



Review Article

PATHOPHYSIOLOGY, LIFESTYLE INTERVENTION AND COMPLICATIONS OF TYPE-2 DIABETES: A REVIEW

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ABSTRACT

Background: Type-2 diabetes mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by insulin resistance and insufficient insulin secretion. This study aims to investigate the pathophysiology comprehensively, assess the impact of lifestyle interventions, and delineate the complications associated with T2DM. **Methodology:** A thorough literature review was conducted to elucidate the multifaceted pathophysiological mechanisms contributing to T2DM. Lifestyle interventions, including dietary modifications and physical activity, were evaluated based on clinical trials, observational studies, evidence-based guidelines, and relevant epidemiological and clinical studies. **Result and discussion:** The pathophysiology of T2DM involves intricate interactions between genetic predisposition, environmental factors, and lifestyle choices. Insulin resistance, inflammation, dyslipidaemia, and oxidative stress collectively contribute to the progression of the disease. Lifestyle interventions, dietary modifications, emphasizing a balanced and nutrient-dense diet, along with tailored exercise regimens, demonstrated efficacy in improving glycaemic control and overall metabolic health. Furthermore, identifying complications in T2DM highlights the importance of early detection, risk mitigation, and comprehensive care strategies. **Conclusion:** This comprehensive study provides insights into the pathophysiology of T2DM, underscores the efficacy of lifestyle interventions, and delineates the diverse complications associated with the condition. It emphasizes the important role of lifestyle-oriented control of T2DM, with a focus on prevention and early intervention to mitigate complications and enhance a holistic and targeted approaches to improve the lives of individuals affected by this chronic metabolic disorder.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired secretion, leading to persistent hyperglycaemia. The pathophysiology of T2DM involves a complex interplay of genetic and environmental factors. Central to the disease process is insulin

resistance, exacerbated by obesity and particularly visceral fat accumulation. This leads to increased hepatic glucose production and reduced glucose uptake by peripheral tissues, thereby contributing to hyperglycaemia [1]. Additionally, beta-cell dysfunction in the pancreas impairs insulin secretion, further exacerbating hyperglycaemia. Chronic inflammation and

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alterations in the gut microbiota have also been implicated in the development and progression of T2DM [2]. Lifestyle interventions are critical in managing T2DM. Recent studies highlight the significant impact of diet and physical activity on glycaemic control and overall metabolic health. Diets rich in whole grains, fruits, vegetables, and lean proteins, while low in refined sugars and saturated fats, have improved insulin sensitivity and reduced blood glucose levels [3]. Specifically, dietary patterns like the Mediterranean diet have demonstrated particular efficacy in managing T2DM [4]. Physical activity, including aerobic exercises and resistance training, enhances glucose uptake by muscles and improves insulin sensitivity. Moreover, behavioural interventions that support weight loss, stress reduction, and smoking cessation also contribute to better glycaemic control and reduced risk of complications [5]. Despite these interventions, T2DM is associated with a range of acute and chronic complications. Acute complications include hypoglycaemia and hyperglycaemic crises, such as diabetic ketoacidosis and hyperosmolar hyperglycaemic state [6]. Chronic complications arise from prolonged hyperglycaemia and include microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular diseases, such as coronary artery disease, stroke, and peripheral artery disease). Recent studies underscore the importance of early detection and aggressive management of these complications to prevent morbidity and mortality. For instance, tight glycaemic control, blood pressure management, and lipid-lowering therapies are critical in reducing the risk of cardiovascular events in patients with T2DM [7].

METHODOLOGY

This study employs a structured approach to comprehensively review the pathophysiology and lifestyle therapies of Type 2 diabetes (T2D), encompassing its etiology and the efficacy of lifestyle interventions. A meticulous search strategy with relevant keywords and filters is implemented using databases like PubMed, Web of Science, Google Scholar, and Embase. Inclusion criteria focus on adult T2D patients, emphasizing lifestyle interventions and complications while excluding irrelevant study types and languages. Data synthesis involves systematic extraction, quality assessment, and analysis using meta-analytical or narrative approaches, complemented by subgroup and sensitivity analyses where applicable. Findings are presented concisely to provide a clear overview of both clinical and research implications.

