropathy (in kidney)
- Neuropathy (in the nerves which shows tingling sensation or numbness in the feet hands. Those resulting from acceleration or increased predisposition to disease processes(66).
- Atherosclerosis
- Frequent or recurrent skin
- Urinary tract infection(66)

**3.4 Diagnostic criteria of diabetic Ketoacidosis(67)**

| **Parameters** | **Mild** | **Moderate** | **Severe** |
|---|---|---|---|
| Plasma glucose | >13.9 | >13.9 | >13.9 (67) |
| Arterial PH | 7.25-7.30 | 7.00-7.24 | <7.00 |
| Serum bicarbonate | 15-18 | 10-14.9 | <10 |
| Urine ketones | ++ | ++ | +++ |
| Serum ketones | +++ | +++ | +++ |
| Anion gap | >10 | >12 | >12 (67) |
| Sensorium | Alert | Alert/drowsy | Stupor/coma |
| Serum sodium | Normal | Low | Low |
| Serum potassium | Normal | High | High |
| Serum phosphate | Normal | High | High (67) |

One to seven percent of documented DKA cases have a blood sugar level of less than 13.9 m mol/l (250 mg/dL), and this level appears to be more prevalent in patients with hepatic impair meant or those who are in patient(68) . Several medicines, including glucocorticoids and thiazides, are well- known cause of hyperglycaemia, which can lead to a DKA. Clinicians should also consider DKA in patient receiving a typical antipsychotic medication which present in hyperglycaemia(69) . A typical antipsychotic has been raised the risk of diabetes, glucose intolerance, and DKA. The healthcare profession should assess the anion gap and ketones levels of such patients. Another antipsychotic medicine must be chosen to help alleviate this problem(70) . The appearance of a patient with DKA varies significantly according on their severity of the event. Patients with mild or moderate illness may experience vague symptoms such as fatigue, lethargy, poor appetite, or headache. In T1D, polyuria and polydipsia may be recent, whereas in T2D, symptoms may have been present for weeks or months(71) . Nausea, vomiting, and stomach pain are common symptoms of DKA and may be attributed to the combined effects of dehydration, hypokalaemia, ketonemia, and delayed gastric emptying. Physical examination may reveal sign of dehydration, such as low skin turgor, decreased axillary sweat, and postural hypotension(72) .

## 4. Management strategies for diabetes and Diabetics Ketoacidosis

### 4.1 Management strategies for diabetes

Insulin is the chosen treatment for managing both T1D and T2D during pregnancy. Pregnancy requires frequent insulin adjustment to meet changing needs, emphasising the significance of daily self-monitoring of blood glucose(73). During the first trimester, women with T1D may have higher levels of hypoglycaemia due to reduced daily insulin requirements. In the second trimester, insulin resistance requires weekly or biweekly dose increase to meet glycaemic typically, basal insulin should account for 50% of total daily doses, whereas prandial insulin should account for 50%. During the late third trimester, insulin levels often stabilise or decrease somewhat(74). Referral to a specialised centre with team -based care, including high -risk obstetrician, endocrinologists, dietitian, nurses and social workers, is recommended due to the complexity of insulin management during pregnancy. None of the currently available insulin formulations have been shown to cross the placenta(74).

#### 4.1.1 Type 1 diabetes

Women with T1D have a higher risk of hypoglycaemia during the first trimester and like other women, have altered counter regulatory response. Pregnancy may diminish hypoglycaemic awareness(75). Educating patients and family members on the prevention, detections and treatment of hypoglycaemia is crucial before, during and after pregnancy to mitigate its hazards. Insulin resistance decrease rapidly with placental delivery. After birthday, women ‘s insulin sensitivity increases and they may need less insulin than before. Pregnancy is a ketogenic condition, putting women with T1D and to a lesser extent, T2D at risk for DKA due to lower blood glucose levels compared to non- pregnant individuals(76). Women with pre-existing diabetes, particularly types 1, requires ketones strips at home and education on DAK prevention(77) .

#### 4.1.2 Type 2 diabetes

T2D is frequently related with obesity. Weight increase during pregnancy is recommended for overweight women at 15-25 Lb and obese women at 10-20Lb(78) . Women with T2D typically have better glycaemic control than those with T1D. However, they may require greater insulin dosages and concentrated insulin formulations. Insulin requirements decrease considerably after birth, just as they do in T1D. T2D can increase the risk of hypertension and other comorbidities, even with better control and shorter duration. Pregnancy loss is more common in the third trimester in women with T2D than in the first trimester in women with T1D(79).

### 4.2 Management strategies for diabetes ketoacidosis

DKA in the intensive care unit within the first 24- 48 hours(80). To manage, focus on optimising hydration, blood glucose, precipitating factors, Ketoacidosis and electrolytes imbalance (e.g. sodium, chloride, potassium). The current guidelines for DKA suggest commencing fluid

resuscitation with isotonic saline based on corrected serum sodium. Insulin can be administered intravenously, intramuscularly, or subcutaneously. This recommendation focuses on correcting electrolytes levels, particularly potassium concentrations in the blood. Bicarbonate supplementation is advised for cases of acidosis with a pH below 6.9(81).

DKA usually happens fast, spanning hours or days. Patients may experience hyperglycaemic symptoms such as polyuria, polydipsia, polyphagia, and weight loss. More severe symptoms include abdominal discomfort, vomiting, dehydration, weakness, abnormal mentation and coma. Abdominal pain should be investigated carefully, as an abdominal process may have caused the Ketoacidosis state. Examination findings include increased skin turgor, Kussmaul respiration, tachycardia, hypotension, abnormal mentation and coma(82) . Hypothermia may also occur. In a hypothermic patient. Normal body temperature may indicate an infection(83).

### 4.3. Pharmacological interventions

Diabetes management varies based on type and severity of the disease. T1DM needs insulin therapy for life, with long-acting (basal) insulins such as glargine, detemir, and deludes maintaining continuous blood sugar control, and rapid-acting (bolus) insulins such as as part, lispro, and gallisin managing peak mealtime(84). Sodium-glucose cotransporter-2 (SGLT2) inhibitors or pramlintide may be added in some cases for extra help. T2DM is treated initially with metformin, but other medications are added as needed. Glucagon-like peptide 1(GLP-1) receptor agonists (liraglutide, similitude) and SGLT2 inhibitors (empagliflozin, dapagliflozin) are excellent choices, particularly in those with cardiovascular or kidney disease, and Dipeptidyl peptidase-4(DPP-4) inhibitors, sulfonylureas, meglitinides, thiazolidinediones (TZDs), and alpha-glucosidase inhibitors provide other options to manage blood sugar(85). Insulin is required later. For DKA—a life-threatening and dangerous complication—therapy is IV insulin to decrease blood sugar, normal saline fluid resuscitation (replacing with D5-1/2 NS as glucose improves), and strict monitoring of electrolytes, particularly potassium replacement to avoid heart complications. Bicarbonate is saved for extreme cases where blood pH is critically low (<6.9)(86). It's also important to identify and treat the underlying cause, infection, missed medication, or other stimulus, to permit proper recovery.

### 1. Pharmacological Interventions for Diabetes

### A. Type 1 Diabetes

| Drug Class | Examples | Mechanism of Action | Usage |
|---|---|---|---|
| Rapid-acting Insulin | Insulin lispro, Insulin as part, Insulin glutinane | Quickly lowers blood sugar | Used before meals (87) |
| Short-acting Insulin | Regular human insulin | Slower onset than rapid-acting insulin | Used 30-60 min before meals (88) |

| | | | |
|---|---|---|---|
| Intermediate-acting Insulin | NPH insulin | Provides baseline insulin coverage | Used twice daily (89) |
| Long-acting Insulin | Insulin glargine, Insulin detemir, Insulin degludec | Provides 24-hour glucose control | Used once daily (90) |
| Ultra-long-acting Insulin | Insulin degludec | Longest duration (~42 hours) | Helps reduce nocturnal hypoglycaemia(90) |

**B. Type 2 Diabetes**

| **Drug Class** | **Examples** | **Mechanism of Action** | **Usage** |
|---|---|---|---|
| Biguanides | Metformin | Reduces liver glucose production | First-line therapy(91) |
| Sulfonylureas | Glimepiride, Glipizide, Glyburide | Stimulates insulin secretion | Risk of hypoglycaemia(92) |
| Meglitinides | Repaglinide, Nateglinide | Short-acting insulin secretagogues | Used before meals(93) |
| Thiazolidinediones | Pioglitazone, Rosiglitazone | Improves insulin sensitivity | May cause weight gain(94) |
| DPP-4 Inhibitors | Sitagliptin, Linagliptin | Inhibits GLP-1 breakdown, increasing insulin secretion | Less risk of hypoglycaemia(95) |
| GLP-1 Receptor Agonists | Liraglutide, Similitude, Exenatide | Enhances insulin secretion, slows gastric emptying | Weight loss benefit (96) |
| SGLT2 Inhibitors | Empagliflozin, Dapagliflozin | Increases glucose excretion in urine | Lowers blood pressure, weight loss benefit (97) |
| Alpha-glucosidase Inhibitors | Acarbose, Miglitol | Slows carbohydrate absorption | Reduces post-meal glucose spikes (98) |
| Insulin Therapy | Various formulations | Required in advanced cases | Used when oral medications fail (99) |

