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Complications of Diabetes Mellitus: From pathogenesis to prevention

Mohammed S Manji[1], Aya lazim Kadhim[1], Rafeef M abdalhussain[1], Baneen H Hashim[1], Aseel A Obeid[1], Mohammed Saleem[2*]

[1] Technician, Babylon University, College of Pharmacy, Babil, Iraq
[2] Department of pharmacology and toxicology, Al-Jameaa Q, Medical College Compus, Babylon, Iraq

Abstract
Diabetes mellitus is a complex metabolic disorder associated with acute and chronic complications that significantly increase morbidity and mortality worldwide. Acute complications, including diabetic ketoacidosis and hyperosmolar hyperglycemic state, arise primarily from insulin deficiency and counterregulatory hormonal imbalances. Chronic complications—such as retinopathy, nephropathy, neuropathy, and macrovascular disease—are driven by prolonged hyperglycemia, oxidative stress, inflammation, and endothelial dysfunction, resulting in progressive organ damage. These complications are further compounded by gastrointestinal manifestations and impaired wound healing, which negatively impact quality of life. Prevention and management strategies emphasize early detection, lifestyle modification, optimal glycemic control, and the use of novel therapeutic agents including SGLT2 inhibitors and GLP-1 receptor agonists, which have demonstrated cardiovascular and renal benefits. Understanding the underlying pathogenesis of diabetic complications is essential for guiding effective prevention and treatment strategies. This review highlights the mechanisms, clinical manifestations, and preventive approaches for diabetes complications, aiming to inform comprehensive patient care and reduce the global burden of the disease.

Keywords: Diabetes Mellitus, diabetic complications, pathogenesis, prevention, microvascular complications, macrovascular complications, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, glycemic control, SGLT2 Inhibitors, GLP-1 Receptor Agonists, lifestyle modification

Introduction

Diabetes mellitus (DM) is primarily characterized by high blood glucose levels (hyperglycemia), polydipsia, and polyphagia. DM is one of the most common metabolic disorders that is increasing at an alarming rate all over the world [1, 2] The number of patients with DM has quadrupled (from 108 million in 1980 to 422 million in 2014) within 34 years only, while the worldwide incidence of diabetes among adults over 18 years of age has risen to 8.5% (2014) from 4.7% (1980) [1]. The WHO estimates that diabetes will be the 7th primary cause of fatality by 2030 [2]. There are mainly four common types of DM. Type 1 DM (T1DM) is caused by the autoimmune annihilation of the pancreatic-β cell with no insulin production [3]. This type is also called insulin-dependent diabetes mellitus (IDDM) [4]. This type of DM is seen in childhood and includes 5–10% of total diabetes patients [1] The major type of diabetes is Type 2 DM (T2DM), which is caused due to insufficient production of insulin or desensitization of insulin receptors that precludes the entry of glucose into the cell [5]. The type is predominantly seen in 90–95% of cases. There is another type of diabetes called gestational diabetes mellitus (GDM) that occurs only during pregnancy. GDM occurs in approximately 5–15% of pregnant women varying in ethnicity and regions [1, 2] Multifarious factors including genetic defects, pancreatic obstruction, surgery, organ transplantation contributes to the onset of this type of diabetes [6]. In the case of 40–60%, women having GDM can develop DM after 5–10 years of pregnancy. Impaired glucose tolerance is potent to be expressed as T2DM whereas uncontrolled diabetes is the potential threat for the onset of other diseases like cardiovascular disease (CVD), blindness, renal failure, neurological disorder, the imbalanced osmolality of blood, hypertension, peripheral neuropathy, and many other diseases [7] Monogenic diabetes, which is often misdiagnosed as T1DM or T2DM is caused by a mutation in a single gene or a cluster of genes [8]. It is an autosomal-dominant disease and patients with this have varying signs, symptoms, and clinical courses.

The aim of this review is to explore the pathogenesis, clinical spectrum, and preventive strategies of diabetes mellitus complications. By addressing the underlying mechanisms that contribute to both acute and chronic complications, and by summarizing current approaches for early detection and prevention, this review seeks to provide a comprehensive understanding that may guide improved patient care and reduce the global burden of diabetes-related morbidity and mortality.

