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Microvascular and Macrovascular Complications of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a rapidly growing global health issue, with over 537 million adults affected and projections indicating an increase to over 643 million by 2030. This paper explores the multifaceted impact of T2DM, focusing on the progression to microvascular and macrovascular complications, including retinopathy, neuropathy, nephropathy, coronary artery disease, cerebrovascular disease, and peripheral artery disease. These complications arise from atherosclerosis which can be caused by chronic hyperglycemia and insulin resistance, which leads to extensive damage to blood vessels and nerves. Preventive strategies and early intervention are crucial for managing T2DM and mitigating its associated risks. This paper discusses the importance of lifestyle modifications as foundational elements in controlling blood glucose levels and preventing complications. It also reviews current pharmacological treatments, including metformin, SGLT2 inhibitors, and GLP-1 receptor agonists, as well as emerging therapies targeting AMP-activated protein kinase (AMPK) to enhance insulin sensitivity and metabolic control. Early detection through regular screenings and diagnostics, alongside a comprehensive management plan, is vital for slowing disease progression and improving patient outcomes. The integration of preventive measures, innovative treatments, and vigilant monitoring offers a promising pathway to reduce the burden of T2DM and enhance the quality of life for affected individuals.

Introduction

Every year, the world has seen a growing prevalence of Type 2 diabetes mellitus (T2DM). According to the International Diabetes Federation, there are more than 537 million adults with diabetes in the world today. According to current predictions, this number is expected to exceed 643 million people worldwide by 2030. In addition, for every patient diagnosed with T2DM, there is one person with an undiagnosed disease. Therefore, the real number of patients with T2DM is much higher and the issue of T2DM is more significant in our world now more than ever (Nedosugova et al., 2022). This paper will review the cardiovascular complications of diabetes while discussing current pharmacological treatments as well as emerging therapies.

Common risk factors for T2DM such as a family history of the disease, obesity, and an increased age can make someone more susceptible to developing cells that are insulin resistant. Insulin is a hormone released by the pancreas that stimulates glucose uptake in cells. Beta cells of the pancreas are stimulated by an increase in glucose levels in the blood to secrete insulin. If the receptors of a cell cannot recognize insulin, then glucose will not be able to enter the cell - it will remain in the bloodstream. As more and more glucose remains in the bloodstream, the pancreas continues to pump out insulin to compensate for the increased glucose levels, but the glucose levels remain increased because of the insulin resistance of the cells. Constant secretion of insulin by the pancreas causes beta-cell failure from the pancreas overworking itself. Once the beta cells fail, the body can no longer produce its own insulin - the body is insulin deficient and hyperglycemic. Hyperglycemia, high levels of sugar in the bloodstream, can lead to many issues with or within the blood vessels which can lead to a multitude of complications (Hasudungan, 2016).

Mortality from diabetes in 2021 exceeded 6.7 million people, which is more than the total mortality from AIDS, tuberculosis, and malaria (Nedosugova et al., 2022). The main cause of death in patients with T2DM are cardiovascular complications resulting from the progression of atherosclerosis. Atherosclerosis is classified by the buildup of plaque in blood vessels. The blood vessels consist of four layers: the lumen (where the blood flows; contains red blood cells, glucose, plasma, etc.), endothelium, tunica intima, and the tunica media.

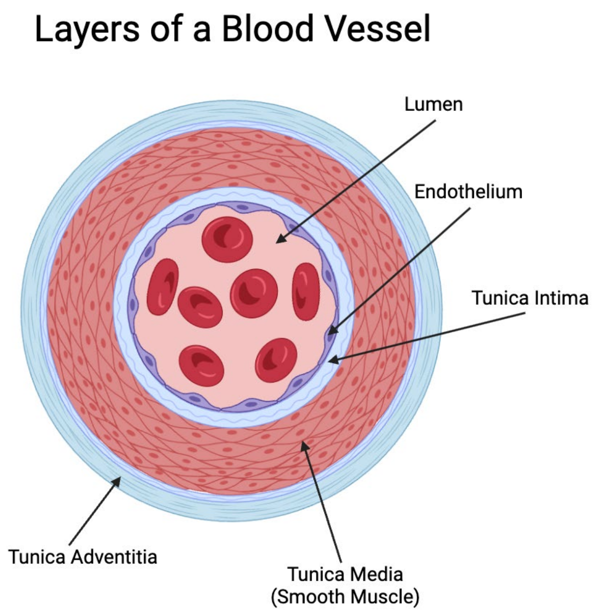

Figure 1. Layers of a Blood Vessel. Created using BioRender.

