Prediabetes: To Be Treated or Not?

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Abstract

Prediabetes (PD) is a bridge between normoglycemia and hyperglycemia or diabetes mellitus (DM) characterized by higher than normal blood glucose but not fulfilling the criteria for type 2 DM (T2DM). PD is defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or hemoglobin A1c (HbA1c) above 5.7% but <6.4%. Individuals with PD are at increased risk of progressing to T2DM at a pace of 5–10% every year and other micro- and macrovascular complications, including cardiovascular diseases. Prevalence of IGT and IFG in 2021 was 9.1% (about 464 million), which is projected to increase to 10.0% (638 million) in 2045; that of IFG was 5.8% (about 298 million), projected to increase to 6.5% (414 million) in 2045 globally. That is why we must seriously take aggressive steps to prevent progression to T2DM and to reduce the morbidity and mortality associated with DM, its complications, and healthcare burden. Why PD is important? Why PD to be treated? Individuals with PD have a 5–10% annual risk of progressing to T2DM and are associated with increased risk of micro- and macrovascular complications like nephropathy, retinopathy, neuropathy, and cardiovascular risks, myocardial infarction, and stroke. To prevent progression or conversion of PD to DM, we must be very aggressive. These are sufficient reasons for treatment of PD by lifestyle intervention or pharmacotherapy, as intensive lifestyle modifications, dietary modification, and enhanced physical activity have been shown to reduce the progression of PD to T2DM by 40–70%. These measures also lead to weight loss and better cardiovascular health. PD develops due to insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Therefore, pharmacotherapy with metformin, pioglitazone, α-glucosidase inhibitors (AGIs), dipeptidyl peptidase IV (DPP IV) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1 RA) targeting these defects are efficacious in preventing T2DM in PD. Diabetes Prevention Program (DPP) has shown 31% reduction in DM incidence with metformin. There is increasing evidence for prevention of DM in adults with PD by pharmacotherapy, but options other than metformin have adverse effects, and there is no unanimity for their use in PD. The role of pharmacotherapy is still debatable, and no consensus is made. We recommend that patients who are at high risk, having a strong family history of DM, signs of severe insulin resistance like acanthosis nigricans, severe obesity, or associated comorbidities, must be considered for disease-modifying pharmacotherapy like SGLT2 inhibitors, DPP IV inhibitors, and GLP1 RA. Those who do not have the above risk factors should be followed up at regular intervals, at least every year. Why PD not to be treated? When we treat DM, our "treat to target" is HbA1c of 7% or less, and organizations like the European Association for the Study of Diabetes (EASD) recommend a stricter target of 6.5%, which is above the diagnostic criteria for PD. Then the million-dollar question arises: are we justified in treating PD, as diagnostic criteria for PD are lower than the DM treatment target of 7% or less? There is another issue of overdiagnosis and overmedication; labeling individuals as PD and treating them with pharmacotherapy may lead to increased medication and healthcare costs, as well as stigma associated with a chronic disease and its treatment. Long-term studies are required to evaluate the risk-benefit of pharmacotherapy. We suggest that persons identified to have PD must be under vigilance and investigated at regular intervals. If they are found to have incremental blood glucose and HbA1c and a high risk of progression or conversion to DM, it is logical to treat. Those who are stable in the prediabetic range without associated comorbidities should be observed regularly and advised lifestyle modification (diet and exercise) and weight reduction.

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Introduction

Prediabetes (PD) is a bridge between normoglycemia and hyperglycemia, characterized by higher than normal blood glucose but less than the diagnostic criteria for type 2 diabetes mellitus (T2DM). PD is a conglomeration of impaired fasting glucose (IFG), defined as fasting plasma glucose (FPG) 100–125 mg/dL; impaired glucose tolerance (IGT), defined as plasma glucose (PG) 140–199 mg/dL after 2 hours of 75 gm oral glucose administration; and/or hemoglobin A1c (HbA1c) of 5.7–6.4%.[1,2] Prediabetics are at increased risk of progressing to T2DM at the rate of 5–10% per annum and of micro- and macrovascular complications.[3]

We are aware that IGT starts much before the diagnosis of diabetes mellitus (DM), as do various micro- and macrovascular complications. That is why it is important to implement interventions in high-risk populations at the PD stage, much before the diagnosis of T2DM, to prevent DM and its complications.

