ORIGINAL RESEARCH PAPER

Diabetology

KEY WORDS:

PREDIABETES – RISKS AND APPROACH FOR MANAGEMENT

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ABSTRACT

The global epidemic, Diabetes, remains the silent killer and one of the most prevalent conditions affecting the quality of life of individuals in the present time. As per International Diabetes Federation (IDF, 2019) statistics, the global prevalence of diabetes is 463 million, projected to be 700 million by 2045. The preceding state of diabetes, commonly referred to as Prediabetes characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), has emerged as an individual contributor for the progression of overt state and complications. This minireview is focused on the state of prediabetes, its associated risk factors, complications, and interventions. The goal is to provide adequate tools & measures for the healthcare professionals that can aid in reducing the global burden imposed by prediabetes.

INTRODUCTION

Diabetes, a chronic metabolic disease, has emerged and established as a major health issue affecting nearly half a billion people worldwide.[1] Today, approximately 463 million people are living with diabetes, and by 2030, the projected number will reach 578 million and 700 million by 2045.[2]

The term Prediabetes' mainly used for people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) is equally imposing the risk and burden on the global healthcare system.[2] IGT and/or IFG holds three-fold importance as firstly they directly manifest the future development of type 2 diabetes (T2DM); secondly, they dispose of an increased risk of cardiovascular disease (CVD); and lastly, timely detection and diagnosis can provide different intervention options and help in the prevention of disease (T2DM).[2]

The progression of T2DM after the diagnosis of IGT or IFG is estimated cumulatively around 26% and 50%, respectively, in 5 years.[3] The higher incidence is linked with the risk factors such as age, weight, genes, and the changing lifestyle and over time implicates to severe damage to the heart, blood vessels, eyes, kidneys, and nerves.[2,3] It is observed that several individuals are completely unaware of their diabetes or prediabetes, or metabolic abnormalities and have been living with high blood glucose levels for many years.[4-7]

For this global epidemic, several studies and programs that aim to identify interventions that can help prevent or delay the onset of diabetes and reduce complications have been conducted. The interventions for prediabetes can be broadly divided into two categories - lifestyle intervention and drug therapy. Multiple clinical trials have shown an impressive efficacy of lifestyle interventions in people with impaired glucose tolerance (IGT); however, the impact on impaired fasting glucose (IFG) seems to be very little. Moreover, drug therapy in prediabetes management has also been shown to reduce the incidence of diabetes; however, limited data with the clinical consequences and recommendations from the guidelines restrict their use.[8]

The current review highlights the risks and complications, particularly the macrovascular and microvascular complications associated with prediabetes, and focuses on the lifestyle and drug interventions for managing prediabetes. This review aims to provide adequate tools & measures for the physicians for these patients that can help reduce the healthcare burden imposed by prediabetes.

Prediabetes – The Progressive Disease

The progression of normoglycemia to prediabetes can be prevented by awareness at an individual and society level and by a timely diagnosis of the predictors of the advancement of the disease. It is imperative that predicting individuals at risk for early dysglycemia would be valuable information that could help target preventive interventions to those at most risk.

The parental history of T2DM for the occurrence of impaired glucose regulation can be a strong predictor; however, it cannot be a universal truth. Dagogo-Jack S et al. (2014) from the POP-ABC study cohort emphasized few baseline factors predictive of future progression from normoglycemia to prediabetes which included older age, gender (male), higher Body Mass Index (BMI), larger waist, and higher abdominal fat mass.[9] Individuals with fasting plasma glucose (FPG) and 2-hr-post prandial glucose at the upper end of the normal range, with lower values for insulin sensitivity, insulin secretion, and disposition index, were also at risk of progressing towards prediabetes.[9,10] Additionally, the lipid profile with higher baseline values of triglycerides (TG) and low-density lipoprotein (LDL), and lower high-density cholesterol (HDL) and adiponectin also contributed to the progression towards prediabetes.[10,11] Moreover, data from the POP-ABC study by Jiang, Y et al. (2016) also emphasized the role of 18 amino acids in the progression process, where it is predicted by the higher baseline levels of asparagine and aspartic acid, glutamine, and glutamic acid, and lower levels of histidine.[10-12]

