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TYPE 2 DIABETES MELLITUS: GLOBAL EPIDEMIOLOGICAL TRENDS, MOLECULAR MECHANISMS AND RISK FACTORS WITH SPECIAL REFERENCE TO UZBEKISTAN

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Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, or a combination of both mechanisms. It represents approximately 90–95% of all diabetes cases and is associated with a wide spectrum of microvascular and macrovascular complications that significantly increase morbidity and mortality worldwide. Due to its progressive nature and multisystem involvement, T2DM has become one of the most pressing global public health challenges of the 21st century.

Over recent decades, the global prevalence of T2DM has increased dramatically, driven by demographic transitions, urbanization, and lifestyle changes. According to international estimates, more than 460 million people are currently affected by diabetes globally, and this number continues to rise across all age groups. The increasing burden is particularly evident in low- and middle-income countries, where rapid economic development is often accompanied by unhealthy dietary patterns, reduced physical activity, and growing rates of obesity. In this context, T2DM has evolved from being a disease of affluence to a widespread metabolic epidemic affecting both developed and developing regions.

The pathophysiology of T2DM is strongly influenced by mitochondrial dysfunction, oxidative stress, and chronic inflammation. Hyperglycemia enhances the production of reactive oxygen species (ROS), particularly within mitochondria, leading to cellular damage, impaired metabolic signaling, and progression of diabetic complications affecting organs such as the heart, kidneys, and skeletal muscles. Dysregulation of mitochondrial dynamics further contributes to disease progression, highlighting the central role of cellular energy metabolism in T2DM development.

In addition to biological mechanisms, multiple modifiable and non-modifiable risk factors contribute to the rising prevalence of T2DM. Advanced age, genetic predisposition, obesity, central adiposity, hypertension, and smoking are among the most significant determinants. Lifestyle factors such as unhealthy diet, physical inactivity, alcohol consumption, and tobacco use play a crucial role in disease onset and progression. Smoking, in particular, is a well-established risk factor for cardiovascular disease and chronic metabolic disorders and has been associated with insulin resistance and impaired glucose metabolism. However, the exact relationship between smoking and T2DM development remains complex and not fully understood, with some studies reporting inconsistent associations.

Pregnancy-related metabolic disorders such as gestational diabetes mellitus (GDM) also contribute to the long-term burden of T2DM. GDM is associated with increased risk of future T2DM in mothers and metabolic complications in offspring. The global rise in maternal age and

obesity has further contributed to increasing GDM prevalence, thereby indirectly influencing the T2DM epidemic.

Emerging evidence also highlights the role of novel molecular regulators, including mitochondrial-derived peptides such as MOTS-c, in metabolic homeostasis. MOTS-c, a 16-amino-acid peptide encoded by mitochondrial DNA, has been shown to regulate insulin sensitivity, oxidative stress response, and inflammatory pathways. Its involvement in metabolic adaptation suggests potential diagnostic and therapeutic implications in T2DM, although further research is required to fully elucidate its clinical relevance.

In Uzbekistan, as in many developing countries, the burden of T2DM is increasing due to rapid urbanization, dietary transitions, reduced physical activity, and high rates of overweight and obesity. Limited awareness, delayed diagnosis, and uneven access to preventive healthcare services further exacerbate disease progression and complications. Understanding the prevalence and contributing factors within local populations is therefore essential for developing targeted prevention and management strategies.

Therefore, this comprehensive review aims to assess the key factors contributing to the rising prevalence of Type 2 Diabetes Mellitus among the global population, with a particular focus on evidence from Uzbekistan. By integrating epidemiological, clinical, and molecular perspectives, this study seeks to provide a holistic understanding of T2DM determinants and support the development of effective public health interventions.

Materials and Methods

This review was conducted using a comprehensive and systematic approach to identify, analyze, and synthesize existing scientific evidence related to the prevalence, pathophysiology, and risk factors of Type 2 Diabetes Mellitus (T2DM). Relevant literature was retrieved from major international scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Additionally, regional publications and reports focusing on Central Asia and Uzbekistan were considered to ensure contextual relevance.

The search strategy incorporated combinations of keywords such as “Type 2 diabetes mellitus,” “prevalence,” “risk factors,” “oxidative stress,” “mitochondrial dysfunction,” “MOTS-c,” “gestational diabetes,” and “Uzbekistan.” Articles published in English and Russian between 2000 and 2025 were prioritized, with particular emphasis on peer-reviewed studies, systematic reviews, meta-analyses, and official reports from international health organizations.

Inclusion criteria consisted of studies addressing epidemiological trends, molecular mechanisms, clinical characteristics, and modifiable risk factors of T2DM. Exclusion criteria included studies with insufficient methodological quality, non-peer-reviewed sources, and research focusing exclusively on Type 1 diabetes or other specific forms of diabetes. Data were extracted, categorized, and critically analyzed to identify consistent patterns, emerging trends, and knowledge gaps.