**2.Pharmacological Interventions for Diabetics Ketoacidosis**

| Medication | Examples | Mechanism of Action | Usage |
|---|---|---|---|
| Intravenous (IV) Insulin | Regular insulin | Suppresses ketone production and lowers blood glucose | Given as continuous IV infusion (99) |
| IV Fluids | Normal saline (0.9% NaCl), Half normal saline (0.45% NaCl), Dextrose 5% | Replenishes fluid loss and maintains circulation | First-line therapy for dehydration(100) |
| Potassium Replacement | Potassium chloride (KCl), Potassium phosphate | Prevents hypokalaemia caused by insulin therapy | Given if serum K+ <5.3 mEq/L (101) |
| Bicarbonate Therapy (Rarely Used) | Sodium bicarbonate | Corrects severe acidosis (pH <6.9) | Only used in extreme cases(81) |
| Electrolyte Replacement | Magnesium sulphate, Phosphate | Maintains electrolyte balance | Given based on lab results (81) |

**4.1.1 Treatment for Type 1 Diabetes mellitus**

**1. Insulin Therapy (Lifelong Requirement)**

Insulins are classified based on their onset, peak, and duration of action.

| **Type of Insulin** | **Examples** | **Onset** | **Peak** | **Duration** | **Usage** |
|---|---|---|---|---|---|
| Rapid-acting | Lispro, Aspart, Glulisine | 10-30 min | 1-2 hrs | 3-5 hrs | Pre-meal bolus (102) |
| Short-acting | Regular insulin | 30-60 min | 2-4 hrs | 6-8 hrs | Used in IV infusion for DKA (60) |

| | | | | | |
|---|---|---|---|---|---|
| Intermediate acting | NPH (Neutral Protamine Hagedorn) | 1-2 hrs | 6-10 hrs | 12-18 hrs | Basal insulin, given twice daily(103) |
| Long-acting | Glargine, Detemir | 1-2 hrs | No peak | 24 hrs | Basal insulin, given once daily (90) |
| Ultra-long acting | Degludec | 1-2 hrs | No peak | >42 hrs | Provides stable glucose control (90) |

**Insulin Delivery Methods:**

- **Subcutaneous Injections**: Most common, using syringes, pens, or pumps.
- **Insulin Pumps**: Continuous Subcutaneous Insulin Infusion (CSII), mimics physiological insulin secretion.
- **Inhaled Insulin**: Afrezza is a rapid-acting insulin alternative(104).

**B. Treatment for Type 2 Diabetes Mellitus**

**1. First-Line Therapy:** Metformin **(**Biguanide) is often the initial medication prescribed due to its effectiveness, safety profile, and affordability.

**2. Second-Line Agents (Added if HbA1c target is not met)**

| Class | Examples | Mechanism of Action | Benefits | Side Effects |
|---|---|---|---|---|
| **Sulfonylureas (SUs)** | Glipizide, Glyburide, Glimepiride | Stimulate insulin release from beta cells | Rapid glucose reduction | Hypoglycaemia, weight gain (93) |
| **Meglitinides** | Repaglinide, Nateglinide | Short-acting insulin secretagogues | Useful for postprandial control | Hypoglycaemia, weight gain (93) |
| **Thiazolidinediones (TZDs)** | Pioglitazone, Rosiglitazone | Improve insulin sensitivity | No hypoglycaemia, improved lipid profile | Weight gain, fluid retention, heart failure risk (105) |

| | | | | |
|---|---|---|---|---|
| **DPP-4 Inhibitors** | Sitagliptin, Linagliptin | Inhibit incretin degradation, enhancing insulin secretion | Well tolerated, no weight gain | Nasopharyngitis, pancreatitis risk(106) |
| **GLP-1 Receptor Agonists** | Liraglutide, Semaglutide, Dulaglutide | Enhance insulin secretion, suppress appetite | Weight loss, cardiovascular benefits | GI side effects (nausea, vomiting)(107) |
| **SGLT-2 Inhibitors** | Empagliflozin, Canagliflozin, Dapagliflozin | Promote renal glucose excretion | Weight loss, BP reduction, cardiovascular benefits | Risk of UTIs, diabetic ketoacidosis, dehydration (108) |
| **Alpha-Glucosidase Inhibitors** | Acarbose, Miglitol | Delay carbohydrate digestion | Useful for postprandial control | GI side effects (flatulence, diarrhea) (98) |
| **Insulin Therapy** | (When required) | Mimics physiological insulin response | Necessary in late-stage T2DM | Risk of hypoglycaemia and weight gain (109) |

**Combination Therapy:**

- Dual or triple therapy is used if monotherapy fails.
- **Example:** Metformin + GLP-1 receptor agonist + SGLT-2 inhibitor for synergistic effects(110).

**2. Diabetic Ketoacidosis (DKA)** is a serious and life-threatening complication of type 1 Diabetes Mellitus. Imagine your body as a car that usually runs on gasoline (glucose). In DKA, it's like the car is out of gas and starts using an alternative fuel (fat) instead. This process produces harmful substances called ketones, which build up in the blood and make it acidic(111).

**A. Pharmacological Management of DKA**

The involves careful and systematic pharmacological interventions, with insulin therapy being the cornerstone. Think of insulin therapy as the key to unlocking the body's ability to use glucose again, essentially reversing the dangerous build -up of ketones and bringing high blood sugar levels back down to safer territories(112). DKA fluid resuscitation is crucial to correct dehydration and improve blood flow. Patients typically start with an initial administration of 0.9% sodium chloride (NaCl) solution, commonly known as normal saline, receiving 1-2 liters over the first 1-2 hours. This helps to rehydrate the body swiftly. Once their sodium levels are stable, the maintenance fluid changes to 0.45% NaCl to continue hydration without overloading

the body with sodium. Additionally, when blood glucose levels drop below 250 mg/dL, dextrose is added to the fluids to prevent hypoglycaemia (Dangerously low blood sugar levels)(56).

**4.2 Insulin Therapy in Diabetic Ketoacidosis**

To avoid exacerbating hypokalaemia insulin therapy should be postponed until serum potassium levels reach 3.3 mEq/L and continued following intravascular volume expansion(113) . Traditionally, with the exception of mild episodes of DKA, a continuous intravenous infusion of normal insulin has been the preferred treatment to limit Lipolysis. Because of technical constraints, accompanying life – threatening illnesses, and institutional policies, DKA treatment with intravenous regular insulin is primarily provided in the critical care unit(114) . The standard is an initial intravenous bolus of regular insulin at 0.1 unit/kg body weight, followed by a continuous infusion at 0.1 units/kg/h. Alternatively, an intravenous infusion of normal insulin at a beginning rate of 0.14 units/ kg/h (10 units / h in a 70-kg patients) without the priming loading dosage was recently advocated in prospective randomised research. Insulin glulisine can be used for acute intravenous treatment of DKA, although the choice depends on institutions preferences and cost- effectiveness(115) . The predicted decrease in serum glucose concentration within the first hour is 50 mg/dL. If this is not accomplished, re address hydration status and then titrate insulin infusion by doubling every hour until a consistent glucose fall of 50 to 75mg/h is achieved. When the serum glucose reaches 200- 250mg / dL the insulin infusion rate is decreased to 0.02-0.05 units/ kg per hour and dextrose (5-10%) is added to the intravenous fluid to prevent precipitous falls in plasma osmolality, thereby allowing continued insulin administration with the goal serum glucose between 140 and 200 mg/dL and resolution of metabolic acidosis. The ideal route of insulin administration remains stable in the acute treatment of DKA and includes regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injection. Overwhelmingly, experts have recommended intravenous insulin infusion as the treatment of choice in the intensive care setting, as a predictable means of administration allowing for maximal peaks insulin with in the first hour of treatment(116) .

**5. Nutritional consideration of Diabetes and diabetics ketoacidosis**

**5.1 Nutritional consideration of Diabetes management**

The focus on a diet rich in fruit, vegetable, whole grains, lean protein, and healthy fat. Avoid sugary snacks and beverages. monitor carbohydrates intake as it directly affects blood sugar levels. Choose complex carbs like whole grains over simple carbs. keep portion sizes in check to avoid overeating. Eat regular meals and snacks to maintain steady blood sugar levels stay hydrated with water instead of sugary drinks. Reduce intake of foods with added sugars. Include sources of healthy fats like avocados, nuts, and olive oil(117).

