CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Review Article*

DIABETES COMPLICATIONS AND HOW TO CONTROL IT: ARTICLE REVIEW

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Abstract:

Diabetes complications result from prolonged high blood sugar damaging organs. Common complications include cardiovascular disease, neuropathy, retinopathy, nephropathy, foot problems, skin conditions, and gum disease. Control strategies involve blood sugar management, medication adherence, diet, exercise, cardiovascular health, foot care, eye care, kidney health, skin and gum care, and education/support for effective management. This review will discuss the most common complications of diabetic cases and how to avoid and control them.

Keywords: *Diabetes – Complication – Control.*

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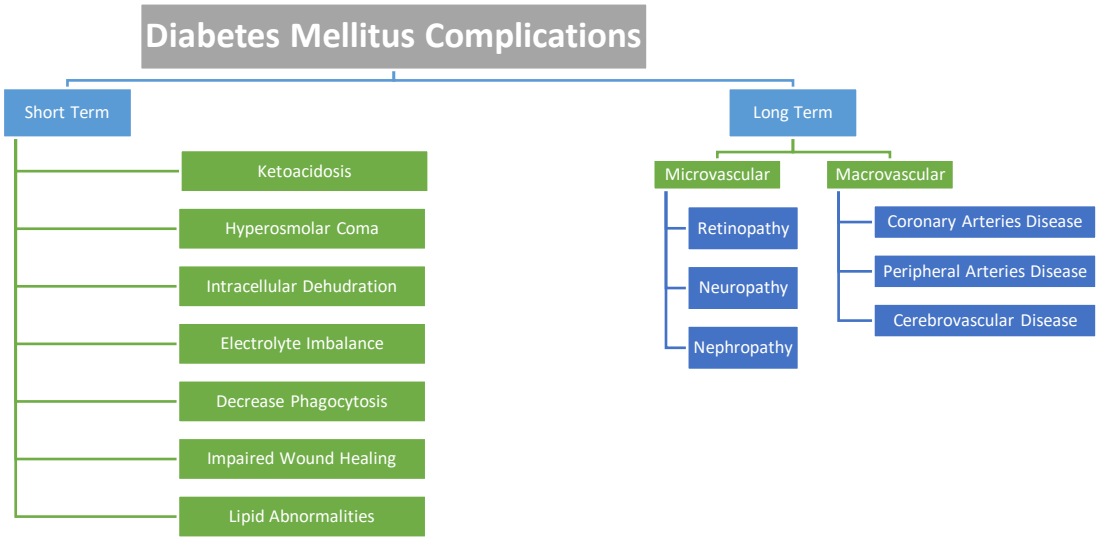
Please cite this article in press as Tharwat Abdullah Ahmed Almanasef et al, ***Diabetes Complications and How to Control It: Article Review.,*** *Indo Am. J. P. Sci, 2017; 4(10).*

INTRODUCTION:

The complications in diabetes arise from a combination of factors primarily linked to chronic hyperglycemia and insulin resistance, which lead to a cascade of metabolic disturbances affecting various organ systems. Uncontrolled diabetes mellitus (DM) has profound long-term effects on various organ systems, leading to a multitude of chronic complications. The onset of subclinical DM can precede clinical manifestations by approximately 10 years, during which time chronic complications may develop unnoticed.(1) One of the primary mechanisms driving these complications is persistent hyperglycemia, which stimulates the production of reactive oxygen species (ROS) in mitochondria, leading to oxidative stress and mitochondrial DNA mutations. This hyperglycemic memory perpetuates a cycle of ROS-induced damage, contributing to the pathogenesis of diabetic complications through the interaction of advanced glycation end products (AGEs) with their receptor (RAGE).(2) The complications of uncontrolled diabetes can be categorized into short-term and long-term effects. Short-term effects include ketoacidosis, hyperosmolar coma, intracellular dehydration, electrolyte imbalance, decreased phagocytosis, impaired wound healing, and lipid abnormalities. Long-term effects are more severe and include nephropathy, neuropathy, retinopathy, cataract formation, increased perinatal mortality, and vascular disease complications. (3)