RESULTS AND DISCUSSION

Approximately 80-90% of individuals with T2D exhibit insulin resistance, where cells fail to respond effectively to insulin. This results in elevated blood glucose levels. β -cells in the pancreas may fail to produce sufficient insulin, contributing to hyperglycaemia. Studies indicate that β -cell dysfunction is key to T2D progression [8]. Western (American) dietary patterns consisting of high calories, excess sugar, and sedentary lifestyles are the main causes of diabetes type 2 causes [9]. Diabetic nephropathy is the leading cause of end-stage renal disease worldwide. It affects approximately 20-40% of individuals with diabetes and is characterized by proteinuria, hypertension, and progressive decline in kidney function. Obesity is a global issue that has been associated with a higher prevalence of type 2 diabetes [10]. Approximately 60-70% of individuals with diabetes develop diabetic neuropathy, leading to symptoms such as pain, numbness, and tingling in the extremities. Studies have shown that tight glycaemic control can reduce the risk of neuropathy by up to 60%. Research indicates that having visceral obesity, ectopic fat, or liver fat increases the risk of type 2 diabetes (T2D) more than having a high body mass index (BMI) [11–14]. Approximately 70% of deaths in individuals with diabetes are due to CVD. This is consistent with studies showing that liver fat and visceral obesity at modest levels can occur in obese people without metabolic dysregulation [15–16]. Diabetes increases the risk of stroke by 1.5 to 3 times compared to individuals without diabetes. Hyperglycaemia, hypertension, dyslipidaemia, and inflammation contribute to the increased risk of stroke in individuals with diabetes. Remarkably, people who develop type 2 diabetes (T2D) but fall into the categories of being simply overweight or within a normal weight range, such as those in Asia, have ectopic fat deposition, reduced muscle mass, and visceral obesity, all of which contribute to a BMI that is normal or almost normal [17].

A. Pathophysiology of Type 2 Diabetes

Recent studies have expanded our understanding of the pathophysiology of type 2 diabetes mellitus (T2DM), emphasizing the complex interplay between genetic and environmental factors. Insulin resistance remains a central feature of T2DM, and obesity, particularly visceral fat accumulation, is a significant contributing factor. A study demonstrated that visceral adiposity is strongly associated with insulin resistance and hyperglycaemia due to increased free fatty acids and inflammatory cytokines, which impair insulin

signaling pathways [18]. Additionally, beta-cell dysfunction continues to be a critical component, with recent research highlighting the role of glucotoxicity and lipotoxicity in exacerbating beta-cell apoptosis and reducing insulin secretion [19]. The role of chronic inflammation and gut microbiota alterations has also been further elucidated. For instance, a study showed that dysbiosis in the gut microbiota contributes to systemic inflammation and insulin resistance, suggesting potential therapeutic targets for modifying gut flora to improve metabolic outcomes.

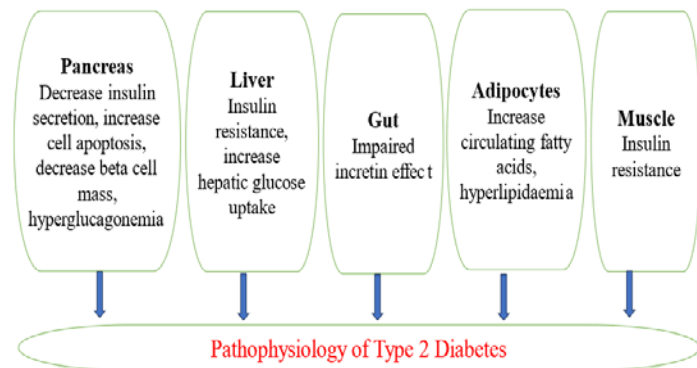


Figure 1: Representing associated pathogenesis of Type 2 Diabetes mellitus

B. Lifestyle intervention of Type 2 Diabetes:

Lifestyle interventions remain a cornerstone in managing T2DM, with numerous studies affirming their efficacy in improving glycaemic control and reducing complications. Dietary modifications have shown substantial benefits, particularly those promoting a Mediterranean diet. A randomized controlled trial confirmed that adherence to a Mediterranean diet significantly reduced HbA1c levels, improved lipid profiles, and enhanced insulin sensitivity compared to a standard low-fat diet [21]. Physical activity, encompassing both aerobic and resistance training, has been demonstrated to improve glucose uptake and enhance insulin sensitivity. A meta-analysis found that regular physical activity led to an average 0.7% reduction in HbA1c levels, underscoring the importance of exercise in T2DM management [22]. The Diabetes Prevention Program Outcomes Study (DPPOS) continues to show the long-term benefits of intensive lifestyle interventions in reducing the incidence of T2DM among high-risk individuals [23]. Physical activity interventions, including aerobic and resistance training, have reduced HbA1c levels of 0.5% to 1.0% and reduced body weight by 2% to 5%. Weight management interventions have led to weight loss of 5% to 10%

of initial body weight and reductions in HbA1c levels of 0.5% to 1.5% in individuals with Type 2 diabetes [24].

