Editorial

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Ideal Combination of Oral Hypoglycemic Agents for Patients with Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is characterized by systemic insulin resistance and increased hepatic glucose production with initial compensatory insulin secretion by pancreatic β-cells, followed by progressive failure of these cells. Beyond this traditional triad, additional factors have been recognized as contributors to the pathophysiology of T2DM: (1) increased peripheral lipolysis, (2) decreased incretin effect, (3) increased glucagon secretion from pancreatic a-cells, (4) increased glucose reabsorption threshold in the kidney, and (5) impaired appetite control due to neurotransmitter dysfunction [1]. Although recently developed drugs, especially sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA), provide cardiovascular and renal protection in addition to glycemic control effects, attempts to achieve target glycemic levels and prevent cardiovascular disease in patients with T2DM are unsatisfactory. These difficulties arise from a combination of lifestyle management challenges, medication complexities, multiple pathogenetic mechanisms that are not yet fully understood, individual differences, psychological factors, and the progressive nature of the disease.

Like the American Diabetes Association (ADA) and European Association for the Study of Diabetes recommendations, the Korean Diabetes Association recommends selecting medications based on the presence of comorbidities [2,3]. In choosing a hypoglycemic agent, the ADA recommends that the first choice for adults with T2DM who have comorbidities or are at high risk for comorbidities should be medications shown to reduce the risk of cardiovascular and kidney disease. These treatments should also assist in weight control and maintenance [4]. Therefore, SGLT2 inhibitors are generally early choices. Although the early use of GLP1-RAs is increasing, their high cost and injetable form limit their widespread use. According to the ADA's recommendations on the use of glucose-lowering medications in high-risk T2DM patients, low-dose thiazolidinedione (TZD) is recommended when blood sugar levels do not reach the target level even with the combined use of SGLT2 inhibitors and GLP1-RA. In addition, TZDs, especially pioglitazone, have been shown to improve various cardiovascular risk factors, including insulin resistance, vascular inflammation, endothelial function, high-density lipoprotein cholesterol (HDL-C) levels, and triglyceride and free fatty acid levels. TZDs have been shown to reduce the risk of stroke in patients with T2DM and impaired glucose tolerance [5]. These benefits, however, must be balanced with potential risks of fluid retention and weight gain.

In this issue of *Diabetes & Metabolism Journal*, Heo et al. [6] conducted a phase 3 clinical trial comparing the efficacy and safety of pioglitazone 15 mg with placebo as add-on therapy in patients with T2DM not adequately controlled with dapagliflozin and metformin. At week 24, there was a significant reduction in glycosylated hemoglobin (HbA1c) in the pioglitazone group compared to the placebo group. Additionally, a higher proportion of patients achieved HbA1c <7% or <6.5%. A TZD and an SGLT2 inhibitor may have synergistic effects in controlling glycemia based on the different mechanisms of action of the drugs. TZD enhances insulin sensitivity and preserves β-cell function, while SGLT2 inhibitors reduce glucose

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reabsorption in the kidneys, leading to lower blood sugar levels. Also, the addition of pioglitazone significantly improved triglyceride, HDL-C levels and the homeostatic model assessment of insulin resistance. The incidence of treatment-emergent adverse reactions was similar between the two groups, and the incidence of adverse events related to fluid retention due to pioglitazone was low. The most problematic aspects of using pioglitazone are weight gain and fluid retention, but in this study, the incidence of these side effects was reduced compared to previous reports by using this drug in combination with dapagliflozin. This is encouraging regarding the safety profile of pioglitazone.

Recently, Cho et al. [7] published a study comparing pioglitazone 15 mg and pioglitazone 30 mg with a control group in patients with T2DM who failed to reach target blood sugar levels with metformin and dapagliflozin. Their study showed a significant blood sugar lowering effect with both dosages of pioglitazone. Also, slight increases in body weight and edema suggested that pioglitazone, even at a higher dose, is generally well-tolerated when added to metformin and dapagliflozin [7]. A recently published systematic review on the effects of pioglitazone and SGLT2 inhibitors or GLP1-RAs on the outcomes of T2DM revealed that combined pioglitazone and SGLT2 inhibitor treatment for 24 to 52 weeks provided greater reductions in HbA1c, body weight, and systolic blood pressure than did monotherapy [8]. Moreover, one observational trial reported a significant reduction in heart failure risk with combined pioglitazone and SGLT2 inhibitor therapy compared to standard care [9]. Despite the many advantages of TZDs, such as blood sugar control and cardiovascular disease prevention, side effects have limited their use in clinical practice. Based on these results, a TZD and SGLT2 inhibitor combination is one of the ideal treatment options. This combination maintains the net effect of each drug and reduces the side effects of both.

Long-term effective treatment of patients with T2DM is difficult; and the social burden is high because of high mortality and morbidity due to microvascular and macrovascular complications. The goal of diabetes treatment is to maintain long-term blood sugar control by combining drugs that can correct multiple etiologies, minimize side effects, and ultimately prevent cardiovascular disease and microvascular complications. This study has had some limitations, such as only low-dose pioglitazone was tested; the study population was composed entirely of Koreans; and the observation period was only 24 weeks. Despite these limitations, the study's evidence concerning the benefits of combining metformin, SGLT2 inhibitor, and TZD, among various three-drug combination therapies, is clinically useful in the treatment of patients with T2DM. In this regard, the Heo et al. [6] study published in this issue is of considerable clinical value in the treatment of T2DM. Prospective studies which confirm the safety and effectiveness of glycemic control over a longer period of time and determine outcomes for cardiovascular and microvascular complications with a large number of participants from diverse ethnicities are expected.

CONFLICTS OF INTEREST

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

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