The endothelial cells do not require insulin to uptake glucose, so as the levels of glucose in the bloodstream increase, the levels of glucose in the endothelial cells increase as well. As the glucose metabolizes in the mitochondria of the endothelial cells, the byproduct radioactive oxygen species (ROS) is produced. Increased levels of ROS cause increased levels of protein kinase activity, which can then result in increased levels of the nuclear factor kappa B. The nuclear factor kappa B is an inflammatory transcription factor; it increases the expression of inflammatory cell receptors and increases vascular permeability. An increased vascular permeability can cause the monocytes of the inflammatory cell receptors and LDL cholesterol to enter the tunica intima. As the monocytes enter the cell tissue, they transform into macrophages. The macrophages will then start to consume the LDL cholesterol, forming a foam cell or a cell filled with lipids. The foam cells release a growth factor which causes the smooth muscle of tunica media to migrate inward and tighten the opening of the vessel. In addition, the foam cells join together in clusters, and then rupture, releasing the lipids and growth factors into the lumen. The buildup of such debris within a blood vessel can lead to plaque formation. Large buildup of plaque from atherosclerosis can lead to atherothrombosis, or the formation of blockages that restrict the flow of blood. Such blockages in blood vessels can lead to Microvascular and Macrovascular complications (Hasudungan, 2016).

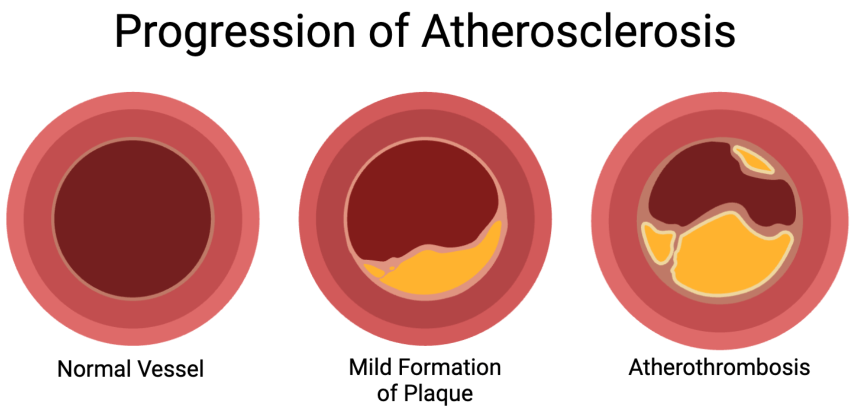

Figure 2. Progression of Atherosclerosis. Created using BioRender.

Microvascular Complications

There are three types of blood vessels in the human body: arteries, capillaries, and veins. Microvascular refers to the smallest blood vessels in the human body — the capillaries. Capillaries are thin and delicate vessels that directly transport blood to the body's cells and organs. Because of their fragile composure, they are often the first to be affected by atherosclerosis. The three main microvascular complications are retinopathy, nephropathy, and neuropathy.

Retinopathy

Retinopathy is a complication that relates to our eyes. There are capillaries around our eye that supply blood to our retina. Hyperglycemia can cause them to easily become clogged with plaque, leading to structural changes that can impair vision over time. In its initial stage, non-proliferative diabetic retinopathy (NPDR), small blood vessels in the retina can weaken and leak fluid or blood into the retina, causing swelling and the formation of deposits called exudates. At this stage, patients may not experience noticeable symptoms, emphasizing the importance of regular eye examinations for early detection.

Retinopathy can then advance to proliferative diabetic retinopathy (PDR), where more severe complications arise. New, fragile blood vessels begin to grow on the retina's surface and into the vitreous gel that fills the eye. These abnormal vessels are prone to bleeding, leading to the formation of scar tissue that can distort or detach the retina, severely impairing vision. Symptoms of advanced diabetic retinopathy include blurred vision, floaters, dark spots, and eventually complete vision loss if left untreated (Fowler, 2008).

