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**REVIEW ARTICLE**

# Evaluation of Mechanisms and Therapeutic Opportunities of Thiazolidinediones in Insulin Sensitization

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**Abstract:** Thiazolidinediones (TZDs) are a group of insulin-sensitizing drugs that have primary application in the treatment of Type 2 Diabetes Mellitus (T2DM). By activating peroxisome proliferator-activated receptor gamma (PPARγ), TZDs increase insulin sensitivity in adipose tissue, skeletal muscle, and the liver, thereby optimizing glucose metabolism and lipid homeostasis. Their effectiveness in blood glucose control, however, is tempered by concerns about side effects such as weight gain, edema, cardiovascular risks, and increased bone fracture risk, and thus their sub-universal use. More recent studies on TZDs include the synthesis of novel derivatives with enhanced safety profiles, multi- or dual-targeting agents, and PPAR-γ-independent effects, aimed at minimizing side effects and preserving insulin-sensitizing activity. Additionally, personalized medicine strategies using genetic and biomarker-based approaches aim to optimize TZD therapy by aligning treatment with a patient's unique metabolic profile. TZDs outside diabetes also hold potential for the treatment of other diseases, such as non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome. This review generally discusses the mechanisms, clinical uses, safety issues, and future perspectives on TZD research, explaining their evolving role in metabolic disease management. Future progress is destined to enhance their therapeutic utility through novel drug design and precision medicine strategies.

**Keywords:** Thiazolidinediones, type 2 diabetes mellitus, ppar-γ, insulin sensitization, glucose metabolism, lipid homeostasis, NAFLD, metabolic syndrome, precision medicine, pharmacological advances.

## 1. INTRODUCTION

Diabetes Mellitus (DM), and specifically T2DM, is a chronic metabolic disease defined by hyperglycemia due to insulin resistance and defective insulin secretion. T2DM represents the overwhelming majority of diabetes in the world and has a substantial public health impact through its rising prevalence and with its serious complications, such as cardiovascular disease, neuropathy, nephropathy, and retinopathy [1]. The treatment of T2DM remains problematic, with lifestyle changes and traditional pharmacologic therapy often falling short of sustained glycemic control or meaningful correction of underlying insulin resistance [2, 3]. Insulin resistance (IR) is a primary pathologic characteristic of T2DM and a driving force in disease development [4]. It is characterized by a diminished ability of insulin to promote the uptake of glucose, particularly in the liver, skeletal muscle, and adipose tissue. This results in compensatory hyperinsulinemia, beta-cell dysfunction, and ultimate failure of glucose homeostasis [5,6]. Treating insulin resistance is thus important for preventing disease progression and reducing the risk of associated complications [5]. TZDs, a family of insulin-sensitizing drugs, have become an important pharmacologic strategy for increasing insulin sensitivity. TZDs work mainly by activating PPAR-γ with resultant increased glucose uptake and enhanced lipid metabolism [7]. Fear of adverse consequences, including weight gain, edema, and cardiovascular risks, even though it is quite effective at controlling blood sugar levels, has restrained its broader clinical application [8, 9]. The pathophysiology of T2DM has a number of significant factors. Insulin resistance is a condition in which the body cells resist insulin, typically associated with central obesity and elevated blood glucose levels. Pancreatic beta-cell dysfunction prevents the pancreas from secreting enough insulin to compensate for insulin resistance, influenced by genetics, long-term hyperglycemia,

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