Classification of Complications

1. Acute Complications

1.1 Diabeteic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most common acute hyperglycaemic emergency in people with diabetes mellitus. A diagnosis of DKA is confirmed when all of the three criteria are present — ‘D’, either elevated blood glucose levels or a family history of diabetes mellitus; ‘K’, the presence of high urinary or blood ketoacids; and ‘A’, a high anion gap metabolic acidosis [9]. The biochemical criteria for the diagnosis of DKA are hyperglycemia (blood glucose level >200 mg/dL [>11.1 mmol/L]), venous pH less than 7.3 or serum bicarbonate level less than 15 mEq/L (<15 mmol/L), and ketonemia (blood β-hydroxybutyrate concentration ≥3 mmol/L) or moderate or severe ketonuria. Diabetic ketoacidosis (DKA) continues to have high rates of morbidity and mortality despite advances in the treatment of diabetes mellitus. DKA results from insulin deficiency from new-onset diabetes, insulin noncompliance, prescription or

illicit drug use, and increased insulin need because of infection [10, 11] This insulin deficiency stimulates the elevation of the counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Without the ability to use glucose, the body needs alternative energy sources. Lipase activity increases, causing a breakdown of adipose tissue that yields free fatty acids. These components are converted to acetyl coenzyme A, some of which enter the Krebs cycle for energy production; the remainder are broken down into ketones (acetone, acetoacetate, and β-hydroxybutyrate). Ketones can be used for energy, but accumulate rapidly. Glycogen and proteins are catabolized to form glucose. Together, these factors promote hyperglycemia, which leads to an osmotic diuresis resulting in dehydration, metabolic acidosis, and a hyperosmolar state

1.2 Hyperosmolar Hyperglycemic State

The hyperosmolar hyperglycemic state (HHS) is a syndrome characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of ketoacidosis. The exact incidence of HHS is not known, but it is estimated to account for <1% of hospital admissions in patients with diabetes. Most cases of HHS are seen in elderly patients with type 2 diabetes; however, it has also been reported in children and young adults [12] HHS is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis. These metabolic derangements result from synergistic factors including insulin deficiency and increased levels of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) [12, 13]. Hyperglycemia develops because of an increased gluconeogenesis and accelerated conversion of glycogen to glucose (glycogenolysis) and by inadequate use of glucose by peripheral tissues, primarily muscle. From the quantitative standpoint, increased hepatic glucose production represents the major pathogenic disturbance responsible for hyperglycemia in DKA [14]. As the glucose concentration and osmolality of extracellular fluid increase, an osmolar gradient is created that draws water out of the cells. Glomerular filtration is initially increased, which leads to glucosuria and osmotic diuresis. The initial glucosuria prevents the development of severe hyperglycemia as long as the glomerular filtration rate is normal. However, with continued osmotic diuresis, hypovolemia eventually occurs, which leads to a progressive decline in glomerular filtration rate and worsening hyperglycemia.

2. Chronic Complications

1. Microvascular Complications

1.1 Diabetic Retinopathy

Diabetic retinopathy is characterized by a spectrum of lesions within the retina and is the leading cause of blindness among adults aged 20–74 years [15]. These include changes in vascular permeability, capillary microaneurysms, capillary degeneration, and excessive formation of new blood vessels (neovascularization). The neural retina is also dysfunctional with death of some cells, which alters retinal electrophysiology and results in an inability to discriminate between colors. Clinically, diabetic retinopathy is separated into nonproliferative and proliferative disease stages. In the early stages, hyperglycemia can lead to intramural pericyte death and thickening of the basement membrane, which contribute to changes in the integrity of blood vessels within the retina, altering the blood-retinal barrier and vascular permeability [15]. In this initial stage of nonproliferative diabetic retinopathy (NPDR), most people do not notice any visual impairment. Degeneration or occlusion of retinal capillaries are strongly associated with worsening prognosis [15], which is most likely the result of ischemia followed by subsequent release of angiogenic factors including those related to hypoxia. This progresses the disease into the proliferative phase where neovascularization and accumulation of fluid within the retina, termed macula edema, contribute to visual impairment. In more severe cases, there can be bleeding with associated distorting of the retinal architecture including development of a fibrovascular membrane which can subsequently lead to retinal detachment [15]. Diabetic retinopathy develops over many years, and almost all patients with type 1 diabetes [16] and most having type 2 diabetes [16], exhibit some retinal lesions after 20 years of disease. Furthermore, whereas in type 1 diabetes the major vision threatening retinal disorder appears to be proliferative retinopathy [16], in type 2 diabetes there is a higher incidence of macula edema. Nevertheless, only a minority of such patients will have progression resulting in impaired vision. In addition to maintenance of blood pressure and glycemic control, there are a number of treatments for diabetic retinopathy that have efficacy in reducing vision loss. These three treatments include laser photocoagulation, injection of the steroid triamcinolone, and more recently vascular endothelial growth factor (VEGF) antagonists into the eye, and vitrectomy, to remove the vitreous. However, there is no agreed medical approach to slow disease progression before the use of these rather invasive treatments

