Defying the Odds: Conquering Prediabetes for a Diabetes-Free Tomorrow

Prediabetes is a known risk factor for progression to diabetes mellitus and is also associated with higher risks of vascular complications. In 2021, around 720 million individuals worldwide were impacted by prediabetes and it is projected that this number will rise to about one billion people by the year 2045.[1] According to the ICMR -INDIAB study, India had 101 million cases of diabetes and 136 million individuals with prediabetes in 2021. The nationwide prevalence of prediabetes which included urban and rural areas of nearly all states of India was reported as 15.3%.[2] A similar study from the urban metro of Delhi reported an even higher prevalence of 21%.[3] This huge burden of prediabetes points to a worsening of the type 2 diabetes burden in our country in the coming decades. Also, given the high conversion rates of prediabetes among Indians, we can expect this to happen much sooner in the coming years itself. The consistently high prevalence of prediabetes even in rural areas of several states in India is particularly alarming as it points to the spread of the diabetes epidemic to rural India. The good news though, is that type 2 diabetes can be prevented with effective interventions in the prediabetic stage. The onus is now on us to discover novel interventions that are more effective in halting its progress to type 2 diabetes and make them available to policy makers to implement at a national level.

People diagnosed with prediabetes, defined by impaired fasting glucose, impaired glucose tolerance, or both, exhibit varying degrees of insulin resistance and beta cell dysfunction. Those with impaired fasting glucose tend to have elevated endogenous glucose production due to hepatic insulin resistance with reduced hepatic glucose clearance and impaired beta cell function. On the other hand, impaired glucose tolerance is primarily characterized by resistance in skeletal muscles, leading to delayed glucose uptake, along with beta cell dysfunction. The Asian Indian Phenotype with its associated high insulin resistance has been shown to hasten progression to type 2 diabetes.[4] However, a recent study on the relative contributions of insulin resistance and beta cell dysfunction in prediabetes among Asians[5] has shown that the defect in beta cell function and insulin secretion is greater than insulin resistance in Asians with prediabetes, predisposing them to rapid progression to development of type 2 diabetes even in mild insulin resistance. In other words, beta cell dysfunction appears to be the main predominant defect in both IFG and IGT.[6] It would appear that it is a combination of higher insulin resistance and greater beta cell dysfunction that is responsible for the rapid conversion of prediabetes to diabetes in Indians. This has important therapeutic implications whereby a twin strategy to reduce stress on beta cells by diet and pharmacologic interventions as well as appropriate lifestyle measures to decrease central obesity and insulin resistance needs to be adopted to prevent or slow the evolution to diabetes.

Individuals with prediabetes have an increased risk of cardiovascular events. A comprehensive analysis of prospective studies, involving 10,069,955 individuals from 129 studies with a median follow-up period of 9.8 years, demonstrated that baseline prediabetes was linked to heightened occurrences of cardiovascular disease (incidence rate per 10,000 person-years: 58.3 for those with normal glucose regulation vs. 67.0 for those with prediabetes) and all-cause mortality (incidence rate per 10,000 person-years: 73.6 for those with normal glucose regulation vs. 81 for those with prediabetes).[7] Although there have been conflicting reports of the association of prediabetes with heart failure, a recent meta-analysis conducted in 2021,[8] which involved 15 studies encompassing a total of 9,827,430 individuals, found a significant association between prediabetes and the occurrence of incident heart failure in comparison to individuals with normoglycemia.

Microvascular complications of diabetes are also common among individuals diagnosed with prediabetes. Diabetic retinopathy (DR) starts to develop early in the progression of dysglycemia and occurs at an early stage of diabetes with glycemic measures, particularly HbA1c, being the most influential independent risk factors for DR across various glycemic levels, even before an official diabetes diagnosis.[9] However, there's limited evidence that interventions to prevent diabetes, reduce the subsequent occurrence of diabetes-related retinopathy, which is generally mild and not sight-threatening. Therefore, based on currently available information, it doesn't appear necessary to screen for retinal changes in individuals with prediabetes.[9] A systematic review indicated a higher prevalence of peripheral neuropathy in individuals with prediabetes.[10] Hence, screening might be considered in this population. Prospective studies have also demonstrated that the risk of chronic kidney disease is greater in individuals with prediabetes compared to those with normal glucose levels and the relative risk for chronic kidney disease ranged from 1.10 to 1.50, varying based on the definition of prediabetes.[11] An increased occurrence of cognitive impairment has also been reported in prediabetes.[12] A recent study from India reported that vascular complications related to diabetes were present in over 10% of individuals with prediabetes.[13] Vascular complications were noted nearly half as frequently in prediabetes as in those with known type 2 diabetes and almost as frequently as in newly diagnosed diabetic patients.