Treatment strategies for diabetic retinopathy focus on slowing or halting its progression and preserving vision. Tight control of blood sugar levels through diet, exercise, and medication is crucial in managing the disease. Blood pressure and cholesterol levels must also be monitored and controlled, as hypertension and dyslipidemia can increase retinal damage. In early stages, careful monitoring by an eye care specialist can guide interventions such as laser therapy (photocoagulation) to seal leaking blood vessels and reduce swelling, or injections of anti-VEGF medications into the eye to inhibit the growth of abnormal blood vessels. In cases where retinal detachment or extensive bleeding occurs, surgical procedures like vitrectomy may be necessary to restore vision and prevent further damage (Wang & Lo, 2018).

Regular and comprehensive eye examinations are pivotal for detecting diabetic retinopathy early when treatment options are most effective. In many cases, diabetic retinopathy may present itself before a patient is diagnosed with diabetes. Therefore, early intervention not only improves the chances of preserving vision, but can also detect early stages of diabetes as well as reduce the risk of irreversible vision loss associated with advanced stages of the disease.

Neuropathy

Neuropathy is a common complication of T2DM, affecting more than 50% of individuals with the condition. There are many types of neuropathy, the most common type being Distal Symmetric Polyneuropathy (DSP). DSP primarily impacts the extremities, such as the arms and lower limbs, and is characterized by sensory loss, pain, numbness, and tingling in these areas. DSP often begins in the distal legs and can lead to issues like loss of balance, frequent falls, foot trauma, infections, and in severe cases, amputation (Feldman et al., 2019).

Other types of neuropathy associated with diabetes include autonomic neuropathy, which can affect various bodily systems such as the cardiovascular system (cardiac autonomic neuropathy), gastrointestinal tract (gastroparesis), and the urogenital system (diabetic cystopathy and sexual dysfunction).

Early diagnosis and screening are critical for managing diabetic neuropathy and preventing its progression. Diagnostic tools like the Toronto Clinical Neuropathy Score and the Michigan Diabetic Neuropathy Score assess the severity of neuropathy. Nerve conduction studies (NCS) measure motor and sensory nerve function, while skin biopsies can assess intraepidermal nerve fiber density (IENFD) for detecting small-fiber neuropathy. Additional diagnostic methods may include quantitative sensory tests, laser Doppler flare imaging, and corneal confocal microscopy (Feldman et al., 2019).

Management of diabetic neuropathy involves a multifaceted approach. Pain management is a key component with a focus on non-opioid medications such as anticonvulsants (gabapentin, pregabalin), serotonin and norepinephrine reuptake inhibitors (duloxetine), and tricyclic antidepressants (amitriptyline). For autonomic neuropathy, treatment varies based on the specific subtype and may include strategies such as volume repletion, physical activity, and low-dose fludrocortisone for cardiac autonomic neuropathy. Prevention strategies are centered around optimizing glucose control, addressing metabolic risk factors, and incorporating lifestyle interventions like regular exercise.

Several risk factors contribute to the development of diabetic neuropathy. These include the duration of diabetes and higher HbA1c levels, which are linked to an increased risk of neuropathy. Metabolic factors such as insulin resistance, hypertension, and obesity are commonly associated with neuropathy. Components of metabolic syndrome, including hypertriglyceridemia, hypertension, abdominal obesity, and low HDL levels, also play a role in its development.

Diabetic neuropathy primarily involves the damage of sensory and autonomic axons, which are the delicate fibers that connect neurons and allow them to communicate. Schwann cell dysfunction and mitochondrial dysfunction contribute to axonal damage. Additionally, hyperglycemia and hyperlipidemia play significant roles in nerve injury through altered glucose metabolism and lipid effects.

Nephropathy

Diabetic nephropathy is a critical complication that frequently affects individuals with type 2 diabetes mellitus (T2DM). This condition is caused by prolonged high blood glucose levels that damage the kidneys' intricate network of tiny blood vessels, glomeruli. The glomeruli are essential for filtering waste products and excess fluids from the blood. As these blood vessels become damaged, the kidneys' ability to perform this crucial function diminishes, leading to a gradual decline in kidney function and a high probability of progressing to end-stage renal disease (Qi et al., 2017).

