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PERSPECTIVE, OPINION, AND COMMENTARY

Prediabetes: A High-Risk Condition for Developing Diabetes

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Diabetes is a metabolic disease that causes high blood sugar levels lasting longer than normal. Insulin production and/or action in diabetes is affected by insulin deficiency. The pancreas either does not produce enough insulin (type 1 diabetes), or it produces insufficient insulin to control blood sugar, or its beta cells have decreased insulin sensitivity (type 2 diabetes). Low insulin levels can cause diabetes during pregnancy, and a lack of insulin affects hormone balance [1].

Studies conducted in recent years have shown that diabetes is one of the most serious diseases, with its prevalence increasing worldwide [2], especially in developed countries [3].

The risk of developing type 2 diabetes depends not only on age, obesity, poor nutrition, and lack of exercise, but also on various genetic and metabolic factors such as race, family history, previous gestational diabetes, and smoking. Additionally, diabetes increases health risks due to associated conditions like central or abdominal adiposity, weight gain, hypertension, hypercholesterolemia, poor nutrition, and unhealthy behaviors [4].

Many risk factors for this disease are well known. Some are gender-specific, such as gestational diabetes. Polycystic ovary syndrome (PCOS) is associated with metabolic syndrome, including insulin resistance and beta cell dysfunction. Dysglycemia in women with PCOS is often related to impaired glucose tolerance (IGT), with a prevalence of approximately 30%. Therefore, both younger and older women with PCOS are at an increased risk of developing type 2 diabetes [5].

The second important factor in children is high blood sugar, which increases the risk of long-term complications. Additionally, type 2 diabetes in young adults may progress more rapidly and cause greater damage compared to those who

develop it later in life, resulting in an earlier onset of the disease and reduced survival [6]. Type 2 diabetes is recognized as a chronic disease with complications such as diabetic retinopathy, kidney disease, and diabetic ketoacidosis. It also elevates the risk of complications including high blood pressure, stroke, myocardial infarction, and lower extremity amputation [7].

Diabetes is also linked to oral health issues. Gum disease and diabetes are common comorbid conditions, and the American Diabetes Association (ADA) reports that people with diabetes experience increased severity and frequency of gum disease [8]. Epidemiological studies have shown that diabetes heightens morbidity and mortality rates, and cancer has been suggested as a new complication of diabetes [9].

In addition to its severe complications, diabetes remains a significant health and economic burden [10]. Decades of research have shown that the disease disproportionately affects minorities [10].

In the United States, minorities and low-income adults are at a higher risk of developing diabetes and its related complications [11].

The World Health Organization (WHO) estimates that more than 440 million people worldwide are living with this disease and predicts that this number will reach 592 million by 2035. By 2045, the prevalence of diabetes among people aged 20-79 is expected to increase to 10.9% (700 million). By 2030, the economic burden of diabetes is projected to rise to $2.1 trillion due to various contributing factors [12].

The increasing prevalence of diabetes worldwide is a major public health concern, and while effective treatment remains elusive, evidence of successful interventions has been documented over the past two decades [13].

To prevent type 2 diabetes, a deeper understanding of its causes is essential. Traditionally, diabetes prevention has focused on well-known risk factors, including genetics, lifestyle, behavior, and environmental influences, as well as prenatal and epigenetic factors. The risk of developing diabetes in adulthood can be passed from generation to generation through epigenetic changes, creating additional avenues for transmission. Therefore, in the context of epigenetics, it is crucial to target both genetic and environmental drivers of the diabetes epidemic for effective prevention [14].

Many randomized studies have shown that the risk of diabetes can be significantly reduced through changes in diet and physical activity. These interventions have been associated with a 15-70% relative reduction in diabetes risk over a period of 1-6 years [15]. The Centers for Disease Control and Prevention (CDC) established the National Diabetes Prevention Program (NDPP), which promotes lifestyle changes aimed at reducing body weight by 5-7% and engaging in 150 minutes of moderate-intensity physical activity each week [16].