Diet: Meals low in density are considered to offer greater protection against foods high in density; dairy products that have undergone fermentation may be superior to those that have not; and eating fish is not necessarily linked to an increased risk of diabetes. A systematic review highlighted that dietary patterns rich in whole grains, fruits, vegetables, lean proteins, and low in refined sugars and saturated fats are associated with improved glycaemic control and insulin sensitivity. The study emphasized the benefits of the Mediterranean diet, which is high in monounsaturated fats from olive oil, nuts, and seeds and includes moderate consumption of fish and poultry in reducing HbA1c levels and improving lipid profiles in patients with T2DM [25]. A randomized controlled trial was conducted and demonstrated that a low-carbohydrate, high-fiber diet significantly reduced postprandial glucose levels and improved insulin sensitivity. Participants who adhered to this diet experienced a greater reduction in HbA1c compared to those on a traditional low-fat diet, indicating the effectiveness of macronutrient composition in diabetes management [26]. Recent research has also explored the role of plant-based diets in T2DM management. A study found that adherence to a plant-based diet, particularly one that emphasizes whole plant foods over refined carbohydrates and added sugars, was associated with a lower risk of developing T2DM and better glycaemic control in those already diagnosed with the condition. Plant-based diets' anti-inflammatory properties and high fiber content contribute to their beneficial effects [27]. In addition, specific dietary components have been investigated for their impact on T2DM. For example, a study showed that incorporating legumes into the diet can significantly improve glycaemic control and reduce insulin resistance. Legumes' high fiber and protein content, along with their low glycaemic index, make them a valuable component of a diabetes-friendly diet [28]. A study reported that early time-restricted feeding, where eating is confined to 6 hours in the early part of the day, improved insulin sensitivity, beta-cell responsiveness, and blood pressure in men with prediabetes, suggesting a possible benefit for those with T2DM as well [29]. A meta-analysis published in the Journal of the American Medical Association (JAMA) found that low-carbohydrate diets were associated with a greater reduction in HbA1c levels compared to higher-carbohydrate diets (mean difference: -0.44%; 95% CI: -0.66% to -0.22%) [30]. Following four years,

in comparison to the low-fat control group, the Mediterranean diet groups had a higher rate of progression and prevalence of type 2 diabetes associated much with heart diseases. Mediterranean diet was associated with a 23% reduced risk of developing Type 2 diabetes. A randomized controlled trial published in the American Journal of Clinical Nutrition found that a low-fat vegan diet reduced HbA1c levels (-0.96%) more than a conventional diabetes diet (-0.56%) after 22 weeks. The Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes consuming fruits, vegetables, whole grains, lean protein, and low-fat dairy products, has been shown to lower blood pressure and improve lipid profiles in individuals with Type 2 diabetes. A systematic review and meta-analysis published in Diabetes Care found that adherence to the DASH diet was associated with reductions in systolic blood pressure (-5.2 mmHg) and LDL cholesterol (-2.53 mg/dL) in individuals with Type 2 diabetes [31].

Physical activity: Regular physical activity reduces the risk of developing Type 2 diabetes in high-risk individuals. According to cohort studies, an interquartile rise in physical activity resources was linked to a 19% reduction in T2DM risk [32]. A systematic review confirmed that aerobic exercise significantly lowers HbA1c levels and improves insulin sensitivity in individuals with T2DM. The review analyzed multiple randomized controlled trials and found consistent evidence that moderate to vigorous aerobic exercise, performed for at least 150 minutes per week, significantly reduces HbA1c and improves overall cardiovascular health, thereby reducing the risk of macrovascular complications [33]. A study demonstrated that a 16-week resistance training program significantly improved muscle mass and strength, which enhanced glucose uptake and reduced HbA1c levels. Participants in the resistance training group showed better glycaemic control than those who did not engage in this form of exercise [34]. A randomized controlled trial found that participants who engaged in combined training experienced greater improvements in HbA1c, body composition, and cardiovascular fitness than those who participated in aerobic or resistance training alone. The study suggested that the synergistic effects of combined training provide optimal benefits for metabolic health in T2DM patients [35]. Recent research has also explored the benefits of incorporating flexibility and balance exercises into the physical activity regimen for T2DM patients. A study found that adding yoga and tai chi to traditional exercise programs significantly