Discussion

Impaired fasting glucose, IGT, and HbA1c alone or in combination constitute PD. Prevalence of IGT and IFG in 2021 was 9.1%, approximately 464 million, which is projected to increase to 10.0%, approximately 638 million, in 2045; and that of IFG was 5.8%, approximately 298 million, which is projected to increase to 6.5%, approximately 414 million, in 2045 across the globe. PD prevalence was high in developed countries with higher per capita income, and the highest growth for PD would be in lower-per capita income regions. This is an inference from a review of >7,000 publications for PD in the 20–79-year age-group from 40 countries.[4]

Prevalence of DM, PD, and cardiovascular disease (CVD) was found to be high in an observational, retrospective study, "Progression of PD to DM at Veterans Health at Columbia, South Carolina," based on HbA1c criteria by American Diabetes Association (ADA) at 1 and 2 years and thereafter in 72,604 people with PD, with a mean age of 66 years and mean HbA1c of 5.9%. About 55% were hypertensive, and 13% had atherosclerotic cardiovascular disease (ASCVD). A total of 10,710 subjects were lost to follow-up, and the remaining 61,894 patients with PD included 21,954 (35%) who developed T2DM, while 39,940 (65%) remained prediabetic. Older persons and those with higher baseline HbA1c, ASCVD, and hypertension (HT) progressed more to DM. After 2 years, 60% of them developed DM. That is why we must take aggressive steps to prevent progression to T2DM, reduce the morbidity and mortality associated with DM and its complications, and cut the cost of healthcare.

The prevalence of PD is increasing worldwide, and it is projected that >470 million people will have PD in 2030.[5]

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The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, cross-sectional urban and rural population-based survey of >20 years of age from 31 states, union territories, and the National Capital Territory of India. Diabetes and PD were diagnosed using the World Health Organization (WHO) criteria [IFG 110–125 mg/dL PG and IGT as 2-hour post 75 gm glucose (140–199 mg/dL PG)]; WHO does not use HbA1c as criteria for diagnosis of PD.[3] Total 1,13,043 individuals (79,506 rural and 33,537 urban areas) participated in this study. Overall weighted prevalence of diabetes was 11.4%, PD 15.3%, HT 35.5%, generalized obesity 28.6%, abdominal obesity 39.5%, and dyslipidemia 81.2%. All metabolic and noncommunicable diseases (NCDs), except PD, were more frequent in urban than rural areas.[6]

Why Prediabetes is Important? Why Prediabetes is to be Treated?

Prediabetes progresses to DM at the rate of 5–10% annually and is associated with increased risk of various complications, like nephropathy, retinopathy, neuropathy (microvascular), and cardiovascular risks, myocardial infarction, and stroke (macrovascular complications). To prevent progression or conversion of PD to DM, we must be very aggressive.

Diabetes Prevention Program (DPP) has shown lifestyle intervention prevents more conversion of PD to DM compared to metformin.[3] There are sufficient reasons for treatment of PD by lifestyle intervention, as we know that intensive lifestyle modifications, dietary modification, and enhanced physical activity have been shown to reduce the progression of PD to T2DM by 40–70%. These measures also lead to weight loss and better cardiovascular health.[5,7]

In a study of 577 IGT adults from 33 clinics in China, participants were randomly divided into a control group and three lifestyle intervention groups (diet, exercise, or diet plus exercise). They were followed up with active intervention for 6 years to see the long-term effect of the interventions. The primary outcomes were incidence of DM, CVD, CV, and all-cause mortality. Combined lifestyle intervention groups had a 51% lower incidence of DM during intervention and a 43% lower incidence over the period of 20 years. DM incidence was 7% lower in the intervention group vs 11% in the control group annually. Intervention group participants were 3.6 years less exposed to T2DM compared to controls. No statistically significant difference was found in the first CV event, CV mortality, and all-cause mortality in this study, having limited statistical power. About 6 years of lifestyle interventions may delay DM for 14 years.[8]

