

## Pioglitazone: A Better Choice of Drug in the Pre-diabetic Patients with High Risk of Cardiovascular Diseases

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### Abstract

Prediabetes is an intermediate condition between normal glycemia and clinical diabetes. Person with prediabetes condition have more chances of occurring diabetes and its associated cardiovascular disorder. Intervention of prediabetic person reduces its progression to diabetes and other cardiovascular diseases. Pioglitazone, a thiazolidinedione insulin sensitizer acts on peroxisome proliferator activated receptor and have a good response in diabetic condition. Apart from glycemic benefits it has anti-atherogenicity action that prevents the progression of cardiovascular disorder. These emerging effects of the drug pioglitazone on atherosclerosis warrant a better place in the management of diabetic patients with high risk of coronary artery disease.

**Keywords:** Prediabetes; Diabetes; Pioglitazone; Atherosclerosis

### Introduction

Prediabetes is an intermediate stage between normal glycaemia and clinical diabetes. According to Indian Health Services guidelines it is considered a prediabetic condition if fasting blood glucose >100 mg/dl but less than 126 mg/dl [1].

### Epidemiology

According to ICMR-India-DIAbetes (ICMR-INDIAB) study in India there are estimated 77.2 million people have prediabetes and over 65 million people have diabetes [2].

### Prediabetes and atherosclerosis

Prediabetes is a common disorder in most population [3-5] those who have prediabetes are more prone to diabetes and its associated cardiovascular disorders. Studies show that two to three fold increase of heart disease in patients with diabetes compared to people without diabetes [6]. Impaired fasting glucose and impaired glucose tolerance are associated with increased risk of Cardiovascular Diseases (CVD) [7,8]. Early intervention of prediabetes reduces the development of diabetes and CVD [9,10]. In prediabetes patients lifestyle modification and various hypoglycemic agents helps by reducing progression to diabetes [11-13].

### Pioglitazone

Pioglitazone is a Thiazolidinedione which is a synthetic ligand for Peroxisome Proliferator-Activated Receptors (PPARs). It alters the transcription of genes influencing carbohydrate and lipid metabolism, resulting in changed amounts of protein synthesis and, therefore, metabolic changes. Pioglitazone improves glycaemic control in people with prediabetic and Type 2 diabetes by improving insulin sensitivity through its action at PPAR gamma 1 and PPAR gamma 2, and affects lipid metabolism through action at PPAR alpha. The results of these interactions include increases in glucose transporters 1 and 4, lowered free fatty acids, enhanced insulin signaling, reduced Tumor Necrosis Factor alpha (TNF alpha) and remodeling of adipose tissue. Together, these can increase glucose uptake and utilization in the peripheral organs and decrease gluconeogenesis in the liver, thereby reducing insulin resistance [14,15].

Pioglitazone and atherosclerosis: With the completion of the PROactive, Carotid intima-media thickness in Atherosclerosis using

pioGlitzOne (CHICAGO) and Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) studies, pioglitazone probably represents the best studied of all oral glucose-lowering therapies in terms of CV outcomes. The striking congruence of the results from these three studies provides a sound basis for considering the potential macrovascular benefits of pioglitazone.

PROactive was a prospective, multicentre, randomized, double-blind, placebo-controlled outcome study that investigated the effects of pioglitazone on macrovascular outcomes in >5000 high-risk patients with type 2 diabetes and pre-existing macrovascular disease treated with guideline-driven therapy for multiple risk factors. Over the three years of the study period Pioglitazone was found statistically beneficial compared to placebo [16].

The CHICAGO study was a randomized, double-blind, comparator-controlled trial, conducted at 28 clinical sites in a multiracial/ethnic Chicago metropolitan area. Results of a head-to-head comparison of two antidiabetes drugs have shown an advantage for pioglitazone over glimepiride in reducing progression of Carotid Intima-Media Thickness (CIMT) in patients with type 2 diabetes [17].

In PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) 543 patients are compared Glimepiride with Pioglitazone over the 18 months treatment on the basis of coronary intravascular sonography. Pioglitazone 15-45 mg/day significantly slowed the progression of atherosclerosis compared with Glimepiride 1-4 mg/day over 18 months [18].

Similar study was carried out by Aramesh Sarem et al. [19] to test the effects of pioglitazone on both conversions to T2DM (Type 2 Diabetes

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malitus) and progression of atherosclerosis in persons with prediabetes and they concluded that Pioglitazone slowed progression of CIMT, independent of improvement in hyperglycemia, insulin resistance, dyslipidemia, and systemic inflammation in prediabetes. These results suggest a possible direct vascular benefit of pioglitazone [19].

A study performed by Koshimaya et al. [20] in which Pioglitazone was given for 6 months in patients with type 2 diabetes and found significantly decreased in carotid intima media thickness. This study suggests that Pioglitazone can cause inhibition of early atherosclerosis.

#### Role in Atherosclerosis and lipid profile:

- Pioglitazone is known to ameliorate accelerated atherosclerosis, probably through peroxisome proliferator activated receptor Independent and dependent mechanisms to modulate the regulatory/effector T cells imbalance. The inhibition of atherosclerosis may be via increased plasma adiponectin level and the increased expression of AdipoR1 mRNA in vessels [21].
- Pioglitazone ameliorates the hypercholesterolemia-induced rise in Plaque Matrix Metalloproteinase (MMP) and macrophage response (as demonstrated by serial optical molecular imaging) [22].
- Pioglitazone is known to significantly improve the lipid profile. Long-term pioglitazone therapy durably improves triglycerides and HDL cholesterol levels, irrespective of baseline anti-hyperglycemic therapy or statin use [23].
- Pioglitazone increases PPAR liver receptor X and ATP cassette binding transporter (ABC) A1/G1 expressions, which in turn enhance cholesterol efflux from macrophages [24].

