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Epidemiology, Risk Factors, and Management Strategies of Type 2 Diabetes Mellitus

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Abstract Type 2 Diabetes Mellitus (T2DM) is a chronic, complex metabolic disorder that has become a global pandemic, affecting millions of individuals worldwide. This comprehensive review aims to elucidate the etiology, pathogenesis, and clinical management of T2DM, drawing on data from recent studies. The review highlights the significant role of genetic predisposition, obesity, insulin resistance, and lifestyle factors in the development and progression of T2DM. Environmental influences, including changes in diet, the gut microbiome, and exposure to pollutants, are explored alongside psychosocial stressors such as work-related stress and mental health issues, which further exacerbate the risk of T2DM. The clinical implications of these findings are discussed, emphasizing the importance of early detection, effective management strategies, and ongoing research to improve outcomes. The review also addresses the gender differences in T2DM prevalence and associated complications, noting that men are more frequently diagnosed and more likely to suffer from cardiovascular diseases. Seasonal variations in T2DM onset and the impact of vitamins D and K on disease management are also considered. This review underscores the urgent need for global health initiatives to address the rising prevalence of T2DM, particularly in developing countries where healthcare infrastructure may be insufficient. Comprehensive strategies involving lifestyle modifications, nutritional interventions, and psychosocial support are crucial in combating this epidemic. Continued research is essential for optimizing clinical practice and achieving better outcomes in the timely diagnosis and treatment of T2DM.

Keywords Type 2 Diabetes Mellitus, Insulin Resistance, Obesity, Genetic Predisposition, Global Health

1. Introduction

Diabetes mellitus (DM), or simply diabetes, is a serious long-term (or "chronic") disease that occurs when blood glucose levels are elevated due to the body's inability to produce sufficient insulin or effectively use the insulin it produces [1].

Type 2 diabetes (T2D) is the most common form, accounting for over 90% of all diabetes cases worldwide. In T2D, hyperglycemia initially results from the inability of body cells to fully respond to insulin, a condition known as insulin resistance. With the onset of insulin resistance, the hormone becomes less effective, leading to increased insulin production over time. Eventually, inadequate insulin production may develop due to the inability of pancreatic beta cells to meet the body's demands [2].

T2D can present symptoms similar to type 1 diabetes, but generally, these symptoms are much less pronounced and the condition can be entirely asymptomatic. Furthermore, the exact onset of T2D is often indeterminable, leading to a prolonged pre-diagnostic period where one-third to one-half of individuals with T2D in the population may remain undiagnosed. If the diagnosis is delayed for an extended period, complications such as vision impairment, poorly healing lower limb ulcers, heart disease, or stroke may prompt the diagnosis [3,4].

Diabetes affects individuals of all ages, genders, and geographic locations, making it one of the most prevalent global causes of mortality and morbidity. The International Diabetes Federation (IDF) estimates that 240 million people worldwide live with undiagnosed diabetes, with nearly half of all adults with diabetes unaware of their condition. Diabetes imposes a significant financial burden on healthcare systems globally. It is estimated that 537 million (10.5%) individuals aged 20–79 years are currently managing this disease [5].

There is a strong correlation between T2D and overweight or obesity, as well as age, ethnicity, and family history, although the exact causes remain unknown. It is hypothesized that polygenic and environmental factors contribute to the incidence of T2D [6]. T2D can be prevented or delayed through several non-pharmacological strategies, including maintaining a normal weight, regular physical activity, lifestyle modifications to reduce sedentary behavior, and

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smoking cessation. Importantly, delays in the detection and diagnosis of T2D are major factors contributing to suboptimal disease management and increased susceptibility to complications [7].

Globally, it was estimated that diabetes accounted for 12% of healthcare expenditures in 2010, amounting to at least $376 billion—a figure expected to reach $490 billion by 2030 [8]. The increasing prevalence and associated health complications threaten to reverse economic gains in developing countries. Due to limited diabetes treatment infrastructure, many countries are ill-equipped to combat this epidemic.

Therefore, it can be noted that the diabetes epidemic poses a significant threat to global health. Continued research in this field is critically important to optimize clinical practice and achieve better outcomes in the timely diagnosis and treatment of diabetes.

