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Review

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Does Weight Gain Associated with Thiazolidinedione Use Negatively Affect Cardiometabolic Health?

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Thiazolidinediones (TZDs) are oral anti-diabetic drugs that are peroxisome proliferator-activated receptor gamma (PPARγ) agonists and act as insulin sensitizers. The clinical efficacy and durability of the currently available TZDs in improving glycemic control are well established. However, TZDs cause weight gain, which has been thought to be a class effect of TZDs. TZD-associated weight gain may result mainly from increased fat mass and fluid retention and may be in part congruent to the mechanism of action of TZD. Increases in fat mass are almost exclusively limited to subcutaneous fat, while there are no effects or even decreases in visceral fat. Insulin resistance and cardiovascular risk associated with fat accumulation (obesity) depend on body fat distribution, with visceral fat associated with insulin resistance and a greater degree of risk than subcutaneous fat. Therefore, despite TZD-associated weight gain, TZDs are less likely to confer an increased risk of insulin resistance and cardiovascular complications. As patients with diabetes are younger and/or more obese in Korea, TZDs may be a cost-effective treatment option, offering a unique insulin-sensitizing action and good durability for the long-term management of type 2 diabetes.

Key words: Thiazolidinediones, Weight gain, Body fat distribution

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INTRODUCTION

Thiazolidinediones (TZDs) are a class of oral antidiabetic drugs that reduce insulin resistance in peripheral tissues by activating peroxisome proliferator-activated receptor gamma (PPARγ), which is a nuclear receptor.[1,2] Two TZD-class drugs, pioglitazone and lobeglitazone, are currently available in Korea. They are also termed glitazones, referring to the use of "glitazone" as a component of their names.

The glucose-lowering effects of TZD monotherapy and combination therapy in type 2 diabetes patients are well documented in the literature.[3-7] It is widely accepted that insulin resistance is a major risk factor for the development of metabolic syndrome and cardiovascular disease. For this reason, TZDs, whose mechanism of action leads to reduced insulin resistance, have attracted the attention not only for their well-established hypoglycemic effect but also for their potentially favorable effects on metabolic syndrome and cardiovascular disease. For example, the ACT NOW study conducted in 602 patients with impaired glucose tolerance demonstrated that pioglitazone reduced the incidence of diabetes (hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.16-0.49; $P < 0.001$).[8] In the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study, which is a four-year study of 5,238 patients with type 2 diabetes and a history of macrovascular disease recruited from 19 European countries, pioglitazone was shown to have cardiovascular protective effects (HR, 0.84; 95% CI, 0.72-0.98; $P = 0.027$ for the composite endpoint of all-cause death, nonfatal myocardial infarction, and stroke).[9] In 2007, however, Nis-

sen et al.[10] reported the findings of a meta-analysis that rosiglitazone potentially increases the risk of myocardial infarction and cardiovascular mortality (myocardial infarction: odds ratio [OR], 1.43; 95% CI, 1.03-1.98; $P=0.03$; cardiovascular mortality: OR, 1.64; 95% CI, 0.98-2.74; $P=0.06$). Although numerous questions[11] were raised about the reliability of Nissen's study, rosiglitazone was withdrawn from the European market in 2010 after years of heated discussions. The United States Food and Drug Administration (FDA) restricted access to rosiglitazone in 2011, but removed its prescribing restrictions in 2013 based on a series of studies that mitigated the suspicion of the cardiovascular risks of rosiglitazone.[12] However, the use of TZDs is still encumbered with safety issues due to its possible association with increased risks of cardiovascular disease, bladder cancer, fracture, heart failure, and weight gain.

This review paper discussed the mechanism of action of TZDs on weight gain and the so-called "glitazone paradox", the phenomenon that TZD-associated weight gain improves rather than exacerbates insulin resistance.

Mechanism of action of TZD-associated weight gain

All TZD-class drugs have been associated with weight gain, with a dose-dependent relationship observed between TZD therapy and weight gain.[13] TZD-associated weight gain can thus be ascribed to a TZD class effect.[13] Previous studies have demonstrated an average weight gain of 3-4 kg over the first six months of TZD therapy and up to 5 kg over a period of 3-5 years.[9,14] However, TZD-associated weight gain is determined by multiple factors such as the baseline weight, combination medications for the treatment of diabetes, diet control, exercise compliance, and TZD dose.[13] In particular, TZDs are widely prescribed in combination therapy for diabetes, second only to metformin; in such cases, the problem of TZD-induced weight gain may be abated.[5]

TZD-induced weight gain can be explained by various mechanisms. First, the weight gain may result from increased body fat. As mentioned above, the antidiabetic effect of TZD is mediated by PPARγ. PPARγ activation leads to increased fat mass, especially subcutaneous depots.[15,16] Many of the TZD-related studies have reported concurrent findings of increased peripheral subcutaneous fat and decreased visceral fat.[17-25] These findings imply that the use of TZDs leads to fat redistribution tending towards increased subcutaneous fat and decreased visceral fat, with weight gain being attributable to the increase in subcutaneous fat. Second, weight gain can result from increased body fluid volume due to water retention. This effect can be explained by a TZD-induced increase in sodium reabsorption in the distal tubules of the kidney.[13] It is for this reason that TZDs are contraindicated in diabetic patients with New York Heart Association Class III or IV heart failure.[26] Moreover, after the use of TZDs in diabetic patients, care should be taken to check for symptoms of increased body fluid such as edema and dyspnea. Third, improved glycemic control can lead to weight gain. This is not unlike the weight gain after using sulfonylurea (SU) or insulin. The United Kingdom Prospective Diabetes Study (UKPDS) of SU and insulin and the Diabetes Control and Complication Trial (DCCT) of insulin also reported weight gains of 3-5 kg associated with glycemic control.[27] Another mechanism of action of TZDs that can lead to weight gain is enhanced appetite. An animal study reported hyperphagia and weight gain in TZD-fed rats.[28]