In the early stages, diabetic nephropathy may be asymptomatic or present only subtle signs. One of the first indicators is the presence of microalbuminuria—an abnormal amount of albumin (a type of protein) in the urine (Fowler, 2008). As the condition advances, proteinuria becomes more pronounced, and clinical symptoms may begin to emerge. Patients may experience edema (swelling) in the extremities, particularly in the legs, ankles, and feet, due to fluid retention. Persistent high blood pressure often accompanies nephropathy and can further exacerbate kidney damage. Other symptoms include fatigue, reduced appetite, and difficulties with concentration, which arise as kidney function continues to decline.

Diagnosing diabetic nephropathy involves several key tests. Blood tests measure markers of kidney function such as serum creatinine and blood urea nitrogen (BUN). Elevated levels of these markers can indicate reduced kidney function. Urinalysis is crucial for detecting proteinuria, and more specific tests, like the urine albumin-to-creatinine ratio, help assess the degree of protein loss. Imaging studies, such as ultrasound or CT scans, can visualize structural changes in the kidneys, while a kidney biopsy may be performed in some cases to evaluate the extent of damage at a cellular level (Samsu, 2021).

Effective management of diabetic nephropathy in T2DM requires a comprehensive approach aimed at controlling blood glucose levels and managing blood pressure. Blood glucose control is typically achieved through a combination of oral hypoglycemic agents and insulin therapy, tailored to the individual's needs. A diet low in sodium can also help manage hypertension and fluid retention, while restricting dietary protein can reduce the workload on the kidneys. The use of medications such as ACE inhibitors or ARBs is fundamental (Fowler, 2008). These drugs not only lower blood pressure but also provide additional renal protection by reducing proteinuria and preventing further damage to kidney blood vessels. Diuretics may be used to manage fluid buildup and reduce swelling. Engaging in regular physical activity is crucial for reducing cardiovascular risk and supporting overall kidney health. Maintaining a healthy weight and managing stress are also important.

In cases where diabetic nephropathy progresses to end-stage renal disease, more intensive treatments become necessary. Dialysis, which can be either hemodialysis or peritoneal dialysis, is used to perform the blood-filtering functions that the kidneys can no longer carry out. Hemodialysis involves filtering the blood through an external machine, while peritoneal dialysis uses the patient's abdominal cavity as a filter. Kidney transplantation may offer a more permanent solution by replacing the damaged kidney with a healthy donor organ, though this requires lifelong immunosuppressive medication to prevent organ rejection (Qi et al., 2017).

Preventing diabetic nephropathy involves rigorous glycemic control and regular monitoring of kidney function. Early detection and prompt management are key to slowing the progression of the disease. It is crucial that patients with T2DM should have regular check-ups with their healthcare providers to monitor blood glucose levels, blood pressure, and kidney function. By adhering to a comprehensive management plan, individuals with T2DM can significantly improve their quality of life and reduce the risk of severe kidney damage.

Macrovascular Complications

Macrovascular complications involve the larger blood vessels in the body, the arteries and veins, which are crucial for delivering blood to vital organs and tissues. These complications stem from atherosclerosis, where plaque buildup narrows and blocks these major vessels. Such blockages can have severe, life-threatening consequences as they restrict blood flow to essential areas, including the heart, brain, and limbs. The three main macrovascular complications are coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD).

Coronary artery disease involves the narrowing or blockage of coronary arteries, which supply blood to the heart muscle. Common symptoms of CAD include pain in the chest, indigestion, lightheadedness, an increased heart rate, or shortness of breath. Severe cases of CAD can lead to heart attacks. Cerebrovascular disease, including strokes and transient ischemic attacks (TIAs), is another serious complication of T2DM. Strokes can be caused by a blockage in a blood vessel supplying the brain, or hemorrhagic, resulting from the rupture of a blood vessel. When not treated immediately, prolonged CBD can lead to permanent brain damage and memory loss. Peripheral artery disease involves the narrowing of peripheral arteries, typically in the legs, due to atherosclerosis. Common symptoms of PAD include pain or cramping in the legs, pale or discolored skin, itchy or scaly skin, and hair loss.

Hypertension and dyslipidemia, further damages the arterial walls and accelerates plaque buildup. Obesity, frequently associated with insulin resistance and T2DM, amplifies these issues by increasing systemic inflammation and further disrupting lipid metabolism.