**5.2 Nutritional consideration of diabetic ketoacidosis**

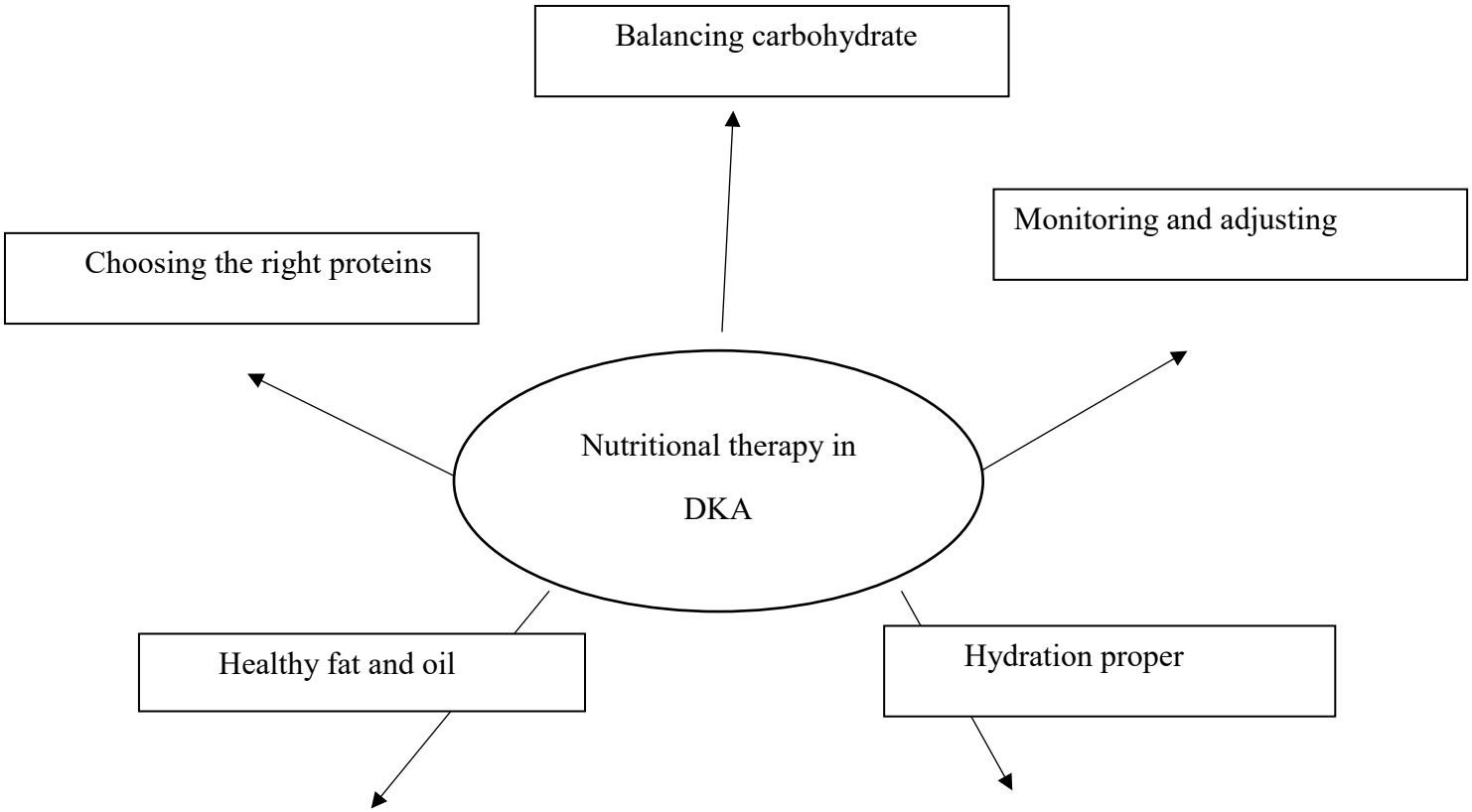
DKA is a critical metabolic complication of diabetes, marked by elevated blood glucose levels, ketone production, and metabolic acidosis. In the initial phase of DKA treatment, the primary focus is on rehydration and correction of electrolyte imbalances. Intravenous (IV) administration of 0.9% sodium chloride solution is commonly employed to address dehydration and sodium deficits. Continuous monitoring of electrolytes, particularly potassium, phosphate, and sodium, is essential, with replacements as needed to prevent complications such as cardiac arrhythmias(118). Once the patient can tolerate oral intake, the

reintroduction of carbohydrates is crucial to prevent hypoglycemia and halt ketone production. Emphasis should be placed on low glycemic index foods, including whole grains, legumes, and vegetables, while avoiding refined sugars to maintain stable blood glucose levels. An intake constituting 15-20% of total daily calories is advisable, with sources such as lean meats, fish, eggs, dairy products, and plant-based proteins like lentils and beans. Given that fat metabolism contributes to ketone production, dietary fat should be cautiously reintroduced. Following the resolution of the acute DKA phase, long-term nutritional strategies should focus on maintaining balanced blood glucose levels. A multidisciplinary approach, involving healthcare providers, dietitians and patient education, is essential to optimize outcomes and support sustained metabolic health(119).

**5.3 Role of diet in diabetes management**

Eat complex carbs with a low glycaemic index, like whole grains, legumes, fruits, and vegetables. These contribute to steady blood sugar level. Keeping track of meal sizes helps to regulate blood sugar levels. To boost cardiovascular health, consume healthy fats, from foods such as nuts, seeds, and seafood. Include lean proteins like poultry, fish, tofu, and beans to improve overall nutrition and satiety. Eating smaller, more regular meals throughout the day can help minimize dramatic changes in blood sugar levels. Reduce your intake of added sugars and sweeteners to avoid rapid blood sugar rises(120).

**5.4 Nutritional therapy in diabetic ketoacidosis**




**Balancing carbohydrate:** Balancing carbohydrate intake is essential to maintain stable blood sugar levels. Complex carbohydrate with a low glycemic index, such as whole grains and legumes, are preferred(121).

**Choosing the right protein:** Proteins that do not significantly raise blood sugar levels are important. Lean sources of proteins like chicken, fish, tofu, and beans are good choices.
**Healthy fats and oils:** Incorporating healthy fats from sources like nuts, seeds, avocados, and olive oil can improve overall health without causing blood sugar spikes(122).
**Hydration proper:** Hydration is crucial, especially during episodes of DKA. Water and electrolyte solutions can help maintain fluid balance and prevent dehydration(118).
**Monitoring and adjusting:** To manage DKA, blood sugar levels must be monitored on a regular basis and the diet adjusted accordingly. A qualified dietician can provide personalized counsel and support(118).

**6.Psychological and behavioural Aspects of Diabetes and Diabetic Ketoacidosis**

The emotional burden of diabetes can contribute to significant psychological challenges, including stress, anxiety, depression, and diabetes – related distress. The constant responsibility of managing glucose levels, following dietary restrictions, and adhering to treatment plans can lead to frustration and emotional fatigue(123).

Diabetes -Related Distress (DRD) are many individuals experience stress and emotional exhaustion due to the continuous demands of diabetes management. feeling of frustration, helplessness, or guit may arise from struggling to maintain optimal blood sugar control(124). The fear of complications such as DKA, hypoglycaemia, and long-term organ damage can cause heightened anxiety. Some individuals become excessively focused on checking blood sugar levels, leading to increased stress and hypervigilance is known as anxiety and fear. Depression is the people with diabetes face a greater risk of developing depression, which can manifest as persistent sadness, low energy, and lack of motivation to manage their condition. Depression can also contribute to neglecting diabetes care, increasing the likelihood of complications. Post -traumatic stress disorder (PTSD) is Severe DKA episodes can be traumatic, leading to PTSD symptoms such as flashback, nightmare, and an intense fear of recurrence. This distress can make it more difficult for individuals to engage in regular diabetes management, as they may avoid situations or behaviours associated with their hospitalization(123).

**6.1 Behavioural Aspects of Diabetes and DKA**

The psychological effects of Diabetes often influence behaviour, impacting self - care practices, adherence to treatment, and overall lifestyle choices. Emotional stress, diabetes - related burnout and mental health struggles can lead to behaviours that compromise proper diabetes management. Successfully managing diabetes requires consistent adherence to insulin therapy, medication, and lifestyle modifications(125). However, stress, depression, or a lack of motivation can result in skipped insulin doses, unhealthy dietary habits, and irregular blood sugar monitoring, increasing the risk of complications like DKA is known as treatment adherence. Disordered eating and diabetes burnout is some individuals develop unhealthy eating patterns, such as skipping meals to avoid insulin injections or binge eating in response to emotional distress. Diabetes burnout, characterized by emotional exhaustion from continuous self-care demands, can lead to complete disengagement from diabetes management. Risk-taking Behaviours is certain individuals may engage in harmful behaviours, such as intentionally skipping insulin (diabulimia) to control weight excessive alcohol consumption, or avoiding medical appointments. These actions can worsen blood sugar control and elevate the risk of DKA. Avoidance and Denial are psychological burden of diabetes can lead to

avoidance behaviours, including refusing to check blood sugar levels or avoiding discussion about diabetes with healthcare providers and loved ones. Such behaviours increase the risk of undetected high blood sugar levels and related complications(125).