Figure (1): Diabetes Mellitus Complications



Short Term Complication of Diabetes:

- Ketoacidosis:

is a serious metabolic condition characterized by the accumulation of ketones in the blood, leading to acidosis. It primarily manifests in two forms: diabetic ketoacidosis (DKA) and alcoholic ketoacidosis (AKA). It results from severe insulin deficiency, leading to hyperglycemia, dehydration, and electrolyte imbalances. Common symptoms include polyuria, polydipsia, weight loss, fatigue, dyspnea, vomiting, and abdominal pain. DKA is often the first presentation of T1DM in children and adolescents, with a significant percentage of cases occurring without prior diabetes diagnosis but can also occur in type 2 diabetes under stressful conditions such as infections or surgery. (4, 5) The condition requires prompt recognition and treatment, typically involving intravenous fluids, insulin, and close monitoring of glucose and electrolyte levels to prevent complications such as cerebral edema, which, although rare, is particularly devastating in pediatric cases. Treatment involves aggressive fluid resuscitation, electrolyte replacement, glucose, and thiamine administration, with a generally good short-term prognosis if managed appropriately. (6, 7) Education on diabetes management, including insulin adjustment during illness and regular monitoring of glucose and ketone levels, is essential to prevent DKA recurrence.

- Hyperosmolar Coma:

Hyperosmolar coma, also known as hyperosmolar hyperglycemic state (HHS), is a severe and life-threatening complication predominantly seen in patients with type 2 diabetes mellitus. It is

characterized by extreme hyperglycemia (plasma glucose level >600 mg/dL), significant hyperosmolality (>320 mOsm/kg), and the absence of ketoacidosis. The condition is rare, accounting for less than 1% of hospital admissions for diabetic emergencies, but it carries a high mortality rate of 10-20%, which is significantly higher than that of diabetic ketoacidosis (DKA). (8) Various factors, including infections, cardiovascular events, and inadequate insulin therapy can precipitate HHS. Sometimes, it can be triggered by less common conditions such as multisystem Langerhans cell histiocytosis (LCH), which can lead to severe hyperosmolar states due to hypothalamic involvement and subsequent diabetes insipidus (DI). (9) Similarly, central diabetes insipidus (CDI) caused by metastatic malignancies, such as breast, lung, or colorectal cancer, can also lead to hyperosmolar hyperglycemic nonketotic coma (HONKC) due to polyuric dehydration. (10) Additionally, hyperosmolar states can be induced by chemoradiotherapy in cancer patients, highlighting the need for vigilance in this population. (11) The clinical presentation of HHS includes severe dehydration, altered mental status, and neurological deficits, which can sometimes manifest as hemiballismus-hemichorea, a rare movement disorder associated with metabolic derangements. Treatment primarily involves aggressive fluid replacement, careful correction of hyperglycemia with low-dose insulin, and monitoring for potential complications. (12)

- Intracellular Dehydration:

Intracellular dehydration is a significant concern in diabetes, particularly because it impacts cellular function and overall metabolic control. This intracellular dehydration is not only a result of hyperglycemia-induced osmotic diuresis but also due to the failure of diabetic individuals to adequately increase their fluid intake to compensate for the losses. (13) The physiological state of hypovolemia, often seen in diabetes, triggers the release of renin and subsequent production of angiotensin II, which is associated with insulin resistance and fat accumulation, further complicating the metabolic landscape. (14) Insulin plays a crucial role in cell hydration by promoting the accumulation of potassium and sodium within cells, thus inducing cell swelling and stimulating anabolic processes such as glycogen and protein synthesis. However, in diabetic states, cellular dehydration impairs insulin signaling, leading to insulin resistance and a catabolic state that sensitizes cells to apoptotic stimuli. (15) This is further exacerbated by the redistribution of intracellular ions like potassium and magnesium during hyperosmolar conditions, which disrupts cellular homeostasis and metabolic control. (16) In cases of severe diabetic ketoacidosis, rehydration therapy has been shown to significantly reduce blood glucose levels and improve tissue glucose utilization even before the administration of insulin, indicating that proper hydration can enhance metabolic control and reduce the concentration of counter-regulatory hormones like cortisol and adrenaline. Additionally, alterations in water compartments, such as increased intracellular water in poorly controlled insulin-dependent diabetes mellitus (IDDM) patients, suggest that water distribution is closely tied to metabolic control and the severity of diabetes. The regulation of aldosterone and renin in response to hydration status further underscores the complex interplay between fluid balance and metabolic regulation in diabetes. Changes in intracellular water content can also affect subcellular organelles, such as mitochondria, where dehydration reduces oxygen utilization and impairs energy metabolism, leading to further metabolic disturbances. (13, 17)