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Results and Discussion

Global Epidemiological Trends of T2DM

The analysis of global data indicates a continuous and significant rise in T2DM prevalence over the past decades. This increase is closely associated with population aging, urbanization, and the global shift toward sedentary lifestyles and energy-dense diets. Notably, the burden of T2DM is no longer confined to high-income countries; instead, it disproportionately affects low- and middle-income regions, where healthcare systems often face limitations in early diagnosis and long-term disease management.

The epidemiological transition observed worldwide demonstrates that T2DM is increasingly diagnosed at younger ages, leading to prolonged disease duration and a higher likelihood of complications. This trend poses a substantial challenge for public health systems due to increased healthcare costs and reduced workforce productivity.

Pathophysiological Mechanisms and Molecular Insights

At the cellular level, T2DM is characterized by a complex interplay between insulin resistance and β-cell dysfunction. Mitochondrial dysfunction has emerged as a central component in this process, contributing to impaired energy metabolism and increased oxidative stress. Excessive production of reactive oxygen species (ROS) disrupts intracellular signaling pathways, damages cellular components, and exacerbates insulin resistance.

Chronic low-grade inflammation further amplifies metabolic dysregulation by promoting cytokine release and interfering with insulin signaling. In this context, mitochondrial-derived peptides such as MOTS-c represent a novel area of investigation. Evidence suggests that MOTS-c plays a protective role by enhancing insulin sensitivity, regulating metabolic homeostasis, and mitigating oxidative stress. However, clinical data remain limited, and further studies are required to validate its therapeutic potential.

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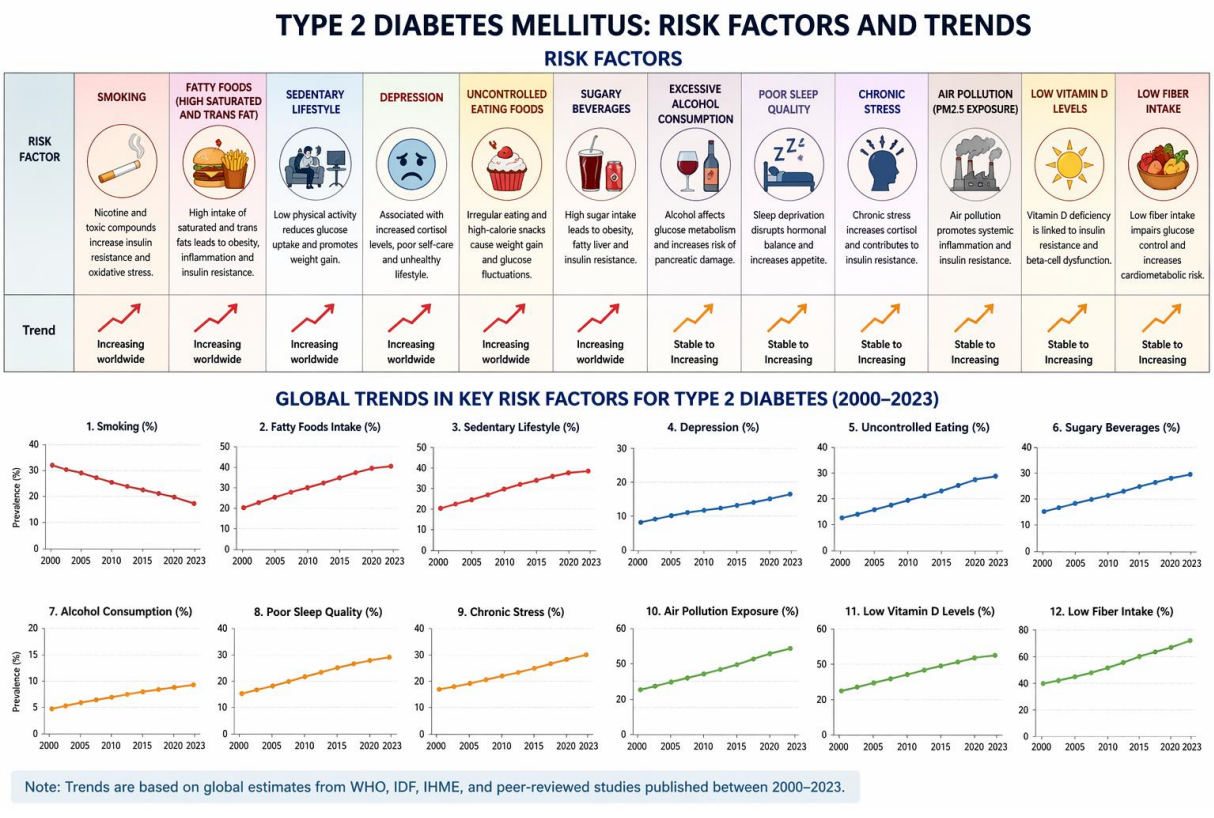
The development of T2DM is influenced by a combination of genetic susceptibility and environmental factors. Among modifiable risk factors, obesity—particularly central adiposity—remains the most significant contributor. Adipose tissue dysfunction leads to altered secretion of adipokines and promotes systemic inflammation, thereby increasing insulin resistance.