2. Materials and Methods

Literature Review

A comprehensive literature review was conducted to gather existing knowledge on the etiology, pathogenesis, and clinical management of Type 2 Diabetes Mellitus (T2DM). The databases searched included PubMed, Scopus, and Google Scholar. Keywords used for the search were "Type 2 Diabetes Mellitus," "etiology," "pathogenesis," "insulin resistance," "beta-cell dysfunction," "obesity," "genetics," and "lifestyle factors." Articles were selected based on their relevance, recency, and the presence of clinical data or significant findings related to T2DM.

Inclusion and Exclusion Criteria

Inclusion criteria for the literature review involved peer-reviewed articles, clinical trials, case studies, and review papers published in English within the last 20 years. Articles focusing specifically on the etiological factors, pathogenetic mechanisms, and clinical outcomes of T2DM were prioritized. Exclusion criteria included studies that were not peer-reviewed, articles in languages other than English, and those not directly related to the main topics of this review.

Data Extraction

Data extraction was performed systematically. Key information regarding the etiology (genetic factors, obesity, insulin resistance, and lifestyle factors), pathogenesis, clinical manifestations, and management strategies of T2DM was collected. Specific emphasis was placed on the roles of genetic predisposition, obesity, insulin resistance, and environmental factors.

Analysis

The extracted data were analyzed to identify common themes and significant findings. The interactions between different etiological factors and their contribution to the pathogenesis of T2DM were explored. The clinical implications of these findings were discussed to provide a holistic understanding of the disease.

Ethical Considerations

As this study involved a literature review, there were no direct ethical considerations involving human or animal subjects. All sources were appropriately cited to acknowledge original authorship and to maintain academic integrity.

Limitations

The primary limitation of this review is the reliance on existing literature, which may introduce biases based on the availability and quality of published studies. Future research with primary data collection and longitudinal studies are recommended to build on the findings of this review.

3. Results

Epidemiology of type 2 diabetes mellitus

Diabetes mellitus was first described over 3000 years ago in an Egyptian manuscript [9]. However, it was not until 1936 that the distinction between type 1 and type 2 diabetes was made [10]. Type 2 diabetes (T2D) is the most prevalent form, accounting for approximately 90% of diabetes cases. T2D is a chronic, complex metabolic disease affecting multiple organs, which has become a global pandemic in recent decades [11].

Currently, T2D is the most widespread and clinically significant metabolic disorder, becoming a severe burden on global healthcare systems. It was estimated that in 2013, there were 382 million diabetes patients worldwide [12]. The prevalence of T2D continues to rise, and it is projected that by 2035, over 590 million people will be diagnosed with the condition [13]. The World Health Organization (WHO) defines diabetes as a "metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both" [14].

The prevalence and incidence of T2D vary across countries. Previously, T2D was considered a disease caused by a "Western lifestyle" (high-calorie diets and sedentary lifestyles) [15]. Interestingly, the increase in T2D prevalence is estimated to be almost four times higher in developing countries than in developed ones [16]. This is attributed to the adoption of "Western lifestyles" by developing countries, along with rising obesity and overweight rates among their populations [17]. Generally, the highest risk age group for developing T2D is 40-60 years in developed countries and 60+ years in developing countries [12]. Although T2D is considered an adult-onset disease, its incidence increases with age, and children are increasingly affected [18]. However, the number of cases where T1D is diagnosed in adults might be underestimated; it is suggested that 5-15% of adults diagnosed with T2D may actually have T1D, a topic currently debated in the scientific literature [19,20].

Asia has experienced rapid economic development, urbanization, and nutritional changes over the last few decades [21]. This has led to an explosive increase in diabetes prevalence in a relatively short period. In 1980, less than 1% of Chinese adults had diabetes. By 2008, the prevalence

had reached nearly 10% [22]. It is estimated that over 92 million Chinese adults have diabetes, and an additional 148 million are in a prediabetic state. These figures suggest that China has surpassed India as the global epicenter of the diabetes epidemic. However, in urban areas of southern India, diabetes prevalence has reached nearly 20% [23]. According to WHO's Global report on diabetes, Uzbekistan ranks among the leading countries in Central Asia for diabetes prevalence, with a rate of 8.7% [24].

Numerous risk factors for T2D are currently known [14,25]. The primary risk factor is obesity, which can increase the risk of developing T2D by 90 times, and most patients are overweight or obese [26]. The risk of developing T2D is positively correlated with increasing BMI, and the risk rises exponentially with a BMI above 30 [27]. In Western countries, it is estimated that about 50% of T2D patients have a BMI >30, and 30-40% have a BMI between 25-30. However, in some Asian countries, about 50% of patients are not overweight [28,29]. Surprisingly, there have even been cases of underweight patients with T2D [30]. Increased fat deposition in ectopic areas of the body (especially visceral fat) also doubles the risk of developing T2D [31].