**6.2 Impact of Diabetic Ketoacidosis on Mental health**

Diabetic ketoacidosis (DKA) is a serious, life-threatening complication of diabetes, clinically characterized mainly by physical manifestations such as extreme dehydration, nausea, vomiting, and altered mental status. The psychological effect of DKA, however, is often overlooked(126). Emotional distress during hospitalization, fear of recurrence, and the lifelong burden of managing diabetes can have desperate effects on the mental health of a patient. In the absence of proper support, these psychological problems can develop into anxiety, depression, and even post-traumatic stress disorder (PTSD), thereby having a serious adverse effect on overall health. Screening and management of these psychological problems are a crucial component of overall diabetes care.

Having DKA is a traumatic event, and most patients develop anxiety and depression following an attack. Chronic worry about when the next attack will occur, the daily stress of managing blood sugars, and worry about long-term complications are common. Physical symptoms of DKA- fatigue, nausea, and weakness- can also lead to a feeling of sadness, frustration, and hopelessness. Some will have generalized anxiety, with excessive worry about blood sugars, another DLA attack, and long-term complications(126). These psychiatric issues must be addressed. Professional counselling, attending diabetes-specific support groups, and stress-reducing activities such as exercise, mindfulness, and creative activities can be helpful in overcoming anxiety and depression.

For others, the intensity of DKA may be so severe that it initiates the onset of PTSD. Those affected may experience frequent flashbacks of the hospital stay, nightmares about the event, or intrusive thoughts that cause severe fear and distress. Symptoms of PTSD may appear as reexperiencing the trauma through frightening dreams or disturbing thoughts, avoidance patterns such as failure to keep appointments or avoidance of blood sugar testing out of fear, and heightened arousal that causes increased irritability, difficulty with concentration, or heightened sensitivity to body sensations. Evidence-based therapy, including cognitive-behavioural therapy (CBT) and eye movement desensitization and reprocessing (EMDR), has been effective in alleviating symptoms of PTSD, allowing individuals to process their trauma and restore a sense of mastery(127).

Mental health is just as vital as physical health in diabetes care. To sustain emotional well-being with diabetes, a good support system needs to be established, with understanding family, friends, and healthcare staff to offer assistance and reassurance(128). Stress coping and self-management are also vital. Regular use of stress reduction exercises like meditation, deep breathing, yoga, or other low-level exercise may reduce stress and improve mood.

The psychological effects of DKA cannot be overestimated. Blood sugar control is most important, but so is treating the mental health issues that may develop after such a traumatic event. Acknowledging the emotional burden of DKA, getting help, and integrating mental health care into diabetes care can enhance well-being and resilience. Nobody needs to bear the burden of diabetes by themselves-support and help are there for those who need it(129).

## 7. Technological Advances in Diabetes Care

### 7.1 Ultrarapid Insulins

In recent years, faster acting insulin analogue have been developed to improve postprandial glycaemic management, preventing or reducing pp glycaemic excursions. Their earlier beginning will also allow for more quicker correction of hyperglycaemia. In September 2017, Novo Nordisk got FDA approval for flaps (a novel insulin as part formulation)(129). Flaps is created by combining niacinamide (vitamin B3), which boosts early absorption, and l-arginine, a stabilizer. In a pooled analysis of six trials evaluating the pharmacokinetics and pharmacodynamic characteristics of flaps in adults with T1D, it consistently demonstrated earlier onset of appearance, greater early insulin exposure, and glucose-lowering effect than traditional insulin as part across all trials. In phase lll trials, fiasps was demonstrated to enhance glucose control compared to insulin as part after mixed meal tolerance testing in people with both T1D and T2D(129). The improved effect of fiasp is also due to earlier inhibition of endogenous glucose. A clinical experiment investigating the compatibility, effectiveness, and safety of Fiasp compared to insulin aspart in continuous subcutaneous insulin infusion (CSII). Fiaspis was shown to be comparably safe and compatible for use in CSII, with no additional safety problems detected in either treatment arm. Fiaspis has been shown to improve pharmacokinetics (PK) and pharmacodynamic (PD) profiles, as well as per person (PP) glucose control, compared to insulin aspart in CSII usage, which is comparable with prior studies for multiple dose injection (MDI) users. Future trials will look into the possible benefits of quicker Insulins in artificial pancreas (AP) device(130).

### 7.2 Smart Insulin

Aside from algorithm driven AP technologies, another approach to glucose-responsive insulin therapy has been the creation of smart insulin. Insulin may sense and respond to glucose, triggering release only when necessary. This can be achieved through glucose-responsive polymer encapsulation or direct alteration of insulin molecules. Juvenile Diabetes Research Foundation (JDRF), a charitable organisation that funds T1D research, ingested in Smart cells, lnc. In 2003.SmartCells was eventually acquired by Merck in 2010, and phase I trials were completed in 2016, after which the drug’s development was halted due to a lack of efficacy in early trials(131).

### 7.3 Inhaled insulins

Despite its inconvenience and discomfort, subcutaneous insulin injections continue to be the major method of insulin Inhaled insulin was a popular “meal insulin” choice since it eliminates the need for inconvenient injections and provides quick insulin action. Despite its potential, inhaled insulin has yet to become widely used. Needle anxiety is likely overestimated, 27 and developing molecules that can be effectively administered and absorbed into the alveoli has been difficult(132). Afrezza was FDA approved in 2014 and is now the only inhaled insulin available on the market. Afrezza is recombinant human insulin adsorbed onto Technosphere These particles are generated by the self -assembly of an inert excipient, fumaryl diketopiperazine. The size of the Technosphere particles facilitates administration of insulin to the deep lung for better systemic absorption. Afrezza has a more rapid onset and shorter duration of action than subcutaneously injected rapid acting insulin analogues. In clinical trials, the median time to peak activity of Afrezza was demonstrated to be 53min, and duration of

action to be 160min (2.5-3h). Its use is connected with less frequent PP hypoglycaemia and slightly lower weight gain(133).

**7.4 Continuous Glucose monitoring systems**

Glucose monitoring (GM) despite significant developments in continuous glucose monitoring (CGM), the vast majority of patients with diabetes worldwide rely on intermittent self-monitoring of blood glucose (SMBG)(133). Furthermore, due to the cost of GM, even habitual insulin users may choose to skip GM on certain days. Efforts to minimise the user cost of GM, aside from government intervention, are unfortunately rare. Accurate SMBG devices are widely available, and increasing their use while decreasing the use of less accurate sensors is a positive trend. CGM advancements. Research and development in CGMs aims to improve accuracy while minimising user calibrations. Additional aims include ease of use, longer wear, miniaturization, more impactful data Management, and secure and reliable connectivity with the cloud and other multiple more improvements have been considered for CGMs, ranging from predictive glucose alerts to integration with AP Additional CGM improvements are being explored. Current CGM trend arrows are potentially valuable, but neither the implementation of the arrows nor how they should be responded to has been guidelines for the use of trend arrows have been published, but they are complex and focus on a particular CGM system(134). To standardised bolus doses, it may be helpful to consider positive or negative glucose trend lines when a CGM system has been shown to accurately forecast glucose levels for 3060 minutes.This would allow for safer and more accurate bolus doses modifications, potentially reducing hypoglycaemia and hyperinsulinemia. Factory calibration of CGMs decreases user errors, improves convenience, saves money on meter -based calibration, and may improve sensor accuracy. A business building an AP system reported using a factory-calibrated CGM to avoid potential inaccuracies caused by user's calibration issues. Although zero calibration appears to be ideal, factory-calibrated sensors may occasionally benefit from meter calibration if readings from an accurate meter significantly differed from those of the Having two to five functional electrodes on each sensor improves accuracy and eliminates readings from failed sensors from the glucose average. Acetaminophen, ascorbic acid (vitamin c), and acetylsalicylic acid might(133).