- Electrolyte Imbalance.

Electrolyte imbalances are a common and significant complication in patients with diabetes mellitus (DM) due to hyperglycemia, which increases plasma osmolality and impairs renal function. This leads to altered electrolyte levels, which affect patients' overall health and management of the disease. Electrolyte disturbances are particularly pronounced in decompensated diabetics, such as those with diabetic ketoacidosis or hyperosmolar syndrome, where potassium, magnesium, and phosphate depletion are common. Hyperglycemia, a hallmark of diabetes, significantly impacts the balance of electrolytes such as sodium (Na^+), potassium (K^+), chloride (Cl^-), calcium (Ca^{2+}), and magnesium (Mg^{2+}) in the body. For instance, hyperglycemia can cause hyponatremia and hyperkalemia, which are linked to short-term metabolic control issues in diabetes mellitus (19). Diabetic patients, especially those with decompensated diabetes, often experience a depletion of potassium, magnesium, and phosphate, which can exacerbate conditions like diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. Chronic hyperkalemia in diabetics is frequently due to hyporeninemic hypoaldosteronism, impaired renal function, and insulin deficiency (18). Studies have shown that diabetic patients exhibit significant increases in glucose, total cholesterol, triglycerides, chloride, and calcium levels, while sodium and

potassium levels tend to decrease, indicating that these imbalances can serve as diagnostic tools and influence the risk of other diseases (20). In low-income countries like Benin, a significant proportion of diabetic patients suffer from hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hyponatremia, with elevated serum potassium levels being particularly notable (21). Furthermore, in cases of diabetic ketoacidosis, patients often present with lower sodium and higher potassium levels compared to individuals with controlled diabetes, highlighting the dependency of electrolyte distribution on plasma glucose levels (22). These imbalances can lead to severe complications, including cardiovascular issues, neuromuscular dysfunction, and increased morbidity and mortality, underscoring the importance of monitoring and managing electrolyte levels in diabetic patients to prevent these deleterious effects.

Decreased Phagocytosis

Impaired phagocytosis in diabetic patients, is a well-documented phenomenon that contributes to their increased susceptibility to infections and complications. Research indicates that monocytes from T2D patients exhibit reduced phagocytic activity, which is not due to decreased expression of phagocytic receptors but rather a functional defect in the phagocytic pathways involving complement and Fc-gamma receptors (FcγRs). (23) This impairment is significantly associated with chronic hyperglycemia, suggesting that poor glycemic control exacerbates the defect. Further studies have shown that peripheral blood mononuclear cells (PBMCs) from T2D patients have a lower percentage of activated macrophages compared to non-diabetic individuals, with phagocytic activity negatively correlated with fasting glucose and HbA1c levels. Importantly, improving blood glucose levels can enhance phagocytic activity, highlighting the potential benefits of metabolic optimization in these patients. (24) Additionally, diabetic wounds suffer from dysfunctional macrophage efferocytosis, leading to an increased burden of apoptotic cells and prolonged inflammation, which complicates wound healing. (25) This chronic inflammation is further compounded by abnormalities in neutrophil-mediated events and a compromised proresolution system involving lipid agonists like lipoxins and resolvins. Specifically, the proresolving lipid mediator resolvin E1 (RvE1) has been shown to rescue impaired neutrophil phagocytosis in genetically engineered diabetic mice overexpressing the RvE1 receptor, although it has no effect in standard diabetic models. (26) Collectively, these findings underscore the multifaceted nature of phagocytic impairment in diabetes, driven by hyperglycemia, chronic inflammation, and disrupted resolution pathways, and suggest that targeted therapeutic strategies to enhance phagocytic function and resolve inflammation could be beneficial for diabetic patients.