#### Role in endothelial dysfunction

- It is known to reduce intracellular superoxide radical generation. Pioglitazone augments Flow-Mediated Dilation (FMD), increases high molecular weight adiponectin, and decreases TNF- $\alpha$  (all linked to an increased glucose disposal) [25].
- It increases the forearm blood flow response to acetylcholine, increases nitric oxide bioavailability, and decreases urinary excretion of 8-hydroxy-2'-deoxyguanosine (a critical biomarker of oxidative stress) [26].

#### Alternative methods of reducing cardiovascular risk in prediabetes

**Therapeutic Lifestyle Management:** Given its safety and the strength of evidence for its effectiveness in improving glycemia and reducing CVD risk factors, the preferred treatment approach for prediabetes is intensive lifestyle management [27]. Therapeutic lifestyle management must be discussed with all patients with prediabetes at the time of diagnosis and throughout their lifetimes. Therapeutic lifestyle management includes medical nutrition therapy (MNT; the reduction and modification of calories and saturated/hydrogenated fat intake to achieve weight loss in individuals who are overweight or obese), appropriately prescribed physical activity, and avoidance of tobacco products, adequate quantity and quality of sleep, limited alcohol consumption, and stress reduction [28].

#### Pharmacologic approaches

For patients in whom lifestyle modification fails to produce necessary improvement after 3 to 6 months, pharmacologic intervention may be appropriate. There is strong evidence from randomized, multicenter

interventional trials that the drug metformin and Acarbose reduce the progression of prediabetes to diabetes. While both agents are less effective than intensive lifestyle management, they do have relatively good safety profiles [27,28].

#### CVD prevention

Low-dose aspirin is recommended for secondary CVD prevention. For primary CVD prevention, its use may be considered for those at high risk (10-year risk >10%) [27]. Low-dose aspirin (75-162 mg daily) is recommended for all persons with prediabetes for whom there is no identified excess risk for gastrointestinal, intracranial, or other hemorrhagic condition.

#### Blood pressure management

Therapeutic recommendations for hypertension start with lifestyle modification, including the DASH diet (Dietary Approaches to Stop Hypertension), reduced salt intake, increased physical activity, and consultation with a registered dietitian [26].

Some patients with prediabetes will require medication to achieve target blood pressure. Hypertension is common among individuals with prediabetes and, given the high rates of CVD in prediabetes, should be managed as aggressively and with the same agents as overt T2DM [26]. Due to their renal and/or CVD benefits, drugs such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are preferred for patients with prediabetes. Other antihypertensive drugs such as vasodilating beta-adrenergic blockers, calcium channel blockers, diuretics, and centrally acting agents should be used as necessary. Multiple agents may be necessary to achieve blood pressure targets.

#### Dyslipidemia

Treatment targets for dyslipidemia are based on established CVD risk reduction recommendations [26].

- In persons with prediabetes and no CVD or minimal CVD risk, a LDL cholesterol goal of <100 mg/dL is the primary therapeutic target. The goal for non-HDL cholesterol is <130 mg/dL.
- The highest-risk patients are those with established CVD or  $\geq$  2 major CVD risk factors. For these patients, LDL cholesterol remains the primary target for therapy with a goal of <70 mg/dL. The non-HDL cholesterol treatment goal is <100 mg/dL.
- HDL cholesterol values >40 mg/dL in men and >50 mg/dL in women are desirable. If triglyceride concentrations are  $\geq$  200 mg/dL, non-HDL cholesterol should become a secondary target.

Therapeutic lifestyle changes are central to controlling lipid levels, but pharmacological therapy should be used to achieve established targets that cannot be achieved with therapeutic lifestyle changes alone [29]. In the absence of contraindications, statins are the treatment of choice for LDL cholesterol. Combination therapy consisting of statins plus bile acid sequestrants, niacin, and/or cholesterol absorption inhibitors should be considered in situations of inadequate goal attainment. Low HDL-C is common in prediabetes. Nicotinic acid is effective in raising HDL-C, but it increases insulin resistance and may accelerate the appearance of overt T2DM.

#### Risks and benefits of pioglitazone compare to other approaches

American Diabetes Association recommends metformin as the

first-line treatment if lifestyle changes don't work. Metformin is a cheap and available as a generic and its side effect profile is well known [30]. The reason that people go from prediabetes to diabetes is that the insulin-producing beta cells fail. By the time someone is diagnosed with prediabetes, they may have lost 70 percent to 80 percent of beta cell function. Pioglitazone improves how the body responds to insulin and protects the beta cells from failing.

Study shows that people in the pioglitazone group experienced more adverse events and gained an average of about nine pounds, and experienced more fluid retention (edema), than people taking the placebo. (The U.S. Food and Drug Administration have warned that, as with other thiazolidinediones, pioglitazone can cause fluid retention, potentially leading to or exacerbating heart failure.) [30].

But the weight gain was somewhat paradoxical because the drug causes fat deposits in superficial tissues, and moves fat out of the liver, heart and abdomen that will ultimately help progression to CVD [30]. So, when the patient is at high risk of CVD, Pioglitazone is a good choice of drug with the addition of lifestyle management.

## Conclusion

In addition to delaying of diabetes from Prediabetic condition, pioglitazone also prevents the progression of atherosclerosis in these patients, thus reducing risk of coronary artery Diseases.

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