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Review Article

Ziabetus (Prediabetes): A Harbinger of Critical Stage in the Continuum of Glucose Metabolism Disorder: A Review

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Abstract

Background: Prediabetes is a metabolic condition characterized by blood glucose levels higher than normal but below the threshold for diabetes mellitus. It represents a critical stage in the progression towards type 2 diabetes mellitus (T2DM) and is associated with an increased risk of cardiovascular disease and other complications. The two major pathophysiologic defects responsible for losing glucose tolerance are insulin resistance and β-cell glucose insensitivity, both appearing in subjects of Intermediate Hyperglycaemia. In classical literature, Unani physicians have described the initial symptoms and factors leading to the pathology, the risk factors are described in terms of 'Su-e-mizaj' as per the concept of Tibb. So, it is considered in the context of Ziabetus which is described as a disease that develops due to Sue-mizaj haar (abnormal hot temperament). The symptoms mentioned in Unani medicine are increased frequency of micturition (ants and flies are attracted to urine), increased thirst, nocturia, dryness of mouth and whole body, fatigue, loss of weight, malaise, and cramps in lower extremities. The modern drug-based approach for the management of Intermediate Hyperglycaemia is associated with inherent drawbacks, including toxicity, tolerability, cost, and efficacy. **Objective:** The purpose of this review is to provide an in-depth understanding of prediabetes concerning the classical literature of Greek medicine based on the analysis of certain parameters like etiopathophysiology, current diagnostic criteria, risk factors, and evidence-based management strategies. By synthesizing findings from epidemiological studies, and clinical trials, this paper aims to enhance understanding of prediabetes and facilitate effective preventive measures and interventions.

Keywords: Prediabetes, Intermediate hyperglycaemia, Impaired Glucose Tolerance, Impaired Fasting Glucose, Insulin Resistance.

Introduction

Prediabetes denotes an intermediary phase of dysglycemia within the spectrum extending from normal blood glucose levels to diabetes[1] It is a dysglycemic state situated between normal glucose tolerance and the definitive diagnosis of type 2 diabetes mellitus (T2DM), represents a condition wherein blood glucose levels suggest abnormal glucose metabolism but do not yet meet the diagnostic criteria for full-fledged diabetes[2]. This term is commonly utilized to denote a stage where glucose levels indicate deviations from normal, yet fall short of meeting the diagnostic threshold for diabetes[3]. The notion of prediabetes surfaced in the late 1970s following advancements in comprehending the natural progression of diabetes.[4,5] In classical medical literature, diabetes is traditionally classified into two categories, distinguished by the presence or absence of sugar in urine. These categories are referred to as ziabetus shakri (ziabetus har), denoting diabetes with sugar in the urine, and ziabetus sada (ziabetus barid), indicating diabetes without sugar in the urine.

This classification system underscores the historical understanding of diabetes and its diagnostic markers.[6,7,8]At present, professional societies have put forth five distinct definitions of prediabetes, which include guidelines from the ADA[2], the WHO[9], and the International Expert Committee

(IEC).[10] The definition of prediabetes based on impaired glucose tolerance (IGT) originated from community-based research, which revealed that a 2-hour postprandial blood glucose level exceeding 140 mg/dL signifies a greater risk for developing diabetes compared to lower 2-hour postprandial glucose values[11]. Conversely, the definition of prediabetes by the American Diabetes Association (ADA) focusing on impaired fasting glucose (IFG) was crafted to align more closely with IGT criteria and to optimize sensitivity in predicting the onset of diabetes.[12] Currently, two distinct clinical definitions of impaired fasting glucose (IFG) are in use: the range of 100–125 mg/dL recommended by the ADA and the range of 110–125 mg/dL recommended by the WHO.[9] In 2009, the International Expert Committee (IEC) proposed a novel definition for prediabetes based on HbA1C levels, suggesting a range of 6.0% to 6.4%.[10] Subsequently, in 2010, the ADA endorsed the use of HbA1C levels ranging from 5.7% to 6.4% to define prediabetes.[2] However, the WHO does not advocate for the utilization of HbA1C in defining prediabetes.[9] The definitions of prediabetes most commonly relied upon are those established by the American Diabetes Association (ADA) and the International Committee of Experts, as well as the World Health Organization (WHO). These definitions rely on assessments of fasting glucose concentrations, postprandial glucose levels two hours after an oral glucose challenge, and/or glycated hemoglobin (HbA1c) values.[13,14]The concept of ziabetes is present in various Unani

texts such as Al Qaanon, Al Hawi, and Kamilus Sana'ah. Unani practitioners historically viewed diabetes as a kidney disorder. Arabian physicians also referred to diabetes by alternative terms such as Moattasha, Atsha, Zalaqul kulliya, Dolab, Dawwarah, Barkar, Barkarya, and Qaramees. [15,16,17,18,19]