Figure 1 summarizes the predictive factors, and similar can be modeled to formulate the risk of progression from normoglycemic towards prediabetes and can be used as a tool for awareness and timely intervention.[9-12]

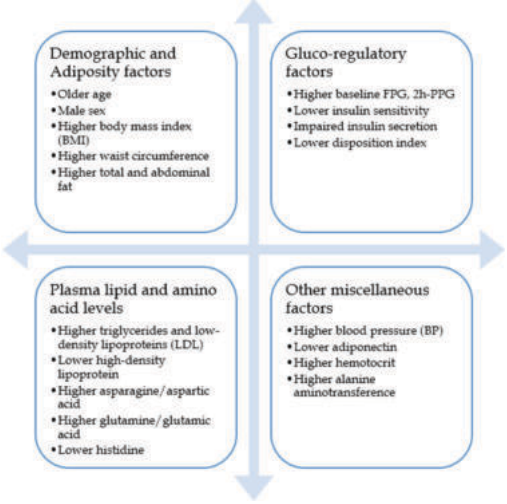

Fig.1 - Predictors of transition from normal glucose regulation to prediabetes

Table 1 - Criteria defining prediabetes

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

(Adapted from Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021)[13]

Table 2 - Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans) who have one or more of the following risk factors: **First-degree relative with diabetes:** • High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) • History of CVD • Hypertension (≥140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) • Women with polycystic ovary syndrome • Physical inactivity • Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

(Adapted from Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021)[13]

Prediabetes – The Evident Risk Factor For T2dm & Associated Complications

The risk of development of T2DM is the most obvious and indisputable sequela of prediabetes with more than 90% probability of cumulative incidence of progression over a 20-year period. With the risk of progression to T2DM, the state of prediabetes itself is positively associated with the spectrum of microvascular and macrovascular complications (Figure 2).[14]

Fig.2 – Risk of microvacular & macrovascular complications (Adapted from Brannick B et al, 2014)14

Macrovascular Complications

Prediabetes and its glycemic abnormalities are directly correlated with the increased risk of adverse CVD events, including myocardial infarction (MI), stroke, or cardiovascular death.[15]

A 1% increase in HbA1c within the normal range directly correlates with the increased 10-year cardiovascular mortality, has been proven since long (Khaw, K. T et al. EPIC-Norfolk study, 2004) and data also suggests that as compared to the individuals with normoglycemia, the presence of IGT is associated with 2x fold increase in cardiovascular mortality. Most of the patients with prediabetes who progresses to T2DM manifest an incremental risk for atherosclerotic disorders, eventually resulting in an increased burden of CVD, stroke, and peripheral vascular disease.[15,16]

Prediabetic dysglycemia is also associated with the components of metabolic syndrome even before the actual diagnosis of T2DM, including insulin resistance (metabolic) syndrome, upper-body obesity, higher waist circumference, hypertriglyceridemia, decreased HDL cholesterol levels, and hypertension putting an individual at more serious danger for related macrovascular complication and end-organ damage.[15,16]

Microvacular Complications

Like T2DM, prediabetes too is strongly associated with the classical trio-pathy of microvascular complications - retinopathy, neuropathy, and nephropathy.[14]

The undetected, undiagnosed, and unawareness of long-term subdiabetic glycemic burden induced by prediabetes increases the susceptibility of individuals for developing the complications. The long-proven data from the Diabetes Prevention Program Research Group (DPP, 2007) showed that approximately 8% of individuals with IGT had retinopathy, and another study showed an estimated 15.5% prevalence of microalbuminuria amongst individuals with prediabetes.[17,18] A review by Papanas N et al. (2011) showed that 25% and 62% of patients with idiopathic peripheral neuropathy have underlying prediabetes, and individuals with prediabetes, 11-25%, are predicted to have peripheral neuropathy, and 13-21% having neuropathic pain.[19]

Restoration Of Normal Glucose Regulation – The Intervention Measures

Lifestyle Modification

For the management of prediabetes, the combination of diet and exercise remains the cornerstone approach that could help in halting the progression of the prediabetes state to overt type 2 diabetes.