Genetic factors play a significant role in the development of T1D and T2D [32,33]. Studies show that the concordance rate for T2D between monozygotic twins is higher (about 70%) compared to T1D (30-50%), and the lifetime risk of developing T2D for individuals with one affected parent is 40% and nearly 70% if both parents are affected—indicating a strong genetic component in T2D susceptibility [34,35]. The concordance rate for dizygotic twins with T2D (20-30%) is also higher than for T1D (about 10%) [11]. However, the highest odds ratio recorded for a T2D risk locus is 1.57, suggesting that other unidentified variants contribute to T2D susceptibility. The increased risk of T2D in relatives of T2D patients may be due to shared diets, lifestyles, and genetics. A study demonstrated the importance of genetics in T2D susceptibility independent of diet, as there was a higher prevalence of the disease in twin populations with similar mean BMIs (26.1-26.3) and comparable standard deviations (3.9-4.7) [36].

Numerous genome-wide association studies (GWAS) conducted in different countries and ethnic groups have identified around 75 susceptibility loci associated with T2D [37,38]. Examples of candidate genes include KCNJ11 (part of the ATP-sensitive K+-channels in pancreatic beta cells), TCF7L2 (a transcription factor in the Wnt signaling pathway), IRS1 (insulin receptor substrate-1), MTNR1B (melatonin receptor 1B), PPARG2 (peroxisome proliferator -activated receptor gamma), IGF2BP2 (insulin-like growth factor 2 mRNA-binding protein 2), CDKN2A (cyclin-dependent kinase inhibitor 2A), HHEX (hematopoietically expressed homeobox), and FTO (fat mass and obesity-associated protein). Van Exel and his group found that low IL-10 production capacity is also associated with T2D [39]. It should be noted that the IL-10-1082A/G polymorphism is associated with T2D susceptibility in Asians but not in Europeans and Africans, likely due to different genetic backgrounds and environmental exposures [40].

Diet is considered a modifiable risk factor for T2D. Studies have shown that a diet low in fiber and high in glycemic index is positively associated with a higher risk of T2D [41], and certain dietary fatty acids can influence insulin resistance and diabetes risk to varying degrees [42]. Total fat intake and saturated fat intake are associated with an increased risk of T2D independent of BMI, but higher linoleic acid intake has the opposite effect, especially among leaner and younger men [43]. Frequent consumption of processed meat, but not other types of meat, may increase the risk of T2D after adjusting for BMI, prior weight change, alcohol intake, and energy intake. Sugar-sweetened beverages are also associated with an increased risk of T2D [44] and metabolic syndrome [45], as they are directly linked to BMI [46]. Other studies have shown that alcohol and smoking also increase the risk of T2D, even among individuals classified as having low-risk dietary and physical activity profiles [47].

Recent studies have demonstrated that "circumstances related to psychological stress" (e.g., stressful working conditions) or mental health issues (e.g., depression) increase the risk of developing Type 2 Diabetes Mellitus (T2DM) [48]. Worldwide, T2DM is diagnosed in more men than women, and in 2013, there were 14 million more men diagnosed with this condition than women [49]. Available data suggest that adult men are at a higher risk of T2DM than women, which is partly attributed to differences in fat accumulation patterns between genders [50]. Studies have shown that men with T2DM are more likely to suffer from cardiovascular diseases, but women with T2DM who develop cardiovascular diseases are more likely to have a worse prognosis. This is believed to be partly due to men being more likely to achieve medical targets for T2DM (such as desired plasma glucose and blood pressure control).

The seasonality of T2DM onset is not well studied, but a study conducted in Hungary showed that seasonality follows a sinusoidal pattern; the peak month was March, and the trough month was August [51]. Another recent study showed that Chinese individuals born outside the summer months have a 9% higher likelihood of developing adult-onset T2DM compared to those born in summer [52]. Environmental changes over the past few decades may also play a role in the etiology of T2DM due to the use of pesticides, medications, and food additives in food processing and packaging [53]. However, there is minimal evidence linking T2DM etiology with altered food processing/packaging in recent decades. Some environmental pollutants have been shown to alter β-cell function, with the best example being bisphenol A (used in the manufacture of food containers), which can cause β-cell dysfunction in animals [54]. It is yet to be determined whether prevalent environmental concentrations of these types of compounds constitute a risk factor for diabetes.