These observations further reinforce the need to understand prediabetes as a concept in the spectrum of dysglycaemia and the need to initiate effective measures to reduce the risk of type 2 diabetes as well as the risk of diabetes-associated vascular complications. Routine screening for microvascular or macrovascular complications in individuals with prediabetes is however not recommended due to a lack of sufficient data regarding its efficacy and cost-effectiveness.

What could be the possible causes of diabetes-related vascular complications in prediabetes? It is now believed that Prediabetes has a similar toxic environment as diabetes for the initiation of microvascular and macrovascular complications.[14] All pathophysiological defects associated with type 2 diabetes have also been documented in prediabetes[15] thus providing the metabolic milieu for the development of vascular complications. CGMS-based studies have demonstrated significant dysglycaemia and glycaemic variability in patients with prediabetes. It has been shown that up to 40% of obese first-degree relatives of type 2 diabetes mellitus patients who had prediabetes displayed significant glycaemic excursions into the diabetic range[16] Individuals in whom these excursions occur for a significant time during the day may well be candidates at risk for development of vascular complications. Whether periods of transient hyperglycaemia are part of normal variability or whether such periods affect the risk of progression to diabetes and the development of diabetic complications is currently unclear. Prediabetic subjects also respond to fat challenge with a higher TG response and endothelial dysfunction compared with normal glucose tolerance subjects especially if they have a first-degree relative with diabetes.[17] All these factors may contribute to enhanced long-term macrovascular and microvascular complication risk reported in prediabetic individuals.

Several studies have shown that intensive lifestyle changes, involving dietary adjustments and increased physical activity, have the potential to prevent the onset of diabetes in individuals with prediabetes but a proportion of individuals fail to respond to such interventions. A trial conducted on prediabetes individuals who were risk stratified into high-risk and low-risk reported greater improvement in cardiometabolic outcomes among high-risk individuals subjected to intensified lifestyle intervention as compared to conventional lifestyle intervention[18]; hence, tailoring lifestyle interventions based on individual risk profiles holds more promise for preventing diabetes. Shu *et al*.[19] investigated on dietary inflammatory index in prediabetes and found that a pro-inflammatory diet, with processed meats, refined carbohydrates, and sugary drinks, is linked to higher glucose and insulin levels, raising prediabetes risk; thus, dietary changes to reduce dietary inflammatory index may help prevent dysglycemia. An analysis of 47 randomized trials involving 26,460 participants provided robust support for the effectiveness of lifestyle modifications which offer the most compelling evidence of effectiveness and should continue to be the recommended strategy for addressing this condition.[20] However, the biggest challenge in clinical practice has been in translating this irrefutable trial evidence to real-world scenarios at the community level.

Numerous randomized clinical trials have shown that metformin effectively lowered the incidence of diabetes in individuals with prediabetes when compared to a placebo. The American Diabetes Association has recommended the consideration of metformin for certain subsets of prediabetes patients, such as those with a BMI of 35 or higher, individuals under 60 years old, women with gestational diabetes history, or those with elevated fasting plasma glucose (≥110 mg/dL) or higher HbA1c levels (≥6.0%) with monitoring for vitamin B12 deficiency.[21] The RSSDI-ESI clinical practice recommendations 2020 recommend that metformin can be initiated if lifestyle modifications do not achieve any benefit after a six-month trial, particularly in overweight/obese individuals, in younger individuals with one or more additional risk factors for diabetes, and in those with IFG + IGT or IFG + HbA1C >5.7%.[22]