The glitazone paradox: the effects of TZDs on body fat distribution (depot-specific effects)

With regard to TZD-associated weight gain, it is not clear how TZD improves rather than exacerbates insulin resistance and how it can lower cardiovascular risk. To better understand the issue, it should be made clear that not all body fat is alike from the perspective of cardiovascular risk. For example, while subcutaneous fat in the hip and thigh areas is not associated with cardiovascular risk, visceral fat such as intrahepatic fat causes insulin resistance and becomes a cardiovascular risk factor.[29] As mentioned above, TZDs exert depot-specific effects on regional adiposity (Fig. 1). In other words, they induce body fat redistribution in the direction of reducing (or at least not accumulating) visceral fat and increasing subcutaneous fat. Not only *in-vitro* and animal studies with TZDs but also numerous clinical studies using imaging techniques such as computed tomography (CT), dual-energy X-ray absorptiometry (DEXA), and magnetic resonance imaging (MRI) as well as anthropometric measures such as waist-to-hip ratio for fat measurement have yielded results supporting this finding.[17-25] The results of studies on the effects of TZDs in patients with non-alcoholic fatty liver disease (NAFLD), such as decreased intrahepatic fat levels and fatty liver and liver fibrosis improvement, may be due to similar mecha-

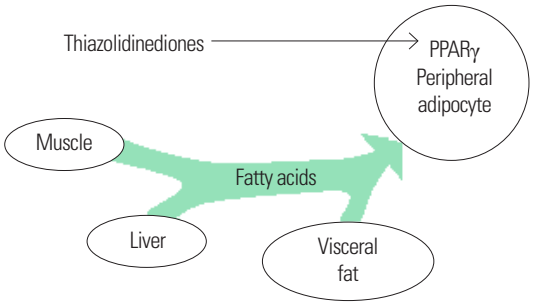

Figure 1. Depot-specific effects on regional adiposity of thiazolidinediones.

nisms.[2,30-32] Although more research is needed to reach definite conclusions, the possible mechanisms by which TZDs exert depot-specific effects are as follows. Activation of PPARγ in subcutaneous adipocytes significantly increases the uptake and esterification of fatty acids, which is stronger than the compensatory fatty acid oxidation. In contrast, activation of PPARγ in visceral adipocytes results in a negligible increase in fatty acid absorption and esterification, and increased fatty acid oxidation. Furthermore, TZDs inhibit the expression of free fatty acid and tumor necrosis factor alpha (TNF-α) and increase adiponectin expression in adipose tissues.[33]

These mechanisms may explain why the use of TZDs causes weight gain, but improves insulin resistance and does not increase cardiovascular risk. In a randomized controlled trial in 33 patients with type 2 diabetes, subcutaneous fat increased and intrahepatic fat levels decreased by 45% in the rosiglitazone-treated group compared to the levels in the control group. Along with these changes, the mean weight increased relative to the baseline in the rosiglitazone-treated group, but insulin resistance improved.[18] A post hoc analysis of the PROactive study revealed that weight gain after use of pioglitazone was associated with improved cardiovascular outcomes.[34]

CONCLUSION

TZD-induced weight gain contributes to significant improvements in insulin sensitivity, defying the common belief that the higher the weight gain, the higher the insulin resistance. This is ascribable to the depot-specific effects of TZDs on body fat distribution, with subcutaneous fat tending to increase rather than visceral fat, which is associated with increased cardiovascular risk. The recent reports of the effects of TZDs on NAFLD may be due to similar mechanisms.

TZDs have suffered a loss of reputation due to safety warnings against rosiglitazone and pioglitazone in relation to cardiovascular disease and bladder cancer, respectively. This situation is reflected in the low proportion of TZD prescriptions (6.5%) among all antidiabetic drugs as reported in the 2015 Diabetes Fact Sheet.[35] However, TZDs offer a range of advantages such as an ideal mechanism of action, efficient blood glucose control with 0.5-1.4% reduction of glycosylated hemoglobin (HbA1c) concentration, good durability, rare hypoglycemic episodes, improved metabolic syndrome, and cardiovascular disease prevention.[1,2,14] A review paper comparing the clinical effects and costs of pioglitazone estimated that its use would reduce cardiovascular, metabolic and cancer deaths by 60 per 100,000 population and increase mortality due to hip fracture by 30 deaths per 100,000 population.[1] The recent report on the anti-atherosclerosis effects of lobeglitazone also suggests its potential for reducing cardiovascular disease.[36] These results suggest the cost-effectiveness of TZDs.

The proportion of diabetes patients with obesity in Korea is steadily increasing.[37] A recent community-based study reported that this upward trend is reflected in the increasing problem of insulin resistance relative to insulin secretion.[38] Moreover, the increasing prevalence of type 2 diabetes among younger individuals[37] highlights the importance of drug durability in consideration of the long journey of diabetes treatment. For these reasons, we should reconsider the use of TZDs.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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