Impaired Wound Healing

Impaired wound healing in diabetic patients is multifaceted and influenced by various physiological and molecular dysfunctions. Diabetes mellitus, affecting millions globally, leads to chronic wounds that are a major cause of hospital admissions and nontraumatic lower extremity amputations due to poor patient compliance and the progressive nature of the disease [2]. The diminished capacity for wound healing in diabetics is attributed to the negative impact of diabetes on signaling molecules, cellular cascades, immune system components, and vascular function, which collectively contribute to ulceration, recurrent infections, and increased healthcare costs [3]. Specifically, diabetic foot ulcers (DFUs) are a significant clinical concern, often resulting in prolonged treatment and high amputation rates. Despite advancements in understanding the pathophysiology of DFUs and the development of bioactive compounds and tissue engineering approaches, current treatments still face limitations from a pharmaceutical perspective [4]. A critical aspect of impaired wound healing in diabetes is the reduced mobilization and recruitment of endothelial progenitor cells (EPCs) from the bone marrow, which are essential for neovascularization and tissue repair. Studies using MMP9 knockout mouse models have shown that diabetes exacerbates inflammation and impairs wound neovascularization, although these impairments can be mitigated by stem cell factor (SCF) administration, which enhances EPC mobilization and neovascularization [5]. Additionally, dysregulation of microRNAs in diabetic patients affects inflammation, extracellular matrix composition, and angiogenesis, further hindering wound healing. Correcting these microRNA imbalances has been shown to expedite wound healing and reverse the diabetic skin phenotype. (27-29)

Lipid Abnormalities

Lipid abnormalities, commonly referred to as dyslipidemia, are prevalent in individuals with diabetes, particularly type 2 diabetes mellitus (T2DM), and significantly contribute to the increased cardiovascular risk observed in these patients. Studies indicate that approximately 83% of diabetic patients exhibit lipid abnormalities, with elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), alongside reduced high-density lipoprotein cholesterol (HDL-C) levels. Specifically, hypertriglyceridemia and hypercholesterolemia are common, with 44% and 28% of diabetic patients affected, respectively. (30) The dyslipidemia in T2DM is characterized by increased TG and decreased HDL-C levels, along with qualitative changes such as increased small, dense LDL particles and glycation of apolipoproteins, which enhance the atherogenic potential of the lipid profile. (31)

Long-Term Complications of Diabetes:

Nephropathy:

Diabetic nephropathy is a significant complication of diabetes mellitus. is the leading cause of end-stage renal disease (ESRD) in many countries, including the United States. (22, 32) DN is clinically characterized by persistent proteinuria, typically more than 0.5 grams over 24 hours, along with retinopathy, hypertension, and a declining glomerular filtration rate (GFR) in the absence of other renal diseases. The condition is marked by a progressive decrease in GFR and is a major determinant of ESRD, with a significant number of patients reaching end-stage renal failure within ten years from the first evidence of proteinuria. (33, 34). Early detection and management are crucial, with routine screening for urinary albumin excretion and GFR being essential for diagnosis and monitoring.