Although thiazolidinediones have demonstrated significant efficacy in lowering hyperglycemia in prediabetes, they have also been linked to weight gain, edema, and congestive heart failure; hence limiting their use in prediabetes.[23] Similarly, despite favourable results, Alpha-glucosidase inhibitors are not used in the standard management of prediabetes mainly due to their lack of tolerability.[23] These may be used where metformin is not tolerated.[22] The RSSDI-ESI guidelines 2020 do not recommend other pharmacological agents such as pioglitazone, orlistat, vitamin D, or bariatric surgery for prediabetes.[22]

GLP-1 receptor analogues have not only shown significant benefits in obesity, but trials on these drugs have also reported good outcomes in prediabetes. Glucagon-like peptide 1 analogue investigated for individuals with prediabetes included liraglutide (linked to risk reduction, with a three-year cumulative diabetes incidence of 2% in the liraglutide group compared to 6% in the placebo group) and semaglutide (by week 68, type 2 diabetes was observed in 0.5% of participants with prediabetes at the beginning in the semaglutide group versus 3.0% in the placebo group within the STEP Program).[23] A dual agonist for glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor, tirzepatide, induces substantial weight loss, but, there is currently no available data regarding its effectiveness in preventing the transition from prediabetes to diabetes. Also, the evidence so far in this regard has been only with injectible agents which is a major limitation in treating those with prediabetes.

A meta-analysis[24] of four randomised controlled trials involving 5655 participants diagnosed with prediabetes revealed a significant association between SGLT2 inhibitors and a decreased risk of developing new-onset diabetes (relative risk: 0.79; 95% CI: 0.68-0.93). Among the individual medications, dapagliflozin and empagliflozin had relative risks of 0.68 (95% CI: 0.52-0.89) and 0.87 (95% CI: 0.72-1.04),

respectively, with no significant heterogeneity between them (P-for-heterogeneity = 0.14). These findings highlight the potential utility of SGLT2 inhibitors for diabetes prevention in high-risk populations with prediabetes.

Zinc supplementation has been shown to reduce the transition from prediabetes to diabetes in several studies. A metanalysis[25] of trials studying the effects of zinc on preventing and managing diabetes has shown significant improvement in glycemic parameters and could be used as adjunctive therapy for the prevention of diabetes in prediabetic individuals. On the other hand, vitamin D supplementation did not succeed in preventing the advancement from prediabetes to diabetes in two significant placebo-controlled randomized trials, which included one study involving individuals with confirmed hypovitaminosis D.[26,27]

Cloro *et al*.[28] investigated the effects of sacubitril/valsartan, a new combination angiotensin receptor blocker and neprilysin inhibitor, on glycemic, metabolic, and echocardiographic factors in individuals with prediabetes and heart failure with reduced ejection fraction (HFrEF). Their findings indicate potential improvements in metabolic control and insulin resistance with sacubitril/valsartan in this specific population. However, additional research is needed to investigate whether neprilysin inhibition could play a role in managing prediabetes in individuals who do not have heart failure.

Prediabetes has remained the primary target of most preventive strategies for diabetes prevention. However, some studies have indicated that preventive measures would be far more effective in halting progression if initiated before prediabetes has set in.[29] In other words, the widespread use of lifestyle strategies for diabetes prevention targeting the entire population much before the onset of prediabetes may be more beneficial. It has also been suggested that prediabetes is a heterogenous entity and different phenotypes with different pathogenetic pathways lead to prediabetes.[30] Hence targeted approaches to diabetes prevention may be needed depending on the specific phenotype and its underlying pathogenetic mechanism. Similarly, research is in progress to develop polygenic risk scores to identify those prediabetic individuals at higher risk of progression to diabetes in whom preventive measures can be targeted. This is an area of extensive research and as of now there is insufficient evidence to recommend a targeted phenotype or genotype-based approach for the prevention of type 2 diabetes.[31]

There is still much to be discovered in the field of prediabetes research. Some of the key themes of current research in prediabetes have focused on identification and risk assessment, intervention strategies and their durability, digital health solutions, metabolic biomarkers, community and public health initiatives and personalized or tailored approaches. This field is constantly evolving and new findings are constantly emerging. Exciting developments that have helped us better understand and characterize prediabetes as well as advances in discovering novel strategies that are not only effective in reducing the risk of its progression to type 2 diabetes but are also easily translatable to the real-world scenario hold promise for halting the diabetes epidemic.

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