Epidemiology

The global prevalence of prediabetes is on the rise, mirroring the increasing rates of obesity and sedentary behaviors. Research published in The Lancet indicates that around 352 million adults worldwide were affected by prediabetes in 2017, with projections suggesting a continued rise by 2045. The prevalence of prediabetes varies among different demographic groups and is influenced by factors including age, ethnicity, socioeconomic status, and urbanization.[20,21] Prediabetes should be recognized not in isolation but rather as a precursor to both type 2 diabetes mellitus (T2DM) and cardiovascular disease, indicating an elevated risk for these health conditions. It is strongly associated with obesity, particularly the accumulation of visceral fat, dyslipidemia marked by increased triglycerides and decreased HDL cholesterol levels, and hypertension. Therefore, the presence of prediabetes warrants thorough screening for all cardiovascular risk factors. Recent studies indicate that around 25% of individuals progress from prediabetes to T2DM within 3–5 years, with approximately 70% expected to develop T2DM over their lifetime.[22,23,24,25,26,27,28]

Etiopathogenesis

Prediabetes is a multifactorial condition influenced by a combination of genetic, environmental, and lifestyle factors. Understanding the etiology of prediabetes is crucial for identifying individuals at risk and implementing targeted prevention strategies.

Genetic Factors:

Genetic predisposition significantly contributes to prediabetes development. Studies on familial history demonstrate an elevated risk of prediabetes and T2DM among individuals- with a first-degree relative affected by diabetes. Through Genome-wide association studies (GWAS), several genetic variants linked to insulin resistance, impaired β-cell function, and diabetes susceptibility have been identified. Genetic variances in pathways regulating insulin signaling, glucose metabolism, and pancreatic β-cell function are implicated in the genetic susceptibility to prediabetes.[29,30]

Insulin Resistance:

Insulin resistance, defined by the diminished responsiveness of target tissues to insulin, stands as a pivotal characteristic of prediabetes. Within skeletal muscle, liver, and adipose tissue, impaired insulin signaling results in diminished glucose uptake and heightened hepatic glucose production. Contributing factors to insulin resistance encompass obesity, a sedentary lifestyle, persistent inflammation, and ectopic fat accumulation. Furthermore, dysregulation of adipokines, notably adiponectin and leptin, intensifies insulin resistance and plays a role in prediabetes pathogenesis.[31,32]

β-Cell Dysfunction:

The gradual decline in pancreatic β-cell function plays a crucial role in the shift from prediabetes to full-blown diabetes. This dysfunction involves insufficient insulin secretion upon glucose stimulation and impaired insulin processing and release. Prolonged exposure to elevated glucose and free fatty acids leads to glucotoxicity, lipotoxicity, and oxidative stress, culminating in β-cell apoptosis and dysfunction. Genetic influences, such as mutations in genes governing β-cell

function, also contribute to the susceptibility to β-cell failure and the progression to type 2 diabetes.[33,34]

Environmental and Lifestyle Factors:

The development of prediabetes is significantly influenced by environmental and lifestyle factors. Obesity, especially visceral adiposity, stands out as a prominent risk factor for insulin resistance and prediabetes. Sedentary behaviors, consumption of high-calorie diets abundant in refined carbohydrates and saturated fats, as well as tobacco use, are correlated with heightened risks of prediabetes and T2DM. Additionally, socioeconomic elements like lower income, restricted access to nutritious foods, and insufficient healthcare resources contribute to variances in prediabetes prevalence and its outcomes.[35,36] The Unani concept of disease causation revolves around the imbalance between temperamental (mizaji) and structural (saakhti) elements. When this balance is disturbed, it leads to illness. For instance, when the temperament of the kidneys becomes excessively hot (Haar), they tend to absorb water from the bloodstream and swiftly pass it to the urinary bladder due to a weakness in the retentive power (Quwate Masika). According to Unani texts, kidneys have an affinity for the watery component of blood, as well as fluids from the liver, stomach, and intestines, contributing to symptoms like excessive thirst (polydipsia).[15,16,17,37] Unani physicians Majoosi, Ibn Sina (980-1037AD), and Samarqandi (Died 1222AD) described some underlying etiopathogenesis in detail. It was supposed that the disease was related to the kidney. The important etiological factors mentioned in USM are the following:

Zofe Gurda, or kidney weakness: It occurs when the kidneys lack the ability to retain water adequately and their retentive capacity (Quwate masika) is compromised. Additionally, the kidneys struggle to metabolize the water received from the liver.[16,17,38]