Prediabetes

One in every 10 adults worldwide has diabetes, and 90% of these cases are type 2 diabetes. As a result, a significant portion of the population is affected by this disease, with prevalence rates in Spain exceeding 12% [17]. Individuals with prediabetes have a 30-70% chance of developing type 2 diabetes within the next 4-30 years [18]. Prediabetes is a condition caused by impaired glucose homeostasis, which alters metabolism and increases the risk of developing type 2 diabetes [19].

Prediabetes is diagnosed by measuring fasting blood glucose (FPG), glycated hemoglobin (HbA1c), or by assessing postprandial glucose levels two hours after a glucose load (2-hour post-glucose test). The term "prediabetes" describes individuals at increased risk of developing diabetes, but it is also associated with a higher burden of cardiovascular disease and poorer outcomes. Consequently, prediabetes is a complex condition that requires self-management and continuous professional care to maintain normal blood sugar levels [20].

Prevalence of Prediabetes

The prevalence and incidence of prediabetes are rising globally [21]. A study of 1,542 healthy Swiss adults found the prevalence of prediabetes to be 30.9%; among these, 79.9% were identified by HbA1c, 9.9% by fasting plasma glucose (FPG), and 10.3% by both methods (impaired glucose tolerance, IGT, according to ADA criteria). In some cases, the diagnosis of prediabetes is based on a single test, such as IGT, while in others, it is determined by the results of multiple tests. According to guidelines, abnormal results in any of the three methods (HbA1c, IGT, or FPG) are not sufficient to confirm a diabetes diagnosis or to guarantee successful treatment.

Screening alone has the potential to reduce the spread of the disease. In 2019, the International Diabetes Federation estimated a high global burden of prediabetes. For individuals under the age of 50, the prevalence was 7.5%, while in older populations, it rose to 28.3%, indicating a concerning increase over the years [22].

Transition from Prediabetes to Diabetes

Individuals with prediabetes have a higher risk of developing type 2 diabetes. Although this risk varies depending on population characteristics, approximately 5-10% of people with prediabetes progress to diabetes each year. Growth estimates from recent large studies align with this trend: the Diabetes Prevention Study reported an annual incidence of 11%. Among participants with impaired fasting glucose (IFG) in the Atherosclerosis Study in the United States, the annual incidence was just over 4%. This rate was 9% among those with IFG and 7% among those with elevated HbA1c levels. Another study demonstrated that the risk of diabetes, based on fasting plasma glucose (FPG) and 2-hour plasma glucose levels, is comparable to the risk assessed using HbA1c [23].

Risk Factors Associated with Diabetes

i. **Obesity**: Obesity is one of the most significant risk factors for diabetes. According to the World Health Organization (WHO), individuals with a body mass index (BMI) over 30 have an 80-90% higher risk of developing diabetes compared to those with a BMI in the normal range (18.5-24.9).

ii. **Family History**: A family history of diabetes significantly increases the risk of developing the disease. Studies indicate that individuals with diabetic relatives are 20-40% more likely to develop diabetes.

iii. **High Blood Pressure**: Hypertension is another major contributor to the risk of diabetes. Research shows that individuals with high blood pressure are 1.5 to 2.5 times more likely to develop diabetes.

iv. **Unhealthy Lifestyle**: Poor lifestyle choices, such as an unhealthy diet and lack of physical activity, are key factors in increasing diabetes risk. According to a study published in the Journal of the American Medical Association (JAMA), leading an unhealthy lifestyle raises the risk of diabetes by 70-80%.

v. **Smoking**: Smoking is a risk factor for diabetes. Studies suggest that smokers have a 30-40% higher risk of developing diabetes compared to non-smokers.

vi. **Age**: Advancing age is strongly associated with an increased risk of diabetes. Reports indicate that approximately 26% of individuals between the ages of 65 and 74 are affected by diabetes.

