



Oldies but Goodies: Thiazolidinedione as an Insulin Sensitizer with Cardioprotection

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Diabetes is a heterogeneous chronic disease which affects 16.7% among the Korean adult aged 30 years and older and more than half of people with diabetes (55.1%) in Korea are obese (body mass index ≥ 25.0 kg/m²) in 2020 [1] suggesting the insulin resistance as a core mechanism to develop type 2 diabetes mellitus (T2DM).

Among Korean adults with T2DM, new antidiabetic medications such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors had dramatically increased from 2002 to 2018; however, the use of insulin and thiazolidinediones (TZDs) remained low and stable from 2002 to 2018 [1].

TZDs are peroxisome proliferator-activated receptor γ (PPAR γ) agonists, which improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production in patients with T2DM [2]. They have long glycemic durability and more weight gain, more edema and less hypoglycemia than metformin or glyburide [3].

Currently, pioglitazone, now generically affordable, and lobeglitazone are available for T2DM in Korea. Lobeglitazone (Chong Kun Dang Pharmaceutical Corporation, Seoul, Korea) was a novel PPAR γ agonist, which was developed and approved in Korea in 2013. Introduction of a p-methoxyphenoxy group at the 4-position of the pyrimidine moiety, which was based on a modification of the rosiglitazone structure induces 12 times higher affinity to PPAR γ compared to rosiglitazone and pioglitazone [4] to meet the demands for a more effective

and safer TZD with lower dose.

Lobeglitazone 0.5 mg showed a favorable glycosylated hemoglobin (HbA1c) reduction (-0.44% vs. 0.16% in the placebo group, $P < 0.0001$) and safety profile over 24 weeks as a monotherapy [5]. In add-on study to metformin with lobeglitazone, it showed similar HbA1c reduction in the pioglitazone to metformin combination group [6] and non-inferior to sitagliptin add-on therapy [7]. In a Korean real-world study, lobeglitazone showed good glycemic-lowering effect, long-term durability of glycemic control and long-term safety profile with no cases of bladder cancer, one case of CHF, and 1.17% fracture rate of all patients [8].

The American Diabetes Association (ADA) 2022 guidelines [9] recommends that first-line therapy depends on comorbidities, patient-centered treatment factors and a GLP-1RA or a SGLT2 inhibitor is recommended as an appropriate initial therapy for individuals with T2DM with comorbidity such as atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD).

For those without compelling comorbidity indication, second-line options may be selected depending on if the highest priority is minimizing hypoglycemia, weight gain, or cost and access. In the current guidelines, TZDs may be considered as second-line agents if the priority is to minimize cost and access or risk of hypoglycemia. However, TZDs are the only class of glucose-lowering agents that primarily target the insulin resistance and have benefit of reducing the risk of ASCVD and improving nonalcoholic steato-hepatitis and β -cell function [10-

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12]. Considering the adverse effects as edema, HF, and weight gain, SGLT2 inhibitors or GLP-1RAs combined with TZDs could be a better option to improve insulin resistance and to target different pathophysiology thereby, minimizing the TZDs-related side effects.

The PROactive trial showed that pioglitazone decreased the 'main secondary endpoint' of all-cause mortality, non-fatal myocardial infarction, and stroke compared to placebo in 5,238 patients with T2DM with prior cardiovascular (CV) event, but there was no significant difference in the primary composite endpoint including additional acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle [10]. As for lobeglitazone, additional clinical studies are expected to provide further evidence of the beneficial CV effects of lobeglitazone because the choice within same TZDs class is to be based on whether there was proven beneficial CV outcome trial. Regarding the limitation of current ADA and Korean guidelines focusing only on the co-morbidities such as ASCVD, HF, or CKD, clinician should consider the aspect of pathophysiology of T2DM as insulin resistance together which concur with obesity when to choose the anti-diabetic agents.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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