**8.5 Artificial pancreas Technology**

Over 30 years ago, a study tilted "Algorithms for adjusting insulin dosage by patients who monitor blood glucose "addressed the technical challenges of today's artificial pancreas. The paper was published in reaction to the introduction of home blood glucose monitoring. In the 1970s, SMBG enabled people with diabetes to acquire real-time data on their blood glucose levels, a first since the discovery of insulin(135). The goal of the research was to offer a collection of algorithms to help patients make real-time optimal therapy decisions based on blood glucose meter data for extra insulin in response to hyperglycaemia. The contemporary artificial pancreas consists of three main components: a continuous glucose monitoring system, an insulin infusion pump, and a control algorithm. Uplike produced one of the earliest continuous glucose sensors in 1967 by immobilising glucose oxidase in a biodegradable membrane. Produced the first commercial continuous glucose monitoring device using a comparable electrochemical sensor. The glucose sensor is introduced via the skin and put at a depth of 8-12 mm in the subcutaneous tissue(136). The sensor monitors glucose in the

interstitial fluid, not the blood. Glucose is measured using a catalytic reaction including the enzyme glucose oxidase immobilised in a polymeric membrane overlaying an electrode sensing device. Insulin pumps, created in the late 1970s, have improved the quality of life and clinical outcomes for diabetics. Modern pumps are compact, dependable electro mechanical devices that provides insulin via a controlled infusion into the subcutaneous tissue. Pumps are made up of a refillable insulin cartridge, a pump mechanism, and a programmed user interface that the patient can use to establish a basal infusion rate or to administer a discrete bolus for meal coverage or hyperglycaemia correction. Since the debut of insulin pumps three decades ago, improvements in microelectronics and consumer electronics have increased the technology's functionality and usability. The control algorithms in the AP make real -time insulin -infusion decisions based on data from the continuous glucose monitor, insulin pump, and other vital information. Parker et al(136). introduced one of the initial current algorithms approaches to the AP in 1999 with their Monetary Policy Committee (MPC) algorithm. Parker and Doyle used a physiology model to manage insulin delivery for individuals with T1D. The glucose insulin dynamics model predicts future glucose levels based on previous insulin administration and glucose measurements. Using a model based predictive algorithm insulin-dosing instructions can be supplied based on projected glucose levels, reducing the temporal delays caused by subcutaneous insulin's delayed action. Devised an MPC algorithm based on a nonlinear model of diabetes patients' physiology. MPC has been employed by numerous another prominent research. Presented the pelvic inflammatory disease (PID) technique as an early attempt to developing AP control algorithm for diabetes management. We provide examples of unihormonal or Bihor monal methods to AP using MPC, PID, follicular lymphoma (FL), and other logical supervision algorithms(137).

**8.Health economics and policy implication in diabetes management**

Health economics and policy are core to diabetes management through influencing access to care, costs of treatment, and health outcomes. Diabetes places a colossal economic burden on patients, the healthcare system, and society, including costs outside medical care to cover lost productivity, disability, and premature death. Investing in cost-saving interventions can reduce the burden of the disease and healthcare costs. Prevention interventions that promote healthier lifestyles, such as better diet and physical activity, reduce the risk of T2D. Detection early through screening averts severe complications and reduces long-term medical expenditures(138). Policies promoting medication adherence, such as insurance coverage and financial assistance, promote better disease control and prevent costly hospitalization. Public health policies also play a crucial role in diabetes management. Expanding insurance coverage for health improves access to essential treatment, while price controls on medications like insulin keep them affordable. Value-based care models enhance more effective control by linking provider reimbursement with patient outcomes. Public health action on a population level, such as taxing sugar-sweetened beverages, improving food labeling, and promoting physical activity, also prevents diabetes. An efficient healthcare system also plays a significant role in diabetes management. Incorporating diabetes management into primary healthcare ensures early detection and better support, while telemedicine and digital health technologies enhance access, particularly in underserved areas. Social and economic inequities also play a crucial role to address, as poor groups often have limited access to affordable care. A comprehensive approach with economic measures and policy interventions is necessary to

reduce the burden of diabetes. Governments, healthcare providers, and policymakers must collaborate to improve care, promote prevention, and ensure sustainable healthcare spending(139).

**8.1 Cost effectiveness of diabetes treatment**

Successful control of diabetes not only entails improvement in health outcomes but also determining economically feasible measures that reduce the economic burden on individuals and health systems. Preventive measures such as healthy eating, exercise, and weight control have been established as some of the most cost-effective and successful measures to avoid the development of T2D(139). Evidence suggests that lifestyle changes have the potential to considerably reduce the risk of developing diabetes, often a more cost-effective measure than pharmacological interventions. In cases where pharmacotherapy is required, metformin is one of the most cost-effective and reliable choices for the treatment of T2D. It has significant health benefits at a relatively affordable cost compared to newer agents. However, newer agents like SGLT-2 inhibitors and GLP-1 receptor agonists have added cardiovascular and renal benefits at a relatively higher economic cost. The cost-effectiveness of these agents is based on the individual patient's needs and the expected long-term benefits(140).

Insulin therapy is critical for T1D patients and those with established T2D. The application of technologies such as continuous glucose monitoring (CGM) and insulin pumps has greatly enhanced glycemic control and minimized complications but, with their high cost, can limit accessibility in most patients(141). In addition, early detection and diagnosis of diabetes are cost-saving measures, as early detection of the disease can avert advanced complications and lower long-term treatment costs. The emergence of digital health and telemedicine has made it possible to introduce new strategies in managing diabetes in a cost-effective and efficient manner. Evidence shows that telemedicine improves blood glucose control and lowers hospitalization rates, making it an acceptable alternative for those residing in remote or underserved communities. As technology advances, the integration of digital health solutions into diabetes care has the potential to enhance accessibility, enhance compliance with medication therapy regimens, and offer greater health outcomes-while simultaneously remaining cost-effective.9.2 Health policies for diabeties prevention.

**8.2 Health Policies for Diabetes Prevention**

Effective health policies are important in improving diabetes care by making treatment more accessible, affordable, and preventive. Properly designed policies not only improve patient outcomes but also reduce the financial burden to patients and healthcare systems. Availability of healthcare services is one of the main goals in diabetes policy. Increased insurance coverage and government subsidies allow patients to afford drugs like insulin, glucose meters, and preventive care(142). Price regulation of drugs and encouragement of generic drug use also reduce the expenses. Financial assistance programs are available in most countries, which try to make treatment for diabetes cost-effective and ensure that patients receive continuous care. Prevention and early detection are main areas of focus in policy design. Public health programs promote healthier lifestyles through better nutrition, exercise, and education. Governments have introduced programs like taxes on sugary drinks and increased labeling of food products to encourage healthier consumer behaviour. Regular screening programs for high-risk groups make it easy to detect diabetes, which prevents serious complications and reduces long-term healthcare costs. In addition, new healthcare models are transforming the practice of diabetes

care. Integration of diabetes care into primary healthcare systems allows patients to benefit from earlier intervention and better long-term care(142). Telemedicine and online health resources have made it easy to access care for people living in remote areas, while value-based care designs ensure that healthcare providers are patient-outcomes-focused instead of service volume-focused. Reduction of disparities in diabetes care is another main policy goal. Most low-income communities are faced with issues like limited access to healthcare, high drug costs, and low health literacy. Subsidized medical programs, community services, and occupational health programs enable everyone, irrespective of their economic background, to effectively manage their diabetes. A successful diabetes health policy integrates prevention, early treatment, new therapies, and equal access to healthcare. Collaborative efforts from government agencies, healthcare providers, and policymakers can establish sustainable solutions that enhance diabetes management and promote healthier lifestyles for everyone(143).

**9. Conclusion and future perspectives**

Diabetes, especially when complicated by DKA, remains a serious global health challenge. While medical advancements-such as new insulin therapies, continuous glucose monitoring, and AP systems-have greatly improved diabetes management, millions of people still struggle with access to care, treatment costs, and the daily burden of managing their condition. The reality is that diabetes isn't just a medical issue; it affects every aspect of a person's life, from their physical health to their mental well-being.

Looking to the future, there is hope. Emerging research in smart insulin, non-invasive glucose monitoring, and AI-driven diabetes management tools could make life easier for those living with the disease. Personalized treatment plans tailored to an individual's unique needs will likely become the norm, helping to prevent complications before they arise. At the same time, public health efforts must focus on prevention, education, and making essential diabetes care more affordable and accessible, particularly in underserved communities. Beyond technology and medicine, we must also acknowledge the emotional toll of diabetes. Supporting mental health, reducing stigma, and fostering a sense of community among those affected by the disease are just as important as any medical breakthrough. The future of diabetes care isn't just about better treatments-it's about making sure that every person, regardless of where they live or their financial situation, has the resources and support they need to live a full and healthy life.

**Refrences**

1. Tripathi BK, Srivastava AK. Diabetes mellitus: complications and therapeutics. Med Sci Monit. 2006;12(7):130-47.
2. Mohajan D. Historical view of diabetics mellitus: from ancient Egyptian polyuria to discovery of insulin. 2023.
3. Blackwood L, Gavin J, Arnott E, Barnett J, Dack C, Johansen J. # DiabetesOnAPlate: the everyday deployment and contestation of diabetes stigma in an online setting. Critical Public Health. 2023;33(2):160-73.
4. Regufe VM, Pinto CM, Perez PM. Metabolic syndrome in type 2 diabetic patients: A review of current evidence. Porto biomedical journal. 2020;5(6):e101.