- Neuropathy:

Diabetic neuropathy is a prevalent complication of both type I and type II diabetes mellitus, affecting nearly 50% of diabetic patients and significantly contributing to diabetes-related morbidity and mortality. It encompasses a broad spectrum of clinical manifestations, primarily categorized into distal symmetrical polyneuropathy and focal or multifocal neuropathies. (35-37) The pathogenesis of diabetic neuropathy is multifactorial, involving oxidative stress, endothelial dysfunction, and chronic inflammation, which collectively cause direct axonal damage and nerve ischemia. Hyperglycemia, lipid metabolism disorders, and insulin signaling abnormalities are key initiating factors, disrupting the normal structure and function of the peripheral nervous system, including myelinated and unmyelinated nerve axons, perikaryon, neurovascular, and glial cells. Clinically, diabetic neuropathy is diagnosed through patient history and symptom exploration, with various diagnostic tests and biomarkers available to assess nerve damage severity. The condition significantly impacts quality of life, contributing to postural instability, reduced functionality, and higher prevalence of depressive symptoms among affected individuals

- Ophthalmic Complications:

ophthalmic complications are among the most common and severe, affecting both type 1 and type 2 diabetes patients. Diabetic retinopathy and maculopathy are major microvascular complications that can lead to irreversible vision damage and blindness, with a prevalence of 9-16% in type 2 diabetes and 24-27% in type 1 diabetes. Regular ophthalmological examinations are crucial for early detection and treatment, with intervals based on individual risk profiles, ranging from every two years for low-risk patients to more frequent checks for those with higher risk. (38) Another significant complication is diabetic cataracts, characterized by cortical or posterior subcapsular opacities, which account for 33% of all visual impairments in diabetics. The intracellular accumulation of sorbitol due to aldose reductase activity leads to osmotic stress and lens opacities, with ongoing research into aldose reductase inhibitors and antioxidants as potential treatments. (39) Additionally, oculomotor palsy, particularly involving the VIth nerve, is a frequent neuro-ophthalmologic complication, often associated with long-standing, poorly controlled diabetes and other risk factors like hypertension and coronary artery disease. Treatment focuses on glucose management and symptomatic relief of diplopia. (40) Systemic control of blood glucose can slow the progression of these complications but often cannot halt them entirely once clinical symptoms appear. Advances in biodegradable polymers and implantable ocular devices offer promising localized treatments that can slowly release medication to potentially stop or even reverse diabetic ocular complications. (41)

- Vascular Disease Complications:

Vascular complications, including disease of coronary arteries, peripheral arteries, and cerebrovascular are more frequent in diabetic individuals due to hyperglycemia and insulin resistance, which lead to

increased reactive oxygen species and a prothrombotic state that accelerates atherosclerosis. The global rise in diabetes prevalence, driven by lifestyle and dietary changes, exacerbates these risks, necessitating comprehensive risk factor modification and antiplatelet therapy to manage cardiovascular outcomes. (42)

How To Control Short-Term and Long-Term Complications in Diabetic:

Controlling both short-term and long-term complications in diabetes involves a multifaceted approach that includes tight glycemic control, blood pressure management, and addressing other cardiovascular risk factors. Short-term control primarily focuses on reducing hyperglycemia to prevent immediate complications such as hypoglycemia and acute metabolic disturbances. Intensive treatment has been shown to reduce the incidence of microvascular complications in the short term and both microvascular and macrovascular complications in the long term, as evidenced by studies like the UKPDS and DCCT. However, the ACCORD study highlighted that overly aggressive treatment could increase mortality, emphasizing the need for a balanced approach that avoids hypoglycemic incidents. (43) Long-term management aims to prevent chronic complications such as retinopathy, nephropathy, neuropathy, myocardial infarction, and stroke. Effective strategies include maintaining near-normal HbA1c levels, as each 1% reduction in glycosylated hemoglobin can significantly lower the risk of microvascular complications by 22% to 35%. Blood pressure control is equally vital, with the use of ACE inhibitors and angiotensin receptor blockers being particularly effective in slowing the progression of renal disease and reducing the incidence of blindness, dialysis, and amputations. Additionally, the use of statins and antiplatelet agents can help in the primary and secondary prevention of macrovascular diseases by lowering LDL cholesterol and reducing inflammation. (44)

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