

The Road to Preventing Diabetes: Addressing Prediabetes and Concomitant Dyslipidemia

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Diabetes Mellitus (DM) is a metabolic affliction which is reflected by chronic hyperglycemia resulting from disturbances in insulin secretion, insulin action or even both, along with associated derangements of lipid, carbohydrate and protein metabolism at the background.¹ Amongst the various types of diabetes encountered, type 2 diabetes mellitus (T2DM) accounts for almost 90% of all the cases.²⁻⁴ A 2 to 6 fold increase in cardiovascular morbidity and mortality is observed in those patients who develop T2DM, which further contributes to the adverse socio-economic burden of diabetes in the long term.⁵⁻⁶ Majority of these patients tend to also suffer from concomitant dyslipidemia, typically characterized by the atherogenic triad of elevated triglycerides (TG), low concentrations of high density lipoprotein cholesterol (HDL-C) and an increased number of small dense low density lipoprotein cholesterol (LDL-C) particles.⁷ Hypertriglyceridemia has been reported as an important risk factor for CVD and may be as prevalent as 50% in T2DM and is often also unresponsive to statin treatment.⁸⁻¹⁰ This typical dyslipidemic feature has been observed in diabetic as well as prediabetic patients and addressed by multiple terms like 'Atherogenic Dyslipidemia', 'Atherogenic Diabetic Dyslipidemia' or just 'Diabetic dyslipidemia' and has been associated with an increased cardiovascular disease (CVD) risk.¹¹⁻¹²

People with prediabetes are at a very high risk of developing T2DM. And as per recent updates in addition to the 425 million diabetics worldwide, there are 352.1 million adults with impaired glucose tolerance (IGT) or prediabetes, who have a very high chance of developing full blown diabetes in the future. Though out of these, not all become diabetic, the conversion rate varies from population to population and from region to region.^{13,14} In India, the ICMR-INDIAB study (2011),

which included both urban and rural population across 4 major Indian states, identified a conversion rate from prediabetes to diabetes, ranging between 7.1 % - 15.2%.¹⁵

Prediabetes, if simply put, would be a metabolic disorder portrayed by insulin resistance along with primary or secondary beta cell dysfunction, which in turn increases the risk of T2DM.¹⁶ The American Diabetic Association (ADA) defines prediabetes as an impaired fasting glucose (IFG) between 100 mg/dL to 125 mg/dL OR as impaired glucose tolerance (IGT) [2-h PG during 75-g OGTT] between 140 mg/dL to 199 mg/dL OR Glycated Hemoglobin (HbA1c) levels between 5.7–6.4%.¹⁷ The common risk factors for prediabetes include family history of diabetes, excess body weight (particularly abdominal adiposity), dyslipidemia, age >45 years, gestational diabetes, high birth weight children, certain ethnic groups, hypertension, and physical inactivity.¹⁸ In a meta-analysis of 18 studies, Ford et al. had concluded that people with prediabetes in general have a 20% increased risk of CVD.¹⁹ Halting the progression from prediabetes to T2DM is therefore an important health intervention strategy which has the potential to improve the health of populations, and reduce health care costs associated with the management and prevention of diabetic complications.

Multiple interventions have been utilized and studied to prevent or delay the progression from prediabetes to T2DM, including pharmacological agents (oral antidiabetic drugs and antiobesity drugs), lifestyle modification (LSM), and herbal remedies.²⁰ Three major randomized studies have shown a positive effect

of LSM on DM prevention.²¹⁻²³ The ADA,¹⁷ therefore recommends exercise as a major part of T2DM prevention. Diet and exercise interventions have demonstrated improvements in insulin resistance and decrease in the incidence of diabetes and cardiovascular events, although long term weight loss is difficult to maintain.²⁴⁻²⁵

In clinical and research studies, pharmacological agents like metformin, α -glucosidase inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones (PPAR- γ agonists) have each shown to prevent the incidence of diabetes to various levels in patients with prediabetes.^{23,26-30} But at present, none of them is approved by the U.S. Food and Drug Administration for diabetes prevention in particular. Metformin though, has a very strong evidence base and also has demonstrated long term safety as a pharmacologic therapy for diabetes prevention.³¹ Apart from metformin, PPAR- γ agonists (pioglitazone) have also shown a potential to decrease the incidence of diabetes, mostly due to their ability to address insulin resistance which lies as the root cause behind the hyperglycemia seen in both T2DM and prediabetes. Although, weight gain and edema were also reported with the glitazones.²⁹

As insulin resistance and dyslipidemia are generally identified as early offenders in the process of developing T2DM and also a part of the metabolic syndrome, the concept of the dual peroxisome proliferator activated receptor (PPAR) α/γ -agonists or glitazars was born.³² And from their chequered history, only one molecule has emerged unscathed into clinical practice after completing the relevant

clinical trials (PRESS V & PRESS VI) and is presently available in India as Saroglitazar.^{33,34} This dual acting molecule combines the significant triglyceride lowering action of a PPAR- α agonist with the antihyperglycemic and insulin sensitizing properties of a PPAR- γ agonist, thereby affecting the two core components that are a part of the metabolic syndrome. It has also not shown a propensity to cause either edema or weight gain till now.³³⁻³⁵ Saroglitazar is presently approved for clinical usage in India since 2013 for the treatment of diabetic dyslipidemia not controlled by statin therapy alone. In the present issue, Bhosle D. et al. have attempted to assess the potential of Saroglitazar for the first time in a prediabetic population having concomitant dyslipidemia, where they have observed, that saroglitazar with its insulin sensitizing and triglyceride action plays a role in controlling the dyslipidemic and HbA1c parameters and thereby may play a part in delaying or preventing the progression of diabetes. This is a first-in-concept study with a relatively smaller sample size, carried out at a single center. There is no doubt though, that this avenue should be further explored in larger, randomized clinical trials to assess the true potential of this Indian molecule i.e. Saroglitazar in population with prediabetes.

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