Baroodate Badan, Jigar wa Gurda: Baroodate Badan, affecting the liver and kidneys, may manifest as diabetes when prolonged exposure to cold affects the entire body or specifically targets the liver or kidneys. This exposure results in a disturbance known as sue mizaj barid, or cold temperament derangement.[7,39,40]

Sue Mizaj Haar Gurda (Hot derangement in the temperament of kidneys): In Sue Mizaj Haar Gurda, characterized by a hot derangement in the temperament of the kidneys, there is an excessive absorption of water from the circulation due to heightened heat or temperament imbalance. Consequently, the kidneys struggle to retain significant amounts of fluid, leading to frequent urination (polyuria). To alleviate the resulting thirst, patients frequently drink water (polydipsia).[8,41]

Sue Mizaj Barid Gurda (Cold Derangement in Temperament of Kidney): In Sue Mizaj Barid Gurda, characterized by a cold derangement in the temperament of the kidneys, there is a risk of developing diabetes due to prolonged exposure to cold temperatures affecting the kidneys. This exposure may induce a state of sue mizaj barid, or cold temperament derangement.

Ittesae Gurda wa Majrae Baul, or the dilatation of kidneys and tubules, results in the inability to retain water for the necessary duration. Consequently, water is swiftly excreted (polyuria).

Clinical Features:

Asymptomatic Manifestation: A significant number of individuals with prediabetes experience no symptoms and may not recognize their condition until it is detected through routine screening or incidentally during health evaluations.[42]

Polyuria and Polydipsia: Elevated blood glucose levels in prediabetes can lead to increased thirst (polydipsia) and frequent urination (polyuria) as a consequence of osmotic diuresis.[43]

Fatigue and Weakness: In individuals with prediabetes, fatigue and generalized weakness may occur due to the impaired utilization of glucose by peripheral tissues, leading to an imbalance in energy utilization.[44]

Blurred Vision: Some individuals with prediabetes may experience temporary visual disturbances, such as blurred vision, as a result of osmotic changes in the eye lens induced by hyperglycemia.[45]

Recurrent Infections: Impaired immune function associated with prediabetes increases the susceptibility of affected individuals to recurrent infections, notably fungal infections like candidiasis and urinary tract infections.[46]

Neuropathic Symptoms: Peripheral nerve damage linked to hyperglycaemia can lead to neuropathic symptoms such as tingling sensations, numbness, or burning pain in the extremities.[47]

Gastrointestinal Disturbances: Individuals with prediabetes may experience symptoms such as abdominal discomfort, bloating, and changes in bowel habits, indicative of gastrointestinal motility issues associated with autonomic neuropathy.[48]

Prediabetes, or intermediate hyperglycemia, often goes undiagnosed for extended periods since it can develop without noticeable symptoms. However, in some cases, individuals may experience symptoms similar to those of type 2 diabetes, such as frequent urination and excessive thirst.[49]

Unani physicians possessed comprehensive knowledge of the clinical manifestations of diabetes. These manifestations could vary in severity among patients. At times, individuals may remain asymptomatic and only discover their condition incidentally during routine medical examinations for other ailments. The clinical features described by Unani physicians include increased urination frequency (often attracting ants and flies to urine), unquenchable thirst, nocturia, dryness of the mouth and body, fatigue, weight loss, malaise, decreased libido and infertility, vaginal and penile infections, cramps in the lower limbs, and numbness in the hands and feet. Additionally, they observed a phenomenon known as Zooban-e-Aza, wherein organs and extremities seem to dissolve, with the resulting secretions being excreted through urine.[50]

Strategies for Management and Lifestyle Interventions:

The foundation of managing prediabetes lies in lifestyle adjustments, encompassing dietary changes, consistent physical activity, and weight control. Structured programs emphasizing behavioral modifications and ongoing commitment have proven effective in preventing or postponing the onset of type 2 diabetes mellitus (T2DM). Pharmacological options, like metformin and specific antidiabetic medications, might be recommended for high-risk individuals or those with accompanying health conditions, with thorough consideration of risks and benefits.[51]

Treatment Approach:

1. Balancing Temperament: In Unani medicine, correcting organ function and temperamental imbalance (Su-e-Mizaj) can be pivotal, potentially preventing the disease from advancing further.

2. Addressing Predisposing Factors: Identify and eliminate factors that contribute to the onset of the disease.

Treatment (Ilaj):

Approaches to managing diabetes in Unani medicine encompass three primary areas:

➤ Adjustments in Diet
➤ Alterations in Lifestyle
➤ Medicinal Interventions

Lifestyle Modifications:

Dietary Adjustments:

Implementing dietary changes, such as adopting a low-glycemic index diet, reducing calorie intake, and increasing fiber consumption, has proven effective in enhancing glycemic control and lowering the risk of progressing to type 2 diabetes mellitus (T2DM).