5. Umpierrez GE. Hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Diabetes complications, comorbidities and related disorders. 2020:595-614.
6. Shruthi K. Study of Serum Phosphate Levels and Its Clinical Significance in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State: Rajiv Gandhi University of Health Sciences (India); 2016.
7. Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, et al. EADSG guidelines: insulin therapy in diabetes. Diabetes therapy. 2018;9:449-92.
8. Güemes M, Rahman SA, Hussain K. What is a normal blood glucose? Archives of disease in childhood. 2016;101(6):569-74.
9. Gregg EW, Buckley J, Ali MK, Davies J, Flood D, Mehta R, et al. Improving health outcomes of people with diabetes: target setting for the WHO Global Diabetes Compact. the lancet. 2023;401(10384):1302-12.
10. Rodrigues Oliveira SM, Rebocho A, Ahmadpour E, Nissapatorn V, de Lourdes Pereira M. Type 1 diabetes mellitus: A review on advances and challenges in creating insulin producing devices. Micromachines. 2023;14(1):151.
11. Rachdaoui N. Insulin: the friend and the foe in the development of type 2 diabetes mellitus. International journal of molecular sciences. 2020;21(5):1770.
12. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature reviews Disease primers. 2019;5(1):47.
13. Eizirik DL, Szymczak F, Mallone R. Why does the immune system destroy pancreatic β-cells but not α-cells in type 1 diabetes? Nature Reviews Endocrinology. 2023;19(7):425-34.
14. Kostopoulou E, Sinopidis X, Fouzas S, Gkentzi D, Dassios T, Roupakias S, et al. Diabetic ketoacidosis in children and adolescents; diagnostic and therapeutic pitfalls. Diagnostics. 2023;13(15):2602.
15. Mezil SA, Abed BA. Complication of diabetes mellitus. Annals of the Romanian Society for Cell Biology. 2021;25(3):1546-56.
16. Association AD. 4. Lifestyle management: standards of medical care in diabetes—2018. Diabetes care. 2018;41(Supplement_1):S38-S50.
17. Qaid MM, Abdelrahman MM. Role of insulin and other related hormones in energy metabolism—A review. Cogent Food & Agriculture. 2016;2(1):1267691.
18. Bankir L, Bouby N, Blondeau B, Crambert G. Glucagon actions on the kidney revisited: possible role in potassium homeostasis. American Journal of Physiology-Renal Physiology. 2016;311(2):F469-F86.
19. Al-Reshed F, Sindhu S, Al Madhoun A, Bahman F, AlSaeed H, Akhter N, et al. Low carbohydrate intake correlates with trends of insulin resistance and metabolic acidosis in healthy lean individuals. Frontiers in public health. 2023;11:1115333.
20. Koyama K, Anno T, Kimura Y, Kawasaki F, Kaku K, Tomoda K, et al. Pathology of ketoacidosis in emergency of diabetic ketoacidosis and alcoholic ketoacidosis: a retrospective study. Journal of Diabetes Research. 2024;2024(1):8889415.
21. Huber W, Zanner R, Schneider G, Schmid R, Lahmer T. Assessment of regional perfusion and organ function: less and non-invasive techniques. Frontiers in medicine. 2019;6:50.

22. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119.
23. Esposito P, Picciotto D, Cappadona F, Costigliolo F, Russo E, Macciò L, et al. Multifaceted relationship between diabetes and kidney diseases: Beyond diabetes. World journal of diabetes. 2023;14(10):1450.
24. Lopez Carrera YI, Al Hammadi A, Huang Y-H, Llamado LJ, Mahgoub E, Tallman AM. Epidemiology, diagnosis, and treatment of atopic dermatitis in the developing countries of Asia, Africa, Latin America, and the Middle East: a review. Dermatology and therapy. 2019;9(4):685-705.
25. Bryant J. Health and the developing world: Cornell University Press; 2019.
26. Ramphul K, Joynauth J. An update on the incidence and burden of diabetic ketoacidosis in the US. Diabetes Care. 2020;43(12):e196-e7.
27. Liu B, Li L, Bai L. Exploring Markers to Classify and Evaluate Ketosis Onset Diabetes: A Randomized Clinical Trails. 2021.
28. Pettus JH, Zhou FL, Shepherd L, Preblick R, Hunt PR, Paranjape S, et al. Incidences of severe hypoglycemia and diabetic ketoacidosis and prevalence of microvascular complications stratified by age and glycemic control in US adult patients with type 1 diabetes: a real-world study. Diabetes care. 2019;42(12):2220-7.
29. Flores M, Amir M, Ahmed R, Alashi S, Li M, Wang X, et al. Causes of diabetic ketoacidosis among adults with type 1 diabetes mellitus: insulin pump users and non-users. BMJ Open Diabetes Research & Care. 2020;8(2).
30. Osborne M, Atari M. Moral Diversity Fosters Cultural Looseness and Unpunished Norm Violations. 2024.
31. Virdi N, Poon Y, Abaniel R, Bergenstal RM. Prevalence, cost, and burden of diabetic ketoacidosis. Diabetes Technology & Therapeutics. 2023;25(S3):S-75-S-84.
32. Hydrie MZI. Risk factors for Type 2 Diabetes Mellitus: Metabolic Syndrome, Insulin Resistance and Primary Prevention. 2012.
33. Barnett T. Addressing Obesity in the Oceanic Population: Challenges, Solutions, and Pathways to Health. Journal of Clinical-Medical Research & Reviews. 2024;8(1):1-10.
34. Metwally AM, Salah El-Din EM, Abdel-Latif GA, Nagi DA, El Etreby LA, Abdallah AM, et al. A national screening for the prevalence and profile of disability types among Egyptian children aged 6–12 years: a community-based population study. BMC Public Health. 2023;23(1):1599.
35. Furusawa T, Pitakaka F, Gabriel S, Sai A, Tsukahara T, Ishida T. Health and well-being in small island communities: a cross-sectional study in the Solomon Islands. BMJ open. 2021;11(11):e055106.
36. LaMonica LC, McGarvey ST, Rivara AC, Sweetman CA, Naseri T, Reupena MS, et al. Cascades of diabetes and hypertension care in Samoa: Identifying gaps in the diagnosis, treatment, and control continuum–a cross-sectional study. The Lancet Regional Health–Western Pacific. 2022;18.
37. Abusalih H, Sabeib ZA. Update of the nutritional situation in the Republic of the Sudan. The North African Journal of Food and Nutrition Research. 2020;4(9):S17-S24.

38. Kiradi PH. Delineation of genetic variants modulating quantitative metabolic traits in an Arab population: University of Helsinki; 2021.
39. Fifita SST, Nonaka D, Cama MT, Filise MI. Factors associated with undiagnosed hypertension among Tongan adults: a cross-sectional study. Tropical Medicine and Health. 2024;52(1):4.
40. Song G. Racial and Ethnic Disparities in Diabetes-Related Healthcare Service Use in the United States, 2016–2020: The Claremont Graduate University; 2022.
41. Marrón-Ponce JA, Flores M, Cediel G, Monteiro CA, Batis C. Associations between consumption of ultra-processed foods and intake of nutrients related to chronic non-communicable diseases in Mexico. Journal of the Academy of Nutrition and Dietetics. 2019;119(11):1852-65.
42. Ranee R, Shahar S, You YX, Ajit Singh DK, Mohamed Sakian NI. Prevalence and Risk Factors of Sarcopenia Among Community Dwelling Older Adults in Klang Valley. Malaysian Journal of Medicine & Health Sciences. 2022;18(1).
43. Alonazy MA. A GIS-Based Analysis of the Incidence and Prevalence of Type 2 Diabetes in Saudi Arabia: Rutgers The State University of New Jersey, Rutgers School of Health Professions; 2019.
44. Souza LCVFd, Kraemer GdC, Koliski A, Carreiro JE, Cat MNL, Lacerda LD, et al. Diabetic ketoacidosis as the initial presentation of type 1 diabetes in children and adolescents: epidemiological study in southern Brazil. Revista Paulista de Pediatria. 2019;38:e2018204.
45. Chang Z, Cai H, Talsma EF, Fan S, Ni Y, Wen X, et al. Assessing the diet quality, environmental impact, and monetary costs of the dietary transition in China (1997–2011): Impact of urbanization. Frontiers in Sustainable Food Systems. 2023;7:1111361.
46. Sultana S. Exploration of diet quality and physical activity level among British Bangladeshi population living in the United Kingdom: Bournemouth University; 2020.
47. Hajek A, Lehnert T, Ernst A, Lange C, Wiese B, Prokein J, et al. Prevalence and determinants of overweight and obesity in old age in Germany. BMC geriatrics. 2015;15:1-13.
48. Tatsuno I, Gerlier L, Olivieri A-V, Baker-Knight J, Lamotte M. Assessing the health and economic burden of obesity-related complications in East-Asian populations: implementation of risk equations in the Core Obesity Model for Japan and model validation. BMJ Public Health. 2024;2(1).
49. Mollaei S. An analysis of Canadian young adults' eating behaviours towards sustainable food choices. 2023.
50. Jones HC, Kiburg KV, Lee MH, O'Neal DN, MacIsaac RJ. Trends in diabetic ketoacidosis in Victoria, Australia 2002–2016. BMC Endocrine Disorders. 2024;24(1):128.
51. Wennergren G, Strannegård IL. Asthma hospitalizations continue to decrease in schoolchildren but hospitalization rates for wheezing illnesses remain high in young children. Acta paediatrica. 2002;91(11):1239-45.
52. Haider R. The Global Burden of Diabetes. International Journal of Clinical and Medical Case Reports. 2024.
53. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular complications of type 2 diabetes mellitus. Current vascular pharmacology. 2020;18(2):117-24.