The Finnish Diabetes Prevention Study (Lindström J et al. 2003) is considered the landmark study for the lifestyle intervention in the management of prediabetes, which showed a significantly greater improvement in each intervention goal in the intervention group to the control. The results included reductions in weight (After 1 and 3 years; intervention group - 4.5 and 3.5 kg respectively vs. control group - 1.0 kg and 0.9 kg respectively), with additional improvements in measures of glycemia and lipidemia and 58% reduction in the risk of development of T2DM as compared to control group.[20-22]

Another classical study, the Diabetes Prevention Program (DPP), emphasizes lifestyle intervention, including diet and physical activity, exhibited similar results that of Finnish Study. The significant outcomes of the Diabetes Prevention Program (DPP) included - lifestyle intervention was a minimum of 7% weight loss/weight maintenance and a minimum of 150 min of physical activity, similar in intensity to brisk walking. The results showed a significant 58% reduction in diabetes incidence in the lifestyle group. Even a 10-year follow-up study showed sustained effects of lifestyle modification on diabetes prevention.[22,23]

Pharmacotherapy

Table 3 - Characteristics of an ideal prediabetes drug[14]

Efficacy should equal or exceed that of lifestyle intervention (>60% diabetes risk reduction)
Mechanism(s) of action should address pathophysiologic defects underlying prediabetes
The effects of drug should normalize glucose metabolism
The drug should have a durable effect that outlasts the period of exposure
The drug should not cause weight gain, but should induce weight loss or be weight neutral
The drug should have minimal toxicity and its use should require no safety monitoring
The drug should be well tolerated, without significant adverse effects
The retail cost of the drug should be less than that of the least expensive drug for diabetes treatment
The drug should be widely available to all patient populations regardless of socioeconomic status

For the management of prediabetes, several trials have been conducted aiming to reduce the incidence of diabetes in those at high risk. Table 4 summarizes the outcome of randomized controlled diabetes prevention trials in individuals with prediabetes.

Table 4 - Randomized controlled diabetes prevention trials in subjects with prediabetes[14]

Study acronym	Intervention	Number of subjects	Details of study population	Risk reduction
DPP[24]	Diet + Exercise or Metformin	3234	IGT adults Mean age – 54 years BMI – 34	After 2.8 years – Metformin group – 31% Lifestyle intervention group – 58%
Finnish DPS[21]	Diet and Exercise	522	IGT adults Mean age – 55 years BMI – 31	After 3.2 years, 58% reduction
ACT-NOW[25]	Pioglitazone	602	IGT adults Mean age – 53 years BMI – 33	Over 2.4 years, 72% reduction with Pioglitazone
STOP-NIDDM[26]	Acarbose	1429	IGT adults Mean age – 55 years BMI – 31	After 3.3 years, 25% reduction
XENDOS[27]	Orlistat + Diet + Exercise	3305	BMI >30 Mean age - 43 years 21% with IGT	After 4 years – Entire Group - 37% reduction IGT subgroup - 45%
IDDP-I[28]	Lifestyle modifications + Metformin or lifestyle modifications	531	IGT adults Mean age – 54.7 years BMI – 25.8	After 30 months – Diet and exercise - 28.5%, Metformin - 26.4% Diet, exercise and metformin - 28.2%
IGT: impaired glucose tolerance; BMI: body mass index.				

It is imperative that the regression from the prediabetic state to the normoglycemia, even if it is transient, predicts a long-term reduction in the risk of glycemic progression to overt T2DM. Moreover, the interventions, including lifestyle and/or pharmacological, can also protect the individuals from diabetic complications and help in reduction in the healthcare burden. Hence, the primary goal of intervention remains the restoration of glycemic levels and secondary being reduction in risk from progression and complications.

SUMMARY

The global burden of prediabetes needs optimum detection, diagnosis, and awareness as the prediabetic state itself is associated with the risk of progression to T2DM with an individual contributor to the development of macrovascular and microvascular complications. It is important for healthcare professionals and public services to offer timely diagnostic tools and interventions, be it a lifestyle and/or pharmacotherapeutic, to prevent this global epidemic.

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