Medications play a crucial role in controlling macrovascular diseases. Antihyperglycemic agents like metformin, SGLT2 inhibitors, and GLP-1 receptor agonists help manage blood glucose levels, which slows the progression of atherosclerosis. Antiplatelet agents such as aspirin or clopidogrel reduce the risk of blood clot formation, decreasing the risk of blockages in blood flow. Statins lower LDL cholesterol levels and stabilize plaques, reducing the risk of arterial blockage. Beta-blockers reduce the workload on the heart and manage blood pressure, while ACE inhibitors help control blood pressure and offer renal protection (Fowler, 2008).

Macrovascular diseases can quickly escalate into life threatening situations. In such severe cases where medication alone is insufficient, procedural interventions may be necessary. Angioplasty and stenting involve inserting a balloon to open blocked arteries and placing a stent to keep them open. Additionally, bypass surgery is also an option; it creates a new route for blood flow around blocked arteries to improve circulation. Managing macrovascular diseases will require lifestyle modifications which are important to prevent an increased risk in severe cases. These changes include adopting a balanced diet, having regular physical activity, and managing weight.

New Emerging Treatments

In each of the Microvascular and Macrovascular sections, treatments for each complication were discussed. However, at the core of all these complications is Type 2 Diabetes, so treating the root cause can help prevent the microvascular and macrovascular complications from escalating and even occurring. The management of T2DM typically involves a combination of lifestyle modifications, medications, and, in some cases, surgical interventions. The primary goals of treatment are to control blood glucose levels, manage associated risk factors, and prevent complications.

Lifestyle changes are necessary in the management of T2DM. Dietary modifications are essential: focusing on a balanced intake of carbohydrates, proteins, and fats while including fiber-rich foods. Weight management is another critical aspect; reducing excess body weight can significantly improve insulin sensitivity and glycemic control. Regular physical activity is also vital, as exercise enhances insulin sensitivity and helps regulate blood glucose levels. Eliminating smoking and moderating alcohol intake will further support overall metabolic health and reduce cardiovascular risk.

Several types of medications are used to manage T2DM, each targeting different aspects of the disease. Antihyperglycemic agents, which include medications such as metformin, remain a popular treatment due to its efficacy in lowering blood glucose levels and its beneficial effects on weight and cardiovascular risk. Metformin works by decreasing hepatic glucose production and enhancing insulin sensitivity. Other antihyperglycemic agents include SGLT2 inhibitors that prevent glucose reabsorption in the kidneys, leading to increased glucose excretion. GLP-1 receptor agonists enhance insulin secretion in response to meals, suppress glucagon release, and slow gastric emptying, thereby reducing postprandial glucose levels and aiding weight loss. Thiazolidinediones improve insulin sensitivity by acting on the peroxisome proliferator-activated receptor gamma (PPAR-γ). However, their use is limited by potential side effects such as weight gain and fluid retention. For some patients, especially those with significant insulin deficiency, insulin therapy may be required. Insulin can be administered as a basal (single intermediate dose), bolus (doses before mealtimes), or mixed regimen, tailored to individual needs. DPP-4 inhibitors work by prolonging the action of incretin hormones that stimulate insulin secretion and inhibit glucagon release. Alpha-glucosidase inhibitors slow carbohydrate digestion and absorption in the intestines, which helps in reducing postprandial glucose spikes (Sharma et al., 2021).

In cases where medication and lifestyle modifications are insufficient, bariatric surgery (such as gastric bypass or sleeve gastrectomy) may be considered, especially for individuals with obesity. This intervention can lead to significant improvements in glycemic control and, in some cases, the elimination of diabetes.

Recently, 5’ AMP-activated protein kinase (AMPK) has emerged as a promising target for the treatment of T2DM and related metabolic disorders. AMPK is a critical regulator of cellular energy homeostasis, often referred to as an ‘energy sensor’ due to its role in detecting and responding to changes in cellular energy levels.

