

## ROLE OF PIOGLITAZONE ON PROGRESSION OF ATHEROSCLEROSIS IN PREDIABETES: A MINI REVIEW

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### ABSTRACT

Prediabetes is an intermediate stage between normal glycemia and clinical diabetes. Individual with prediabetes condition are more prone to diabetes and its associated cardiovascular disorder. Early intervention of prediabetes subjects reduces the development of diabetes and cardiovascular disease. Pioglitazone, a thiazolidinedione (TZD) insulin sensitizer, is known to reduce risk of atherosclerosis in prediabetic and diabetic subjects. Various preclinical and clinical studies have been shown the protective effect of Pioglitazone on atherosclerosis in prediabetic and type 2 diabetic patients. Neutralization of cardiovascular risk factor associated with insulin resistance was turn out to be more important than its effect on blood glucose in spite of its controversy of bladder cancer.

**Keywords:** Prediabetes, Pioglitazone, Atherosclerosis.

### INTRODUCTION

#### Prediabetes

Prediabetes is an intermediate stage between normal glycemia and clinical diabetes. American Diabetes Association defines prediabetes as fasting blood glucose > 100mg/dl but less than 126 mg/dl and 2h plasma glucose < 200mg/dl. According to Indian Health Services Guidelines, prediabetes is defined as fasting plasma glucose > 100 mg/dl but less than 126 mg/dl. [1, 2]

#### Epidemiology

According to Indian Diabetic Federation, India has highest number of diabetic patients in the world. Approx 50 million Indian are affecting by diabetes per year. An ICMR-INDIAB study revealed that an average of 11 % adult (Age 20 or more) has prediabetes in India. Prevalence of prediabetes was found more in urban region (13.2 %) than rural region (8.5%). [3]

#### Prediabetes and Atherosclerosis

Pre-diabetes is a common disorder in most populations. [4-7] Individual with prediabetes condition are more prone to diabetes and its associated cardiovascular disorder. Large numbers of studies have demonstrated that diabetes is a risk factor for cardiovascular disorder. Diabetic patients are associated with 2-4 fold higher risk for developing cardiovascular disease. A linear relationship between blood glucose and cardiovascular disease has been established by various studies. [8-10] Impaired fasting glucose and impaired glucose tolerance are associated with increased risk for CVD. Some studies suggest that risk of CVD developed in those subject with IFG and IGT who progress to diabetes. Diagnosis of prediabetes identify subject at high risk for progression of diabetes and CVD. Early intervention of prediabetes subjects reduces the development of diabetes and CVD. [11-15] Macrovascular complication manifest atherosclerosis and medial calcification. Atherosclerosis frequently accompanies with the development of diabetes. [16]

Life style modification and various hypoglycemic medications have effectively reduced the progression of diabetes in subjects with prediabetes. Few studies reported these hypoglycemic medications can reduce the progression of micro & macrovascular CVD in prediabetes. [17-19]

For many years it was hypothesized that thiazolidinediones (TZDs) might improve clinical cardiovascular (CV) outcomes based on their

insulin sensitizing mechanism of action, favorable metabolic profiles, impact on multiple CV biomarkers and observations in animal studies. [20-23]

#### Pioglitazone

Pioglitazone, a thiazolidinedione (TZD) insulin sensitizer, is a peroxisome proliferator activated receptor gamma (PPAR- $\gamma$ ) agonist. It increases insulin sensitivity by regulating the expression of a variety of genes involved in carbohydrate and lipid metabolism, increases GLUT-4 and glucokinase activity, decreases phosphoenol pyruvate carboxykinase (PEPCK) expression, and decreases production by fat cell of several mediators that may cause insulin resistance, such as tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ) and resistin. [24,25] The prediabetic treatment with pioglitazone, despite significant weight gain, completely prevents the development of diabetes and enhances  $\beta$  cell function with preservation of islet cell changes in rats. [26]

#### Role of Pioglitazone in atherosclerosis

Pioglitazone is known to reduce risk of atherosclerosis in prediabetic and diabetic subjects. Best studies on Pioglitazone of all glucose lowering therapies in terms of cardiovascular outcomes are PERISCOPE, PROactive and CHICAGO.

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 15-45mg/day significantly slowed the progression of atherosclerosis compared with glimepiride 1-4mg/day over 18 months. [27] PROactive was a prospective, multicenter, randomized double blind placebo controlled trial in which effect of Pioglitazone on macrovascular complication in patient with type 2 diabetes was evaluated. Over the three years of study period Pioglitazone was found statistically beneficial compared to placebo. [28] In Carotid intima-media thickness in Atherosclerosis using pioglitazone (CHICAGO) study, Pioglitazone 15-45mg/day was compared with glimepiride 1-4mg/day over 18 months in 462 patients of type 2 diabetes. Pioglitazone significantly slowed the progression of carotid intima media thickness (CIMT), a validated measure of atherosclerosis progression. [27,29, 30]

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

atherosclerosis. [31] A randomized open label study was conducted in Japan to investigate the protective effect of Pioglitazone on progression of carotid intima media thickness (CIMT) in type 2 diabetic patients and found that Pioglitazone may inhibit the progression of atherosclerosis. [32]

Beside above mentioned studies many more studies have been reported on the cardio protective effect of Pioglitazone in diabetic and prediabetic subjects.

#### MECHANISM

Various preclinical and clinical studies have been shown the protective effect of Pioglitazone on atherosclerosis in prediabetic and type 2 diabetic patients. Protective effect of Pioglitazone on progression of atherosclerosis is may be due to following reasons :

- Pioglitazone improves insulin sensitivity and hyperinsulinemia. Insulin insensitivity is known to be associated with accelerated atherosclerosis. [33]
- Antiatherogenic effect of HDL cholesterol have been discussed in various studies. Increase in HDL cholesterol level by Pioglitazone may inhibit the progression of atherosclerosis. [34-37]
- Inflammation is known to be initiated and progress atherosclerosis. [38] Pioglitazone appears to have a direct influence on inflammatory process I vasculature which include inhibition of inflammatory cell infiltration [39], inhibition of endothelial inflammation, monocyte adhesion etc.
- Pioglitazone is known to reduce liver fat and marker of fatty liver disease in type 2 diabetic patients and fatty liver disease is strongly associated with early carotid atherosclerosis. [40-44]

#### CONCLUSION

Pioglitazone is insulin sensitizer which improves and maintain long term glycemic control along with its favorable cardiovascular effect especially macrovascular complications. Neutralization of cardiovascular risk factor associated with insulin resistance was turn out to be more important than its effect on blood glucose in spite of its controversy of bladder cancer.

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