54. Babaniamansour S, Aliniagerdroudbari E, Afrakhteh M, Hosseinpanah F, Farzaneh F, Niroomand M. Can fasting plasma glucose replace oral glucose-tolerance test for diagnosis of gestational diabetes mellitus? Diabetology international. 2021;12:277-85.
55. Baynes H. Classification, pathophysiology, diagnosis and management of diabetes mellitus. J diabetes metab. 2015;6(5):1-9.
56. Krinsley JS, Preiser J-C. Time in blood glucose range 70 to 140 mg/dl> 80% is strongly associated with increased survival in non-diabetic critically ill adults. Critical care. 2015;19:1-11.
57. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: a missed diagnosis. World journal of diabetes. 2021;12(5):514.
58. 14. Children and Adolescents: Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Supplement_1):S283-S305.
59. Luethi N, Cioccari L, Crisman M, Bellomo R, Eastwood GM, Mårtensson J. Prevalence of ketosis, ketonuria, and ketoacidosis during liberal glycemic control in critically ill patients with diabetes: an observational study. Critical Care. 2016;20:1-11.
60. Dhatariya KK, Care JBDSfI. The management of diabetic ketoacidosis in adults—An updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabetic Medicine. 2022;39(6):e14788.
61. Long J, Atkin L, Gronlund T, Lane T, Nandhra S, Wilton E, et al. Research priorities for venous conditions: results of the UK vascular james lind alliance priority setting process. J Vasc Soc GB Irel. 2022;2(1):26-32.
62. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endotext [Internet]. 2021.
63. Correa R, Arini PD, Correa LS, Valentinuzzi M, Laciar E. Identification of patients with myocardial infarction. Methods of information in medicine. 2016;55(03):242-9.
64. Sinha N, Venkatram S, Diaz-Fuentes G. Starvation ketoacidosis: a cause of severe anion gap metabolic acidosis in pregnancy. Case Reports in Critical Care. 2014;2014(1):906283.
65. Adinortey MB. Biochemicophysiological mechanisms underlying signs and symptoms associated with diabetes mellitus. 2017.
66. Verhulst MJ, Loos BG, Gerdes VE, Teeuw WJ. Evaluating all potential oral complications of diabetes mellitus. Frontiers in endocrinology. 2019;10:56.
67. Elendu C, David JA, Udoyen A-O, Egbunu EO, Ogbuiyi-Chima IC, Unakalamba LO, et al. Comprehensive review of diabetic ketoacidosis: an update. Annals of Medicine and Surgery. 2023;85(6):2802-7.
68. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715-35.
69. Kosmalski M, Różycka-Kosmalska M, Basiak M, Okopień B, Pietras T. Diagnosis and management of hyperglycaemia in patients treated with antipsychotic drugs. Endokrynologia Polska. 2022;73(5):872-84.
70. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018;17(3):341-56.

71. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. Journal of internal medicine. 2021;289(6):754-70.
72. Wickham R. Gastrointestinal Symptoms. Core Curriculum for Oncology Nursing E-Book. 2019:342.
73. Wilson DD, McAllister G, West A. Assessing glycaemic control: self-monitoring of blood glucose. British Journal of Nursing. 2011;20(15):919-25.
74. Napoli A. Insulin therapy and diabetic pregnancy. American journal of therapeutics. 2020;27(1):e91-e105.
75. Bahrami J, Tomlinson G, Murphy HR, Feig DS, Group CC. Impaired awareness of hypoglycaemia in women with type 1 diabetes in pregnancy: Hypoglycaemia fear, glycaemic and pregnancy outcomes. Diabetic Medicine. 2022;39(5):e14789.
76. Diguisto C, Strachan MW, Churchill D, Ayman G, Knight M. A study of diabetic ketoacidosis in the pregnant population in the United Kingdom: investigating the incidence, aetiology, management and outcomes. Diabetic Medicine. 2022;39(4):e14743.
77. Coetzee A, Hall DR, Langenegger EJ, van de Vyver M, Conradie M. Pregnancy and diabetic ketoacidosis: fetal jeopardy and windows of opportunity. Frontiers in Clinical Diabetes and Healthcare. 2023;4:1266017.
78. Petersen T. Effects of slide board training on the lateral movement of college-aged football players 2000.
79. Murphy HR, Howgate C, O'Keefe J, Myers J, Morgan M, Coleman MA, et al. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. The lancet Diabetes & endocrinology. 2021;9(3):153-64.
80. Zhou VL, Shofer FS, Desai NG, Lorincz IS, Mull NK, Adler DH, et al. Predictors of Short Intensive Care Unit Stay for Patients with Diabetic Ketoacidosis Using a Novel Emergency Department–Based Resuscitation and Critical Care Unit. The Journal of Emergency Medicine. 2019;56(2):127-34.
81. Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC medicine. 2020;18:1-16.
82. Ashcheulova T, Kovalyova O, Ivanchenko S. General inspection of the patients. Diagnostic significance of symptoms revealed during patient inspection. 2017.
83. Geneva II, Cuzzo B, Fazili T, Javaid W, editors. Normal body temperature: a systematic review. Open forum infectious diseases; 2019: Oxford University Press US.
84. Matloub F. Journal of Family Medicine and Disease Prevention. 2019.
85. Helmstädter J, Keppeler K, Küster L, Münzel T, Daiber A, Steven S. Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits—The role of the GLP-1 receptor. British journal of pharmacology. 2022;179(4):659-76.
86. Olofsson P. Umbilical cord pH, blood gases, and lactate at birth: normal values, interpretation, and clinical utility. American journal of obstetrics and gynecology. 2023;228(5):S1222-S40.
87. Paavola CD, De Felippis MR, Allen DP, Garg A, Sabatowski JL, Juneja R, et al. Insulin. Pharmaceutical Biotechnology: Fundamentals and Applications: Springer; 2024. p. 427-53.

88. Owens DR. Insulin preparations with prolonged effect. Diabetes technology & therapeutics. 2011;13(S1):S-5-S-14.
89. Kent DJ, McMahill-Walraven CN, Panozzo CA, Pawloski PA, Haynes K, Marshall J, et al. Descriptive analysis of long-and intermediate-acting insulin and key safety outcomes in adults with type 2 diabetes mellitus. Journal of Managed Care & Specialty Pharmacy. 2019;25(11):1162-71.
90. Davis CS, Fleming JW, Malinowski SS, Brown MA, Fleming LW. Ultra-long-acting insulins: a review of efficacy, safety, and implications for practice. Journal of the American Association of Nurse Practitioners. 2018;30(7):373-80.
91. Baker C, Retzik-Stahr C, Singh V, Plomondon R, Anderson V, Rasouli N. Should metformin remain the first-line therapy for treatment of type 2 diabetes? Therapeutic advances in endocrinology and metabolism. 2021;12:2042018820980225.
92. Drogovoz S, Kalko K, Borysiuk I, Barus M, Horoshko V, Svyshch O, et al. Potential risks and pharmacological safety features of hypoglycemic drugs. 2021.
93. Mohajan D, Mohajan HK. Oral hypoglycaemic agents: non-insulin medications for type 2 diabetes patients. Innovation in Science and Technology. 2024;3(1):23-31.
94. Derosa G, Tinelli C, Maffioli P. Effects of pioglitazone and rosiglitazone combined with metformin on body weight in people with diabetes. Diabetes, Obesity and Metabolism. 2009;11(12):1091-9.
95. Ahrén B. DPP-4 inhibition and the path to clinical proof. Frontiers in endocrinology. 2019;10:376.
96. Pinkney J, Fox T, Ranganath L. Selecting GLP-1 agonists in the management of type 2 diabetes: differential pharmacology and therapeutic benefits of liraglutide and exenatide. Therapeutics and Clinical Risk Management. 2010:401-11.
97. Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Current diabetes reports. 2016;16(10):92.
98. Aoki K, Sato H, Terauchi Y. Usefulness of antidiabetic alpha-glucosidase inhibitors: a review on the timing of administration and effects on gut hormones. Endocrine Journal. 2019;66(5):395-401.
99. Wong CY, Martinez J, Dass CR. Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities. Journal of Pharmacy and Pharmacology. 2016;68(9):1093-108.
100. Crabtree NE, Epstein KL. Current concepts in fluid therapy in horses. Frontiers in Veterinary Science. 2021;8:648774.
101. HIRMAN MBM. Development And Evaluation Of A Guideline On Potassium Chloride Intravenous Supplementation: Effectiveness, Safety And Cost Implications 2022.
102. Owens DR, Bolli GB. The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications. Diabetes, Obesity and Metabolism. 2020;22(5):743-54.
103. Bradley MC, Chillarige Y, Lee H, Wu X, Parulekar S, Muthuri S, et al. Severe hypoglycemia risk with long-acting insulin analogs vs neutral protamine Hagedorn insulin. JAMA internal medicine. 2021;181(5):598-607.
104. Rai I, Wanjari A, Acharya S. Recent advances in insulin delivery devices and modes of insulin therapy. 2021.