Physical inactivity is another critical determinant, as it reduces glucose uptake by skeletal muscles and contributes to weight gain. Dietary patterns characterized by high intake of refined carbohydrates, saturated fats, and processed foods further exacerbate metabolic imbalance.

Smoking has also been identified as an important, though complex, risk factor. It is associated with increased oxidative stress, endothelial dysfunction, and impaired insulin action. Despite some inconsistencies in epidemiological findings, the overall evidence supports a positive association between smoking and T2DM risk.

Non-modifiable factors such as age, genetic predisposition, and ethnicity also play a crucial role. Individuals with a family history of diabetes are at significantly higher risk, highlighting the importance of early screening and preventive interventions in high-risk populations.



Additional Risk Factors and Their Global Trends

In addition to the previously discussed determinants, several emerging and under-recognized risk factors significantly contribute to the increasing prevalence of Type 2 Diabetes Mellitus

(T2DM). These factors are closely associated with modern lifestyle patterns and environmental changes, and their global trends indicate a steady or accelerating rise.

Poor Sleep Quality and Sleep Deprivation.

Sleep disturbances, including insufficient sleep duration and poor sleep quality, have been increasingly recognized as important contributors to metabolic disorders. Sleep deprivation disrupts circadian rhythms and hormonal balance, particularly affecting cortisol, leptin, and insulin regulation. These alterations promote insulin resistance, increased appetite, and weight gain. Globally, the prevalence of poor sleep has increased over the past two decades, largely due to urbanization, increased screen exposure, and shift-based work patterns, indicating a steadily rising trend.

Chronic Psychological Stress.

Chronic stress plays a crucial role in the pathogenesis of T2DM through sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis and prolonged elevation of cortisol levels. This hormonal imbalance contributes to hyperglycemia, visceral fat accumulation, and impaired insulin sensitivity. In recent years, global stress levels have risen due to socioeconomic pressures, urban living conditions, and occupational demands, making this a steadily increasing risk factor.

Excessive Alcohol Consumption.

Although moderate alcohol intake may have mixed metabolic effects, excessive and chronic consumption is strongly associated with impaired glucose metabolism, pancreatic dysfunction, and increased risk of T2DM. Alcohol also contributes to obesity and liver diseases such as non-alcoholic fatty liver disease (NAFLD), further exacerbating insulin resistance. Global alcohol consumption patterns show a stable-to-increasing trend, particularly in developing regions undergoing rapid socioeconomic transitions.

Air Pollution (PM2.5 Exposure).

Environmental factors such as air pollution have recently been linked to metabolic diseases. Fine particulate matter (PM2.5) induces systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are involved in the development of insulin resistance. Rapid industrialization and urban expansion have led to increased exposure to air pollutants worldwide, especially in low- and middle-income countries, resulting in a rising global trend.

Vitamin D Deficiency.

Vitamin D plays an important role in glucose metabolism and insulin secretion. Deficiency of this vitamin has been associated with impaired β-cell function and increased insulin resistance. Reduced outdoor activity, urban lifestyles, and inadequate dietary intake have contributed to a growing prevalence of vitamin D deficiency worldwide. Current data suggest a gradually increasing trend across various populations.

Low Dietary Fiber Intake.

Dietary fiber is essential for maintaining glycemic control, improving insulin sensitivity, and supporting gut microbiota balance. Diets low in fiber—often replaced by highly processed foods—are associated with increased risk of T2DM. Global dietary patterns have shifted toward refined carbohydrates and low-fiber foods, particularly in urban populations, leading to a steady increase in this risk factor.