Etiopathogenesis of PD is the same as T2DM—insulin resistance, insulin insufficiency, increased hepatic glucose production, incretin defect, lipotoxicity, hypertriglyceridemia, and many more,[5] and therefore metformin, pioglitazone, and α-glucosidase inhibitors (AGIs), dipeptidyl peptidase IV (DPP IV) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1 RA) are found efficacious in reversing the conversion of PD to DM. DPP has shown the efficacy of lifestyle interventions and also metformin, reducing 31% conversion to T2DM. There is increasing evidence for prevention of DM in PD by various drugs, but Food and Drug Administration (FDA) has not approved any medication other than metformin.[3] Pharmacotherapy is debatable, and no consensus has been made. Obesity is a key factor in the etiopathogenesis of T2DM, so weight loss medication like GLP1 RA (semaglutide, tirzepatide) and SGLT2 inhibitors seems to be promising in reversing PD to normal glucose tolerance. Diabetes remission or reversal is a futuristic goal, evident from DIRECT and SOUL trials.

What we recommend is those who are at high risk of developing DM, having a strong family history of DM, signs of severe insulin resistance like acanthosis nigricans, severe obesity, HT, dyslipidemia, history of gestational diabetes mellitus (GDM), and associated comorbidities must be considered for pharmacotherapy with SGLT2 inhibitors, DPP IV inhibitors, and GLP1 RA, and those who do not have the above risk factors should be followed up at regular intervals, or at least every year.

Why Prediabetes Not to be Treated?

Prediabetes includes IFG, IGT, and/or HbA1c of 5.7–6.4%.[1,2] But there are different criteria for the diagnosis of PD by different organizations, like the WHO, which does not consider HbA1c as a criterion for the diagnosis of PD, and FPG is higher than ADA criteria of 100–125 mg/dL. While the National Institute for Health and Care Excellence (NICE) guideline uses the same FPG criteria as WHO, HbA1c is higher than ADA criteria at 6–6.4%. There is unanimity for IGT, and there is no difference between the PG values for IGT. Prediabetics are at increased risk of progressing to T2DM at the rate of 5–10% per annum, as well as micro- and macrovascular complications.[3]

When we treat DM, our "target HbA1c" is 7% or less, and organizations like the European Association for the Study of Diabetes (EASD) recommend a stricter target of 6.5%, which is above the diagnostic criteria for PD. Then the million-dollar question arises: "Are we justified in treating PD," as the diagnostic criteria for PD are lower than the DM treatment target of 7% or less?

Overdiagnosis and overmedication by labeling individuals as PD may lead to increased medication and healthcare costs, as well as stigma associated with a chronic disease, and its treatment is another important issue. Long-term studies are required for evaluating the risk–benefit of pharmacotherapy in PD.

Conclusion

Prediabetes is more prevalent than DM, and the conversion rate of PD to DM is significant, and lifestyle interventions are no doubt helpful and unanimously recommended.

The drug treatment of PD remains a subject of debate, and drug therapy should be individualized based on patient characteristics and risk factors. Further research is needed to evaluate the long-term benefits and risks of various treatment modalities.

But at the same time, when we treat DM, our "target HbA1c" is 7% or less, and EASD recommends a stricter target of 6.5%, still above the diagnostic criteria for PD by HbA1c. Then the question arises: "Are we justified in treating PD?"

What we suggest: people having PD must be under vigilance and investigated at regular intervals, and if they are found to have incremental blood glucose and HbA1C and risk of progression or conversion to DM is high, it is logical to treat. But those who are stable and remain in the prediabetic range without associated risk factors and comorbidities should be screened regularly for progression as well as risk factors and advised lifestyle modification (diet and exercise) and weight reduction.

"Golden Rule is Prevention is better than Cure."

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