105. Hurren KM, Dunham MW. Are thiazolidinediones a preferred drug treatment for type 2 diabetes? Expert opinion on pharmacotherapy. 2021;22(2):131-3.
106. Javed Naim M. A Review of Dipeptidyl Peptidase-4 (DPP-4) and its potential synthetic derivatives in the management of Diabetes Mellitus. Journal of Angiotherapy. 2024;8(1).
107. Wan J, Ferrari C, Tadros M. GLP-1RA essentials in gastroenterology: side effect management, precautions for endoscopy and applications for gastrointestinal disease treatment. Gastroenterology Insights. 2024;15(1):191-212.
108. Kabadi UM, Herba J, Exley S. ADVERSE EFFECTS OF SGLT2 INHIBITORS: A SYSTEMIC REVIEW. 2023.
109. Tatovic D, Narendran P, Dayan CM. A perspective on treating type 1 diabetes mellitus before insulin is needed. Nature Reviews Endocrinology. 2023;19(6):361-70.
110. Goncalves E, Bell DS. Combination treatment of SGLT2 inhibitors and GLP-1 receptor agonists: symbiotic effects on metabolism and cardiorenal risk. Diabetes Therapy. 2018;9:919-26.
111. Stubbs BJ, Cox PJ, Evans RD, Santer P, Miller JJ, Faull OK, et al. On the metabolism of exogenous ketones in humans. Frontiers in physiology. 2017;8:300397.
112. Walters W. Secure borders, safe haven, domopolitics. Securitizations of Citizenship: Routledge; 2009. p. 46-70.
113. Campbell NG, Allen E, Montgomery H, Aron J, Canter RR, Dodd M, et al. Maintenance of serum potassium levels≥ 3.6 mEq/L versus≥ 4.5 mEq/L after isolated elective coronary artery bypass grafting and the incidence of new-onset atrial fibrillation: pilot and feasibility study results. Journal of Cardiothoracic and Vascular Anesthesia. 2022;36(3):847-54.
114. Mendez Y, Surani S, Varon J. Diabetic ketoacidosis: treatment in the intensive care unit or general medical/surgical ward? World journal of diabetes. 2017;8(2):40.
115. Abbott KW, Faude B. Choosing low-cost institutions in global governance. International Theory. 2021;13(3):397-426.
116. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. Journal of Diabetes and its Complications. 2003;17(6):307-13.
117. Locke A, Schneiderhan J, Zick SM. Diets for health: goals and guidelines. American family physician. 2018;97(11):721-8.
118. Rewers A, Kuppermann N, Stoner MJ, Garro A, Bennett JE, Quayle KS, et al. Effects of fluid rehydration strategy on correction of acidosis and electrolyte abnormalities in children with diabetic ketoacidosis. Diabetes care. 2021;44(9):2061-8.
119. Aspry KE, Van Horn L, Carson JAS, Wylie-Rosett J, Kushner RF, Lichtenstein AH, et al. Medical nutrition education, training, and competencies to advance guideline-based diet counseling by physicians: a science advisory from the American Heart Association. Circulation. 2018;137(23):e821-e41.
120. Faswita W, Suarni L, Lauviga A. The Effect of Prolanis Exercise on Reducing Blood Sugar Levels. Caring: Indonesian Journal of Nursing Science. 2021;3(2):30-40.
121. Venn B, Mann J. Cereal grains, legumes and diabetes. European journal of clinical nutrition. 2004;58(11):1443-61.

122. Zevenbergen H, De Bree A, Zeelenberg M, Laitinen K, Van Duijn G, Flöter E. Foods with a high fat quality are essential for healthy diets. Annals of nutrition & metabolism. 2009;54:15-24.
123. Tareen RS, Tareen K. Psychosocial aspects of diabetes management: dilemma of diabetes distress. Translational pediatrics. 2017;6(4):383.
124. Bukari M, Abubakari A, Malechi H, Hinneh T, Garti H, Agbozo F. Resource constraints, patient emotions, and therapy: experiences of healthcare providers in the screening and management of gestational diabetes mellitus in northern Ghana. BMC Health Services Research. 2025;25(1):209.
125. Sarbacker GB, Urteaga EM. Adherence to insulin therapy. Diabetes spectrum: a publication of the American Diabetes Association. 2016;29(3):166.
126. Umpierrez G, Korytkowski M. Diabetic emergencies—ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nature Reviews Endocrinology. 2016;12(4):222-32.
127. Shapiro E. EMDR and early psychological intervention following trauma. European Review of Applied Psychology. 2012;62(4):241-51.
128. Akyirem S, Salifu Y, Bayuo J, Duodu PA, Bossman IF, Abboah-Offei M. An integrative review of the use of the concept of reassurance in clinical practice. Nursing Open. 2022;9(3):1515-35.
129. Varahra A, MacDermid JC, Szekeres M, Walton D, Faber KJ. Understanding individuals' perspectives and experiences of recovery following a proximal humerus fracture: an interpretive description. Disability and Rehabilitation. 2023;45(21):3476-83.
130. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. Diabetes. 2011;60(11):2672-82.
131. Hwang TJ, Carpenter D, Lauffenburger JC, Wang B, Franklin JM, Kesselheim AS. Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA internal medicine. 2016;176(12):1826-33.
132. Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. Nature reviews Drug discovery. 2007;6(1):67-74.
133. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. Jama. 2010;303(14):1410-8.
134. Elbarbary N, Moser O, Al Yaarubi S, Alsaffar H, Al Shaikh A, Ajjan RA, et al. Use of continuous glucose monitoring trend arrows in the younger population with type 1 diabetes. Diabetes and Vascular Disease Research. 2021;18(6):14791641211062155.
135. Clarke S, Foster J. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. British journal of biomedical science. 2012;69(2):83-93.
136. Ribet F, Stemme G, Roxhed N. Real-time intradermal continuous glucose monitoring using a minimally invasive microneedle-based system. Biomedical microdevices. 2018;20:1-10.
137. Dias CC, Kamath S, Vidyasagar S. Design of dual hormone blood glucose therapy and comparison with single hormone using MPC algorithm. IET Systems Biology. 2020;14(5):241-51.
138. Mbata AO, Soyege OS, Nwokedi CN, Tomoh BO, Mustapha AY, Balogun OD, et al. Preventative Medicine and Chronic Disease Management: Reducing Healthcare Costs and

Improving Long-Term Public Health. International Journal of Multidisciplinary Research and Growth Evaluation. 2024;5(06):1584-600.
139. Achor EC, Okon II, Jader A, Ewelike SC, Ibrahim M, Lucero-Prisno DE. Achieving sustainable healthcare cost containment in the United States: the role of collaborative efforts among stakeholders. Discover Health Systems. 2025;4(1):1-10.
140. Morton JI, Marquina C, Shaw JE, Liew D, Polkinghorne KR, Ademi Z, et al. Projecting the incidence and costs of major cardiovascular and kidney complications of type 2 diabetes with widespread SGLT2i and GLP-1 RA use: a cost-effectiveness analysis. Diabetologia. 2023;66(4):642-56.
141. Jendle J, Reznik Y. Use of insulin pumps and closed-loop systems among people living with diabetes: A narrative review of clinical and cost-effectiveness to enable access to technology and meet the needs of payers. Diabetes, Obesity and Metabolism. 2023;25:21-32.
142. Ramadaniati HU, Anggriani Y, Lepeska M, Beran D, Ewen M. Availability, price and affordability of insulin, delivery devices and self-monitoring blood glucose devices in Indonesia. Plos one. 2024;19(10):e0309350.
143. Lambrinou E, Hansen TB, Beulens JW. Lifestyle factors, self-management and patient empowerment in diabetes care. European journal of preventive cardiology. 2019;26(2_suppl):55-63.