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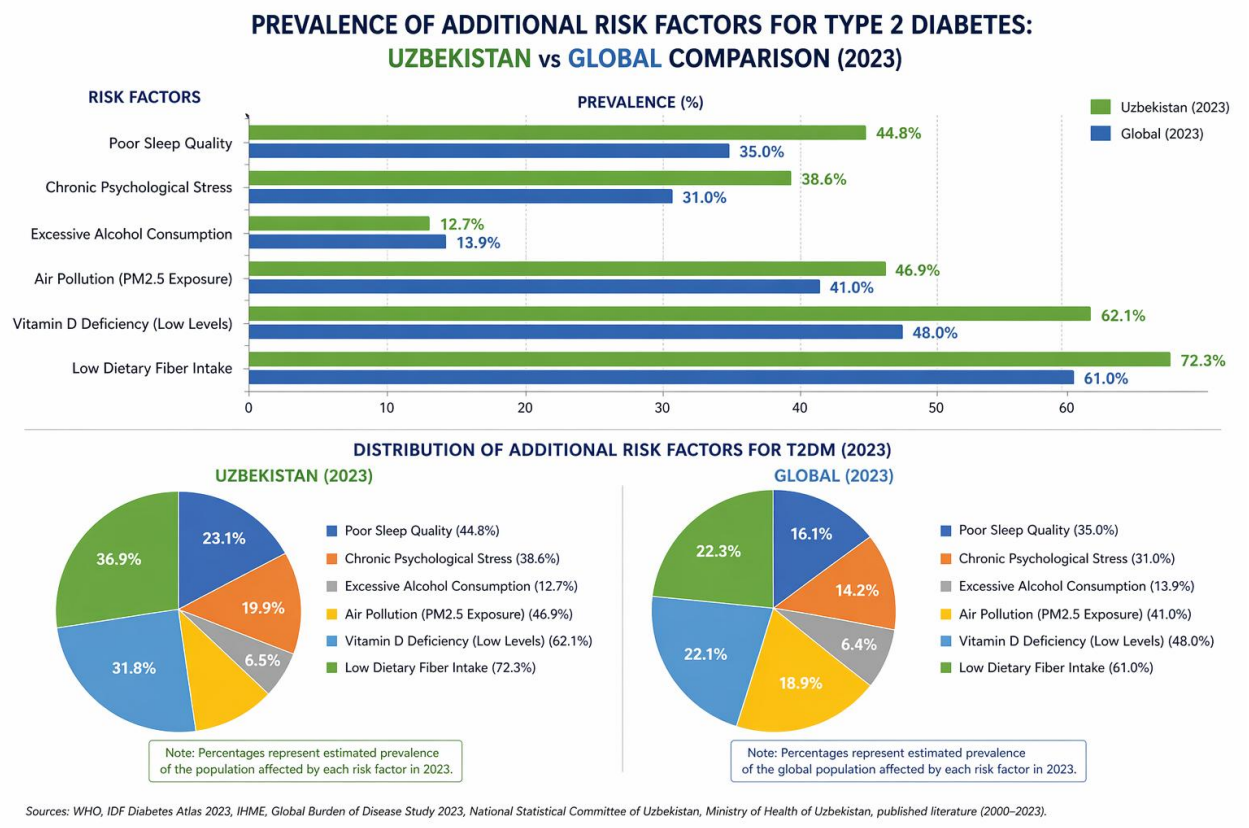

Role of Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) represents an important precursor to T2DM. Women with a history of GDM have a markedly increased risk of developing T2DM later in life. Additionally, offspring of mothers with GDM are more likely to develop obesity and glucose metabolism disorders, contributing to the intergenerational transmission of metabolic diseases.

The rising prevalence of GDM, driven by increasing maternal age and obesity rates, underscores the need for effective screening, monitoring, and postpartum follow-up strategies to reduce long-term health risks.

T2DM in Uzbekistan: Current Situation and Challenges

In Uzbekistan, the prevalence of T2DM has shown a steady increase, reflecting broader global trends. Rapid urbanization, changes in dietary habits, and decreased physical activity have significantly contributed to this rise. Traditional diets are increasingly being replaced by high-calorie, processed foods, while sedentary lifestyles are becoming more common, particularly in urban areas.

One of the major challenges in Uzbekistan is the underdiagnosis of T2DM, as many individuals remain unaware of their condition until complications develop. Limited access to preventive healthcare services, especially in rural regions, further complicates early detection and management.

Moreover, public awareness regarding diabetes prevention and lifestyle modification remains insufficient. Health education programs are often limited in scope, and there is a need for more comprehensive, community-based interventions aimed at promoting healthy behaviors.

Conclusion

The findings of this review highlight that Type 2 Diabetes Mellitus is a multifactorial and rapidly growing global health concern driven by complex interactions between genetic, environmental, and molecular factors. Mitochondrial dysfunction, oxidative stress, and chronic inflammation play central roles in disease pathogenesis, while lifestyle-related factors such as obesity, physical inactivity, and unhealthy diet significantly contribute to its increasing prevalence.

In Uzbekistan, the rising burden of T2DM reflects global patterns but is further compounded by challenges related to healthcare access, early diagnosis, and public awareness. Addressing these issues requires a multifaceted approach that integrates epidemiological monitoring, molecular research, and targeted public health interventions.

Future strategies should focus on early prevention, lifestyle modification, and the development of novel therapeutic approaches, including those targeting mitochondrial function and metabolic regulation. Strengthening healthcare systems and promoting evidence-based policies will be essential to mitigate the growing impact of T2DM both globally and at the national level.

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