1.2 Diabetic Nephropathy

Diabetic nephropathy represents the major cause of end-stage renal failure in Western societies [17]. Clinically, it is characterized by the development of proteinuria with a subsequent decline in glomerular filtration rate, which progresses over a long period of time, often over 10–20 years. If left untreated, the resulting uremia is fatal [18]. Importantly, kidney disease is also a major risk factor for the development of macrovascular complications such as heart attacks and strokes [19]. Hypertension [20] and poor glycemic control frequently precede overt diabetic nephropathy, although a subset of patients develop nephropathy despite good glycemic control [148] and normal blood pressure. Once nephropathy is established, blood pressure is often seen to rise, but paradoxically in the short term, there can be improvements in glycemic control as a result of reduced renal insulin clearance by the kidney [21]. The early diabetic kidney also undergoes significant hypertrophy. This is characterized by enlargement of the kidney via a combination of both hyperplasia and hypertrophy, which is surprisingly often observed at the time of diabetes diagnosis [22]. Hypertrophy is seen within the glomeruli, which is accompanied by mesangial expansion and thickening of the glomerular basement membrane. However, the proximal tubule, which constitutes greater than 90% of the cortical mass in the kidney, accounts for the greatest change in growth in diabetes [23]. As the tubule grows, more of the glomerular (urinary) filtrate is reabsorbed, which increases the glomerular filtration rate (GFR) via a feedback loop from the tubules.

As a consequence of hyperfiltration and the diabetic milieu, the kidney filters increased amounts of glucose, fatty acids, proteins and amino acids, growth factors, and cytokines which are free to trigger a number of pathological pathways such as energetic imbalances, redox abnormalities, fibrosis, and inflammation .Ultimately, the deposition of extracellular matrix in the tubular component of the kidney (tubulointerstitial fibrosis) is postulated to be the major determinant of the progression of renal disease in diabetes [24]. Currently utilized therapies to treat diabetic renal disease largely target systemic blood pressure and/or intraglomerular hypertension. Applied the most widely are interventions which alter the renin-angiotensin system (RAS) which includes angiotensin converting enzyme (ACE) inhibitors [25] and angiotensin II (ANG II) receptor antagonists [25], which are considered first line therapies for diabetic nephropathy. Indeed, this strategy is an important component of most national and international treatment guidelines, along with strict glycemic control. It is important to note that early renal disease is a major risk factor for cardiovascular disease in individuals with diabetes [26]. This suggests that more attention should be paid to the development of nephropathy in the early stages of the disease. However, the role of specific interruption of the RAAS in the prevention and management of early diabetic nephropathy remains controversial, with recent relatively disappointing results in this context [27].

1.3 Diabetic Neuropathy

More than half of all individuals with diabetes eventually develop neuropathy, with a lifetime risk of one or more lower extremity amputations estimated in some populations to be up to 15%. Diabetic neuropathy is a syndrome which encompasses both the somatic and autonomic divisions of the peripheral nervous system. There is, however, a growing appreciation that damage to the spinal cord [28] and the higher central nervous system can also occur and that neuropathy is a major factor in the impaired wound healing, erectile dysfunction, and cardiovascular dysfunction seen in diabetes. Disease progression in neuropathy was traditionally clinically characterized by the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia with subsequent diminishment in oxygen tension and hypoxia. Inhibitors of the renin-angiotensin system and α1-antagonists improve nerve conduction velocities in the clinical context, which is postulated to be a result of increases in neuronal blood flow. Advanced neuropathy due to nerve fiber deterioration in diabetes is characterized by altered sensitivities to vibrations and thermal thresholds, which progress to loss of sensory perception. Hyperalgesia, paresthesia, and allodynia also occur in a proportion of patients, with pain evident in 40–50% of those with diabetic neuropathy. Pain is also seen in some diabetic individuals without clinical evidence of neuropathy (~10–20%), which can seriously impede quality of life [29]. The wide variety of clinical manifestations seen with neuropathy, in addition to impaired wound healing, erectile dysfunction, and cardiovascular disease, can severely impede quality of life. Indeed, autonomic markers can predict which diabetic individuals have the poorest prognosis following myocardial infarction. Consistent with other complications, the duration of diabetes and lack of glycemic control are the major risk factors for neuropathy in both major forms of diabetes [30]. Other than optimization of glycemic control and management of neuropathic pain, there are no major therapies approved in either Europe or the United States for the treatment of diabetic neuropathy. In addition, as is seen with other complications, the mechanisms leading to diabetic neuropathy are poorly understood. At present, treatment generally focuses on alleviation of pain, but the process is generally progressive.