improved glycaemic control and reduced stress levels, which are crucial for managing diabetes. These findings highlight the potential of holistic exercise approaches in enhancing physical and mental well-being in T2DM patients [36]. High-intensity interval training (HIIT) continues to garner attention for its efficacy in T2DM management. A study showed that a 12-week HIIT program significantly reduced HbA1c and visceral fat and improved insulin sensitivity. Participants who engaged in HIIT also reported better adherence and enjoyment than those who performed moderate-intensity continuous exercise, suggesting that HIIT could be a feasible and effective option for many T2DM patients [37]. A study demonstrated that individuals with T2DM who increased their daily step count by 2,000 steps experienced significant improvements in glycaemic control and reductions in insulin resistance. This study underscores the importance of incorporating more physical activity into daily routines to manage T2DM effectively [38].

Oxidative stress: The researchers demonstrated that elevated levels of ROS in adipose tissue impair insulin signaling pathways, leading to decreased glucose uptake and heightened blood glucose levels. This study underscored the importance of managing oxidative stress to improve insulin sensitivity and glycaemic control [39]. The research found that oxidative stress induces apoptosis in beta-cells by activating the JNK pathway and causing mitochondrial dysfunction. This beta-cell damage reduces insulin secretion, further aggravating hyperglycaemia and the progression of diabetes [40]. Recent findings also emphasize the role of oxidative stress in the development of diabetes-related complications. Oxidative stress contributes to vascular complications in T2DM, including retinopathy, nephropathy, and neuropathy. The endothelial dysfunction and inflammation are key drivers of microvascular and macrovascular damage in diabetic patients [41]. A randomized controlled trial investigated the effects of antioxidant supplementation in T2DM patients. The study found that supplementation with vitamins E and C significantly reduced oxidative stress markers and improved fasting blood glucose levels and HbA1c. These findings suggest that antioxidants can mitigate oxidative damage and improve metabolic outcomes [42]. Researchers demonstrated that combining aerobic exercise and a diet rich in antioxidants (such as fruits and vegetables) significantly decreased oxidative stress markers and improved insulin sensitivity. This highlights the potential of non-pharmacological approaches in reducing oxidative stress and

managing T2DM [43]. A study showed that curcumin supplementation reduced oxidative stress markers and improved HbA1c levels, suggesting that natural antioxidants could be beneficial adjuncts in diabetes management [44]. Oxidative stress on the endoplasmic reticulum (ER) is a major contributor to oxidative stress because it produces ROS, as described in figure 2 below.

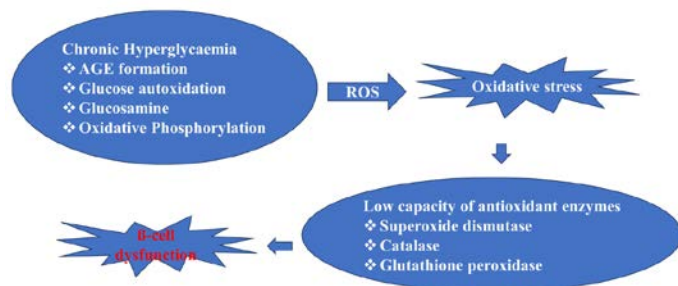


Figure 2: Role of oxidative stress in Diabetes

Socioeconomic status: Independent of whether assessed by educational level, employment, or income, an inverse relationship between socioeconomic conditions and Diabetes was obtained globally during the investigation on nations of low, middle, and high income [45]. Compared to the grouping with high socioeconomic determinants, low levels were linked to a 40–60% greater relative risk [46]. European research found that Body Mass Index (BMI) played a significant role in mediating most of the observed differences [47]. One reasonable conclusion is that when paired with a nutritious diet and lifestyle modifications, a higher income may help lower the prevalence of type 2 diabetes.