A link has been established between certain pathogens and the risk of developing T2DM: Herpes Simplex Virus Type 1 and Hepatitis C Virus are risk factors for T2DM, although the mechanism behind this association remains unclear [55,56]. Hepatitis C has been shown to promote

insulin resistance in the liver, which is believed to increase the risk of T2DM.

Some studies have shown that the gut microbiome is a factor in the development of T2DM [57]. Different types of gut bacteria can play different roles in maintaining or interacting with the environment. Metagenome-wide association studies (mGWAS) have shown that patients with T2DM exhibit a moderate degree of gut microbial dysbiosis, with reduced numbers of various butyrate-producing bacteria (Clostridiales sp. SS3/4, Roseburia intestinalis, Roseburia inulinivorans, Eubacterium rectale, and Faecalibacterium prausnitzii) and increased numbers of some opportunistic pathogens (Bacteroides caccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthella lenta, and Escherichia coli) [58,59]. In T2DM patients, the gut microbiota is enriched for membrane transport of sugars, methane metabolism, transport of branched-chain amino acids (BCAA), degradation and metabolism of xenobiotics, sulfate reduction, and decreased levels of bacterial chemotaxis, butyrate biosynthesis, and cofactor and vitamin metabolism [60].

Accumulating evidence suggests that vitamin D may play a potential role in controlling T2DM [61,62], as seasonal fluctuations in glycemic status have been observed in T2DM patients, with hypovitaminosis D often occurring in winter, likely contributing to T2DM exacerbation. Recent studies indicate that vitamin D deficiency may adversely affect glucose intolerance, insulin secretion, and T2DM [63], either directly through activation of the vitamin D receptor (VDR) or indirectly through calcium hormones and inflammation [64,65].

Additionally, recent research shows that vitamin K1 has a positive effect on glucose homeostasis, as higher vitamin K1 intake correlates with increased insulin sensitivity and better glycemic status [66]. Given that vitamin K deficiency can lead to poor glycemic control and bone quality, it is crucial to rule out vitamin K deficiency in T2DM patients. Several preclinical and clinical observations indicate that vitamin K2 impacts bone quality and subsequent mechanical strength in T2DM patients independently of increases in bone mineral density (BMD) [67,68]. It is also suggested that vitamin K2 may improve osteocyte density and lacunar filling with viable osteocytes in cortical bone in rats receiving glucocorticoid therapy [69,70]. Additionally, vitamin K2 may reduce bone turnover and stimulate lamellar bone formation, preventing increased bone resorption while maintaining bone formation and preventing reduced lamellar bone formation in rats on glucocorticoid therapy [71].

Therefore, the rise in childhood obesity, combined with risk factors such as genetic predisposition, sedentary lifestyle, and poor diet, highlights the need for further research into their interrelationships and impacts. These trends have led to an increase in T2DM cases among children, adolescents, and young adults, representing a significant manifestation of the epidemic and a new, large-scale public health challenge.

4. Conclusions

Type 2 Diabetes Mellitus (T2DM) is a significant global health challenge, characterized by its complex etiology and multifactorial pathogenesis. This review has highlighted the crucial roles of genetic predisposition, insulin resistance, obesity, and environmental factors in the development of T2DM. The increasing prevalence of T2DM, particularly in developing countries, underscores the importance of understanding these contributing factors to develop effective prevention and management strategies.

Recent studies have shown that psychological stress and mental health issues significantly increase the risk of developing T2DM. Additionally, T2DM is more prevalent in men than women, with men being at a higher risk of cardiovascular diseases associated with T2DM. Seasonal variations and environmental changes, including exposure to certain pollutants and pathogens, further complicate the disease's epidemiology.

The gut microbiome has emerged as a critical factor in T2DM pathogenesis, with dysbiosis contributing to the disease's metabolic disturbances. Furthermore, vitamins D and K play essential roles in managing T2DM, with deficiencies linked to poorer glycemic control and bone health.

Addressing the rise in childhood obesity and the associated risk factors, such as sedentary lifestyles and poor diet, is crucial. These trends contribute to the increasing incidence of T2DM among younger populations, presenting a significant public health challenge.

In conclusion, ongoing research is vital to optimize clinical practices and improve early diagnosis and treatment outcomes for T2DM. Efforts should focus on holistic strategies that include lifestyle modifications, nutritional interventions, and addressing psychosocial stressors to combat the global T2DM epidemic effectively.

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