Clinical Manifestation

Gastrointestinal complications of diabetes mellitus are common if diabetes is not treated properly, and generally demand significant medical effort and resources. About 30% of patients with long-standing diabetes mellitus have diabetic autonomic neuropathy, which can affect the enteric nervous system [31]. Patients with diabetes in up to 75% of cases have gastrointestinal symptoms [32] No single risk factor is identified as crucial for the development of diabetic autonomic neuropathy and enteropathy, and the etiology is most likely multifactorial. However, diabetic complications in gastrointestinal tract usually correlate with the duration of diabetes, glycemic control, or with the presence of diabetic autonomic neuropathy, which is often assumed to be the major cause [32]. The whole gastrointestinal tract may be affected, and we can expect motility disorder, abnormal secretion, absorption, and transportation, presented in general with bloating and central abdominal pain as the most frequent complaints [33]. The clinical consequence of colon engagement may be diarrhea, constipation, fecal incontinence, and alternation, or a combination of these symptoms. Considering that these symptoms are ubiquitous in gastrointestinal diseases, diabetic autonomic enteropathy is a generally under- recognized gastrointestinal manifestation of diabetic disease. Ther pathophysiology of diabetic autonomic neuropathy with accompanying sensory-motor disturbances is very complex and has not been completely investigated. It is well known that long-lasting hyperglycemia, which induces nonenzymatic glycation and the formation of advanced glycation end-products (AGE) in diabetic patients, correlates with the presence of diabetic autonomic neuropathy [34]. It is also known that diabetic autonomic neuropathy includes the disorders of the enteric nervous system [34].

Prevention & Management

1. Lifestyle intervention

Lifestyle modification focussing on balanced nutrition, physical activity and smoking cessation is universally recommended for people with diabetes. The Look AHEAD trial examined the effects of an intensive lifestyle intervention – involving dietary caloric restriction and increased physical activity – on cardiovascular mortality, non-fatal MI, non-fatal stroke and hospitalisation for angina in people with T2D. Although the intervention produced greater improvements compared to standard of care in weight, waist circumference, HbA1c, blood pressure and most lipids, these changes did not translate to a significant reduction in cardiovascular outcomes over nearly 10 years of follow-up, and the trial was ceased early on the basis of a futility analysis [35]. Current American Diabetes Association (ADA) guidelines recommend a combination of dietary modification, physical activity and behavioural strategies to achieve and maintain at least 5% weight loss for most people with T2D and overweight or obesity, although

weight loss interventions must always be individualized [36]. At least 150 min per week of moderate-intensity aerobic activity, spread over at least 3 days of the week, is recommended for most adults with T2D [37].

2. Glycaemic Control

Glycaemic targets should always be individualized, but a target HbA1c of less than 7.0% (53 mmol/mol) is appropriate for most patients with diabetes if it can be safely achieved without excessive risk of hypoglycaemia [38]. For people using continuous glucose monitoring, general targets include >70% of the time in range (3.9–10.0 mmol/L), <4% of the time below range and <25% of the time above range; tighter targets are used in pregnancy and looser targets may be appropriate for those at high risk of hypoglycaemia

3. SGLT2 Inhibitors

The introduction of sodium-glucose transport protein 2 (SGLT2) inhibitors into clinical use has resulted in a major paradigm shift in cardiovascular risk reduction in T2D.The EMPA-REG OUTCOME trial, which enrolled participants with T2D and high baseline cardiovascular risk, demonstrated significant reduction in a composite primary outcome of cardiovascular death, MI, stroke and hospitalization for angina, in participants randomized to receive empagliflozin. This composite effect was driven mainly by benefits on cardiovascular and all-cause mortality [39]. A 2022 meta-analysis of 13 trials found that SGLT2 inhibitors reduced the relative risk of cardiovascular death by 14% in people with diabetes [40]. A clear benefit has also been shown in preventing hospitalization for heart failure, in people with either reduced or preserved ejection fraction, regardless of diabetes status, with a relative risk reduction of 23% in a meta-analysis of major trials using empagliflozin and dapagliflozin [41].

4. GLP-1 Agonists

Glucagon-like peptide-1 (GLP-1) agonists, such as SGLT2 inhibitors, have shown significant benefits in both glycaemic control and cardiovascular risk in people with T2D A meta-analysis of eight trials demonstrated a 14% reduction in major cardiovascular events with GLP-1 agonist treatment [42]. Similar to SGLT2 inhibitors, post hoc analyses of cardiovascular outcome trials using GLP-1 agonists have suggested renal benefits, although trials focussing on renal primary outcomes are yet to be reported. In a secondary analysis of the REWIND RCT comparing dulaglutide with placebo, for example, a 15% risk reduction was seen in a composite renal outcome [43].

Conclusion

Diabetes mellitus is associated with a wide spectrum of acute and chronic complications, with macrovascular and microvascular complications being the main contributors to morbidity and mortality. The development of these complications is closely linked to chronic hyperglycemia, oxidative stress, inflammation, and endothelial dysfunction. Understanding the pathogenesis of these complications provides insight into why early detection and strict metabolic control are crucial. Effective prevention strategies, including lifestyle modifications, glycemic control, management of blood pressure and lipids, and regular screening, can significantly reduce the risk of complications and improve patient outcomes. Continuous research and awareness are essential to mitigate the global burden of diabetes-related complications.

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