Physical Exercise:

Engaging in regular physical activities, including aerobic exercises and resistance training, plays a pivotal role in enhancing insulin sensitivity and glucose metabolism among individuals with prediabetes.

Weight Control:

Managing weight through calorie restriction and behavioral interventions has shown significant efficacy in decreasing the likelihood of developing T2DM among individuals with prediabetes.

There exist numerous methods to prevent diseases like diabetes. Individuals can proactively maintain their health by engaging in regular exercise, adopting a balanced diet, and reducing the risk of developing associated conditions. Health organizations like the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have outlined objectives aimed at addressing diabetes. These goals encompass activities such as surveillance to gather diabetes-related data and identify population trends, raising awareness about the condition, and establishing programs to improve diabetes management and patient outcomes**.**

Primary Prevention involves two suggested strategies: Population-wide interventions and Targeted interventions for high-risk groups.

Population Approach:

Given the current knowledge limitations, primary prevention efforts for type 1 diabetes are somewhat constrained and may not be entirely suitable. However, preventive actions primarily involve promoting healthy body weight maintenance through balanced nutrition and regular exercise. This entails ensuring adequate protein consumption, prioritizing dietary fiber intake, and reducing the intake of sugary foods. Furthermore, in select populations, addressing other potentially contributing factors such as protein deficiency and dietary toxins may also be considered.

High-Risk Approach:

No distinct high-risk strategy specifically targets type 1 diabetes. However, the development of non-insulin-dependent diabetes mellitus often correlates with a sedentary lifestyle, overeating, and obesity. Addressing these factors can potentially reduce the risk of diabetes and its associated complications. Considering that alcohol consumption can indirectly elevate diabetes risk, it's advisable to avoid it. Individuals at risk should also steer clear of diabetogenic medications like oral contraceptives. Additionally, it's wise to minimize factors that promote atherosclerosis, such as smoking, high blood pressure, elevated cholesterol, and high triglyceride levels.[52]

Several Unani physicians like Razi, Majoosi, Ibne-Sina and Mohammad Azam Khan had prescribed several medicinal plants either single or as a constituent of compound formulations, for the treatment of Ziyabetus Shakari.[5,6,8,9] Single drugs (Mufrad Advia) Following single drugs have been used in Unani medicine since ancient times:[17,52,53,54,55]

Neem (Azadirachta indica): Neem is primarily employed for blood purification and helps regulate blood sugar levels.

Methi (Trigonella foenum): This herb aids in reducing blood sugar levels and is a rich source of dietary fiber.

Mango leaves (Mangifera Indica Linn) The therapeutic effect of mango leaves (Mangifera Indica Linn) on Diabetic Nephropathy is notable. It demonstrates significant inhibition of extracellular matrix expansion and accumulation in glomeruli, along with a reduction in transforming growth factor-beta-1 overexpansion, among patients with Diabetic Nephropathy.[56]

Darchini (Cinnamon zylanicum Linn):

Cinnamon possesses insulin-like properties, rendering it beneficial for managing diabetes. This herbal remedy has demonstrated efficacy in lowering blood glucose levels, along with cholesterol and triglycerides. Moreover, cinnamon supplementation enhances antioxidant levels within the body and contributes to the reduction of metabolic syndrome.[56]

Jamun (Eugenia Jambolana Linn):

The extract derived from jamun pulp exhibits hypoglycemic activity within 30 minutes of administration, whereas the seeds of the fruit require 24 hours to show similar effects. Furthermore, there is an observed increase in serum insulin levels following administration of the extract, which also demonstrates inhibitory effects on insulinase activity from the liver and kidney.

Conclusion

In summary, while the medical community continues to grapple with the complexities of preventing and treating pre-diabetes and diabetes, a renewed emphasis on holistic approaches, particularly those rooted in Unani medicine, offers a promising avenue for exploration. Unani dietary principles, with their focus on balance and moderation, provide a compelling framework for addressing metabolic imbalances associated with pre-diabetes. By promoting the consumption of nutrient-rich foods, emphasizing adequate hydration, and advocating for regular mealtimes, Unani dietary approaches aim to optimize metabolic health and prevent the progression of diabetes. Furthermore, the concept of Riyazat, or therapeutic exercise, plays a pivotal role in Unani medicine's approach to diabetes management. Through prescribed physical activities tailored to individual needs and capabilities, Riyazat not only enhances physical fitness but also helps regulate blood sugar levels, improve insulin sensitivity, and mitigate cardiovascular risk factors. As we navigate the evolving landscape of diabetes prevention and management, integrating Unani dietary principles and Riyazat into mainstream healthcare practices holds the potential to enhance therapeutic outcomes, empower individuals to take charge of their health, and foster a holistic approach to wellness.

Conflict of Interest: The authors declare that there is no conflict of interest.

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