Genetic factors: Animal models, particularly rodents, have been instrumental in elucidating the genetic basis of T2DM. A study utilized a mouse model with targeted deletion of the Tcf7l2 gene, a key transcription factor implicated in T2DM. The deletion impaired glucose tolerance, reduced insulin secretion, and beta-cell dysfunction. This study demonstrated the crucial role of TCF7L2 in maintaining beta-cell function and glucose homeostasis, thereby underscoring its relevance in T2DM pathogenesis [48]. Another significant study used a knockout mouse model to explore the impact of genetic variants in the SLC30A8 gene, which encodes the zinc transporter ZnT8. The researchers found that mice lacking SLC30A8 exhibited decreased insulin secretion and increased susceptibility to diet-induced diabetes. This study proved that ZnT8 is essential for proper insulin granule function and beta-cell health, highlighting

its potential as a therapeutic target for T2DM [49]. Epigenetic modifications have also been studied in animal models to understand their role in T2DM. A study investigated the effects of high-fat diet-induced DNA methylation changes in the liver of mice. The researchers identified specific methylation patterns associated with insulin resistance and altered expression of genes involved in lipid and glucose metabolism. These findings suggest that dietary factors can induce epigenetic changes contributing to T2DM, and targeting these modifications might offer new therapeutic avenues [50]. Research focused on the role of the FTO gene, a known genetic risk factor for obesity and T2DM, in mice. By creating a conditional knockout of FTO in adipose tissue, the study demonstrated that loss of FTO led to increased body fat, insulin resistance, and impaired glucose metabolism. This study highlighted the significant role of FTO in regulating energy balance and metabolic processes, providing insights into how genetic predispositions can lead to T2DM [51]. Studies on animal models have also examined the interplay between genetic factors and environmental influences. Research on transgenic mice carrying human T2DM-associated genetic variants in the PPARG gene showed that these mice developed insulin resistance and glucose intolerance when fed a high-fat diet. This study illustrated how genetic susceptibility interacts with environmental factors, such as diet, to exacerbate T2DM risk, emphasizing the importance of lifestyle interventions alongside genetic risk management [52]. Advances in gene editing technologies, such as CRISPR/Cas9, have facilitated the study of gene function in T2DM. A study employed CRISPR/Cas9 to knock out the Pdx1 gene in mice, a critical regulator of pancreatic development and insulin production. The knockout mice exhibited severe hyperglycaemia, reduced beta-cell mass, and impaired insulin secretion, confirming the pivotal role of Pdx1 in maintaining pancreatic function and glucose homeostasis [53].

Tea, Alcohol, and Smoking: Green tea, rich in polyphenols like catechins, has garnered attention for its potential protective effects against T2DM. Studies suggest that green tea consumption is associated with improved insulin sensitivity and reduced oxidative stress, factors crucial in T2DM pathogenesis [54]. Similarly, black tea, containing flavonoids and other bioactive compounds, shows promise in enhancing glucose metabolism and reducing T2DM risk [55]. Moderate alcohol intake has been linked to a decreased risk of T2DM, attributed to the presence of polyphenols and other bioactive compounds

in alcoholic beverages. However, heavy alcohol consumption poses significant risks, contributing to insulin resistance, pancreatic beta-cell dysfunction, and liver damage, all exacerbating T2DM development [56]. Cigarette smoking is a well-established risk factor for T2DM, contributing to insulin resistance, inflammation, and oxidative stress. Recent studies highlight that both active smoking and exposure to second hand smoke elevate T2DM risk, emphasizing the importance of smoking cessation in T2DM prevention [57]. Three or more cups of coffee daily are associated with a 25–30% lower risk. Epidemiological study suggests that consuming more than three cups of coffee per day may lower your risk of type 2 diabetes by 10% to 15%. Nonetheless, it appears that alcohol use and the risks are related in a dose-dependent manner [58]. Prospective cohort study meta-analyses found that heavy smokers had a significantly greater relative risk of diabetes (risk ~1.6) compared to lighter smokers (risk ~1.3) or ex-smokers (risk ~1.2) [59]. Remarkably, recent research in a sizable multi-ethnic cohort found no correlation between smoking and type 2 diabetes incidentally [60].