Complications of Diabetes

Prediabetes is associated with several complications, including both microvascular and macrovascular issues. In addition, prediabetes increases the risk of major hematological events, such as myocardial infarction, stroke, and cardiovascular death.

Microvascular Complications: Microvascular complications are prevalent in individuals with prediabetes and diabetes [24]. Numerous studies have indicated an association between prediabetes and early kidney disease, highlighting an increased risk for chronic kidney disease [25]. Furthermore, prediabetes may elevate the risk of diabetic retinopathy, although results vary across studies. For example, a study involving over 5,000 Indian participants found that ophthalmoscopy-confirmed retinopathy was directly related to diabetes. However, subtle changes, such as a reduction in retinal vessel diameter or an increase in retinal vein or artery width, have also been linked to prediabetes, though these findings remain inconclusive. Additionally, peripheral neuropathy is a frequent complication in prediabetic individuals, potentially leading to pain, instability, and even amputation [26].

Macrovascular Complications: Prediabetes is a significant risk factor for not only type 2 diabetes but also macrovascular diseases. Even among those who do not progress to diabetes, prediabetes poses an independent risk for conditions such as atherosclerosis. Prediabetes, often occurring alongside metabolic syndrome, substantially increases the likelihood of atherosclerosis. Moreover, there is strong evidence showing elevated levels of fibrinogen and high-sensitivity C-reactive protein (CRP) in individuals with prediabetes, further linking it to cardiovascular issues. Erectile dysfunction has also been observed with increased frequency in people with prediabetes, potentially signaling vascular impairment [27]. In addition, cognitive decline and certain cancers have been associated with prediabetes, although the connections are still being investigated [28].

Many studies have confirmed that prediabetes, as defined by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) under the criteria set by the American Diabetes Association (ADA), is linked to cardiovascular diseases, including heart disease, stroke, and peripheral artery disease. Most of these studies demonstrate an elevated risk of cardiovascular disease due to IFG, even after adjusting for confounding factors such as total cholesterol, low-density lipoprotein (LDL), smoking, blood pressure, and obesity markers. Despite the widespread prevalence of prediabetes and its association with diabetes, few countries have developed national policies for its prevention and control. However, five countries have initiated lifestyle intervention programs, and in some cases, medical interventions with metformin. Improved health education

can empower individuals to take responsibility for both their own health and that of their families [29].

Diagnosis of Prediabetes

Early diagnosis of prediabetes is important for identifying elevated blood sugar levels before they progress to type 2 diabetes. Several tests are commonly used to detect prediabetes, including:

- **HbA1c Test:** This test provides a reflection of the average blood sugar level over the past two to three months by measuring the amount of sugar bound to hemoglobin in the blood. Normal HbA1c values indicate healthy blood sugar levels, whereas elevated values suggest higher blood sugar and a potential risk of prediabetes.
- **Fasting Blood Sugar Test:** This test is typically done after an individual has fasted for 8 to 12 hours, usually first thing in the morning. A normal fasting blood sugar level is below 100 mg/dL. A result between 100 and 126 mg/dL indicates the possibility of prediabetes.
- **Oral Glucose Tolerance Test (OGTT):** Also known as the blood sugar test after a glucose load, this test measures blood sugar levels after consuming a glucose solution. Blood sugar is tested both before and at specific intervals after the glucose intake. A post-glucose load value between 140 and 199 mg/dL signals an increased risk of prediabetes [30].

Conclusion

prediabetes serves as an early warning sign of elevated blood sugar levels that may lead to type 2 diabetes. Key diagnostic tests, including the HbA1c test, fasting blood sugar test, and post-load glucose test, help identify this condition.
Early detection of prediabetes enables individuals to implement lifestyle changes and interventions that can significantly lower their risk of progressing to diabetes.

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- **Consent for Publication**

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