AMPK is activated in response to increased levels of AMP (adenosine monophosphate) relative to ATP (adenosine triphosphate), reflecting a state of low cellular energy. Once activated, AMPK facilitates a shift from anabolic (energy-consuming) processes to catabolic (energy-producing) activities. This shift includes promoting lipolysis (breakdown of fats), β-oxidation (fatty acid oxidation), glycolysis (breakdown of glucose), and enhancing glucose uptake by cells. Simultaneously, AMPK inhibits processes that consume energy, such as gluconeogenesis (glucose production), glycogenesis (glycogen synthesis), lipogenesis (fat synthesis), and cholesterol biosynthesis (Sharma et al., 2023).

One of the notable mechanisms by which AMPK enhances glucose uptake is through the translocation of GLUT4 (glucose transporter type 4) to the cell membrane, a process controlled by the TBC1D1 protein. This mechanism is crucial for improving insulin sensitivity and glucose management in skeletal muscle, particularly when combined with insulin and exercise.

Pharmacological agents that activate AMPK can offer many benefits for managing T2DM and its complications. Several natural and synthetic compounds have been identified as AMPK activators. Biguanides, such as metformin, are common examples of AMPK activators, contributing to their effectiveness in T2DM management. Recent research has expanded the scope of AMPK activation through novel compounds. For instance, some compounds have been reported to be approximately 20 times more potent than mogrol in activating AMPK, significantly increasing their effectiveness. Some studies have explored isoquinoline derivatives, modifying the benzyl ring of berberine, a known AMPK activator. These derivatives demonstrated enhanced stimulatory effects on glucose consumption and inhibitory effects on gluconeogenesis. These compounds exhibited an increase in glucose consumption compared to berberine and showed potent effects in promoting AMPK phosphorylation. Additionally, several compounds, including AMP, 5-aminoimidazole-4-carboxamide riboside (AICA riboside), A-592107, and A769662, have shown significant AMPK activation and beneficial effects in T2DM treatment and related complications. These agents offer promising avenues for enhancing glucose management and metabolic control in T2DM (Sharma et al., 2023).

Conclusion

Type 2 diabetes mellitus (T2DM) is a global health crisis, with its prevalence steadily increasing and its impact extending beyond glucose imbalance. The increasing number of affected individuals underlines the urgent need for effective strategies to manage and mitigate this disease before further complications arise. This paper has reviewed the complex connections between T2DM and its associated complications, highlighting the critical importance of early intervention and comprehensive management.

The prevention of both microvascular and macrovascular complications is vital for an effective management of T2DM. These complications, which include retinopathy, neuropathy, nephropathy, coronary artery disease, cerebrovascular disease, and peripheral artery disease, result from atherosclerosis which can be caused by the detrimental effects of prolonged hyperglycemia and insulin resistance. The progression to these severe complications is often subtle, emphasizing the need for close monitoring and proactive treatment strategies.

The paper has explored various preventive strategies and treatments that target the early stages of T2DM. Addressing the root causes through lifestyle modifications—such as adopting a balanced diet, engaging in regular physical activity, and achieving weight management—remains fundamental. These interventions not only improve glycemic control but also play a pivotal role in mitigating the risk of developing both microvascular and macrovascular complications.

Pharmacological treatments further complement lifestyle changes. Medications such as metformin, SGLT2 inhibitors, and GLP-1 receptor agonists are crucial in managing blood glucose levels and preventing disease progression. Emerging therapies, particularly those targeting AMPK activation, offer promising advancements in enhancing insulin sensitivity and glucose metabolism. By activating AMPK, these novel therapies may significantly improve metabolic control and reduce the risk of complications associated with T2DM.

Effective management also requires regular screening and early detection of complications. For instance, regular eye examinations can identify diabetic retinopathy before significant vision loss occurs, while nerve conduction studies and urinalysis are crucial for early diagnosis of neuropathy and nephropathy. By integrating these diagnostic tools with a proactive treatment approach, healthcare providers can significantly slow the progression of these complications and improve patient outcomes.

The fight against T2DM requires a multifaceted approach that combines preventive strategies with innovative treatments. By focusing on early intervention, lifestyle modifications, and advanced pharmacological therapies, it is possible to curb the progression to severe microvascular and macrovascular complications. Ultimately, a coordinated effort in these areas can enhance the quality of life for individuals with T2DM and reduce the global burden of this pervasive disease. The ongoing development of new therapies and a comprehensive approach to disease management hold promise for a future where the impact of T2DM is significantly reduced, leading to improved health outcomes and a better quality of life for millions worldwide.

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