C. Complications of Type 2 Diabetes

Managing T2DM complications has seen significant advances with early detection and comprehensive management strategies. Acute complications such as hypoglycaemia and hyperglycaemic crises remain a concern, particularly with intensive glycaemic control. A study highlighted that the incidence of severe hypoglycaemia can be mitigated by personalized treatment plans and continuous glucose monitoring [61]. Chronic complications, including microvascular and macrovascular diseases, continue to pose significant morbidity and mortality risks. Recent evidence from the UKPDS follow-up study indicates that tight glycaemic control, blood pressure management, and lipid-lowering therapies significantly reduce the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy [62]. Additionally, macrovascular complications, which encompass cardiovascular diseases, benefit from comprehensive cardiovascular risk management. The EMPA-REG OUTCOME trial demonstrated that empagliflozin, an SGLT2 inhibitor, significantly reduced cardiovascular mortality in patients with T2DM and established cardiovascular disease [63]. People with type 2 diabetes mellitus thus have an 8–2 increase in cardiovascular mortality, with coronary artery disease being responsible for 75% of these patients' deaths [64]. Heart-related autonomic neuropathy is

linked with a risk of developing issues related to other target organs, such as retinopathy, nephropathy, and angiopathy. It is contingent upon the length of diabetes and the level of glycaemic control [65]. About 20% of asymptomatic FD patients are thought to have cardiovascular autonomic neuropathy. The most significant issue for individuals with diabetes is the chronic problems that come with the condition. Table 1 [66] below mentions these are the most prevalent ones.

Table 1: Representing Type 2 diabetes complications and extension [8, 36]

Complications	Extended disease consequences
Macroangiopathy	Vascular lesions that lead to hypertension, coronary artery disease, artery narrowing, strokes, and erectile dysfunction in men.
Diabetic retinopathy	It causes damage to the vessels of the eye, leading to blindness in Western countries.
Diabetic nephropathy	It results in renal insufficiency and kidney damage.
Diabetic neuropathy	It is related to sensory disturbances, walking difficulty, muscle atrophy, injuries with wound formation, and intense pain in the lower extremities. It also results in hypotension, tachycardia, indigestion, nausea, orthostatic urinary incontinence, diarrhea, and/or constipation.
Diabetic foot	Occurrence of lesions at knees and below and are related to pain, sensory disorder, wounds and ulcers, skin dryness, complicated with severe local infections resulting in the development of gangrene with amputation of the fingers.
Miscellaneous	Osteoporosis, arthropathies, liver damage, myopathy, and susceptibility to infections are often linked to diabetes mellitus.

Prevention of complications of T2DM: A comprehensive approach to the prevention of Type 2 Diabetes Mellitus (T2DM) involves proactive management strategies to mitigate or delay

potential complications associated with the condition [67]. Key preventive measures include:

- Continuously monitor blood glucose levels and ensure they align with recommended ranges.
- Embracing a nutritious & well-balanced diet, incorporating essential food groups, and avoiding excessive high-sugar and processed foods intake.
- Incorporating regular physical activity into daily routines promotes cardiovascular health and contributes to blood glucose regulation.
- Ensuring cholesterol levels are within the normal range, as elevated levels can contribute to diabetes-related complications.
- Managing body weight within a healthy range through balanced nutrition and regular exercise.
- Attending routine health checkups to monitor overall health and detect potential diabetes-related issues early on.
- Taking medications as prescribed by healthcare providers to manage diabetes and prevent complications effectively.
- Quitting smoking or avoiding tobacco use, as smoking exacerbates diabetes-related risks and complications.

CONCLUSION

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and beta-cell dysfunction, driven by genetic, environmental, and lifestyle factors leading to chronic hyperglycaemia. Lifestyle interventions such as diet modification, increased physical activity, and weight management are crucial in improving insulin sensitivity and reducing oxidative stress, thereby mitigating disease progression. Advances in pharmacological treatments and precision medicine offer promising personalized prevention and management strategies. Despite these advancements, T2DM remains associated with significant complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy. Effective management requires comprehensive risk factor control, early detection, and targeted therapies. A multifaceted approach combining lifestyle changes, pharmacotherapy, and personalized medicine is essential for managing T2DM and reducing its healthcare burden, underscoring the need for ongoing research and innovation.

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Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Mrinmoy Basak designed the study to ensure a robust and effective review framework. He also played a critical role in drafting and editing the manuscript's content, contributing to its overall coherence and quality. Moksood Ahmed Laskar wrote the manuscript's content, carefully articulating the research findings and discussions; he also served as the corresponding author. All authors read and approved the final manuscript, confirming their agreement with the content and conclusions presented.

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