ROLES OF THIAZOLIDINEDIONES IN TYPE 2 DIABETES MELLITUS TREATMENT AND WEIGHT GAIN

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ABSTRACT

Type 2 diabetes mellitus is a serious public health problem in the world and its treatment is still a major therapy challenge. Thiazolidinediones (TZDs) are a class of anti-diabetic drugs that are used widely to increase insulin sensitivity by activating Peroxisome-Proliferator-Activated-Receptor-gamma (PPARγ). Activated PPARγ makes critical alterations in the transcription of genes that regulate glucose and lipid metabolism. However, TZDs have side effects, such as weight gain, edema, congestive heart failure, and bone fracture. Also, they stimulate adipogenesis and hyperphagia, and cause weight gain. In this review, we discuss the mechanism by which TZDs increase insulin sensitivity, and cause weight gain.

Keywords: Thiazolidinediones, weight gain, diabetes, insulin, PPARγ.

1. INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia over a prolonged time. It can be classified into three broad categories: type 1, type 2, and other types. Type 1 diabetes mellitus is caused by an absolute or near absolute deficiency of insulin. Type 2 diabetes mellitus is characterized by the body not responding effectively to insulin. Other types of diabetes might result from pregnancy, surgery, use of certain medicines, various illnesses, and other specific causes [1]. Among them, type 2 diabetes mellitus is the most common condition. It accounts for almost 90% of all cases of diabetes mellitus in adults worldwide [2]. It is estimated that, by 2030, the number of patients with diabetes in the world will increase by 54% [3]. It is essential to control blood glucose levels for the prevention of complications of the disease. Medications for type 2 diabetes mellitus include metformin (biguanides), sulfonylureas, acarbose, meglitinides, gliptins, and thiazolidinediones [4]. Insulin resistance is a key to the anomalies of the pathogenesis of type 2 diabetes mellitus [5]. Thiazolidinediones (TZDs) are a class of major anti-diabetic drugs that are widely used to increase insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPARγ) and ameliorate diabetic [6, 7]. However, TZDs have side effects, such as weight gain, edema, congestive heart failure, and bone fracture [8]. Here, we focus mainly on the effect of TZDs on weight gain.

2. MECHANISM, METABOLISM, AND INTERACTION OF THIAZOLIDINEDIONES

2.1. The mechanism of TZDs on type 2 diabetes mellitus

Peroxisome Proliferator-Activated Receptor gamma (PPARγ) is a key regulator of adipogenesis. PPARγ belongs to the nuclear receptor superfamily of ligand-inducible transcription factor [9, 10]. It expresses highly in white and brown adipocytes and controls the genes that involve in adipocyte differentiation, lipid metabolism, and insulin sensitivity. PPARγ has been well characterized, and used as a molecular target of many agonists for the treatment of diabetes [11].

TZDs, including troglitazone, pioglitazone, and rosiglitazone, are a group of PPARγ agonists which have been approved for clinical use in the treatment of type 2 diabetes since 1997. They exert their anti-diabetic effects by increasing insulin sensitivity via activation of PPARγ [6, 7]. There are several ways by which TZDs inhibit the levels of hyperglycaemia and hyperinsulinaemia and enhance insulin sensitivity in the liver, muscle, and adipocytes tissue. In one way, TZDs promote binding of the PPARγ-RXR complex to Peroxisome-Proliferator-Response-Elements (PPRE) in the promoter region of key target genes that are involved in glucose and lipid metabolism, and in energy balance [7, 12]. In another way, TZDs ameliorate insulin resistance by activating endocrine signaling from adipocytes to skeletal muscle cells via activation of PPARγ. Furthermore, TZDs mediate glucose homeostasis by the reduction of FFA levels [13-15]. It has been suggested that TZDs also protect pancreatic beta cell function [15, 16]. In addition, TZDs suppress or neutralize the action of adipocyte-derived tumor necrosis factor-α (TNF-α), which is expressed highly in obesity and insulin resistance, and is able to induce a variety of catabolic effects [17-19]. Moreover, TZDs have been found to enhance insulin signaling by stimulating tyrosine phosphorylation of insulin receptor, and insulin receptor substrate 1 (IRS-1), and inhibiting the MAPK pathway [19, 20]. Recently, it has been reported that TZDs increase adiponectin secretion in adipose tissue, inhibit lipolysis, and release of transforming growth factor-β (TGF-β) [6, 21]. Furthermore, TZDs block the Ser273 phosphorylation of PPARγ by cyclin-dependent kinase (Cdk) 5, and prevent the development of insulin resistance [22]. Taken together, the data suggest that TZDs have beneficial effects on insulin sensitivity, and insulin resistance via the activation of the PPARγ.

2.2. Metabolic pathway and drug interactions of TZDs

Thiazolidinediones are metabolized in the liver by multiple cytochrome P-450 (CYP) isoenzymes, mainly by CYP2C8, CYP3A4 and CYP2C9. Pioglitazone is metabolized in vitro principally by CYP2C8, and to a lesser extent by CYP3A4. Biotransformation rosiglitazone is catalyzed by CYP2C9 and CYP2C8 [23, 24]. Other CYP isoforms seem to play a minor role in the biotransformation of pioglitazone. TZDs are generally used in combination with other glucose-lowering agents. Most frequently with metformin, possibly with sulfonylureas or insulinotropic agonists. Less frequently with α-glucosidase inhibitors, or various compounds aimed at preventing or treating cardiovascular diseases, especially lipid-lowering agents. TZDs are exposed to numerous drug-drug interactions, because TZDs, and drugs co-administered with them are metabolized via cytochrome P450 (CYP). In particular, we note the greater than 50% decrease in rosiglitazone and pioglitazone plasma concentrations by rifampicin, and the greater than 2-fold increase by gemfibrozil. TZDs can be taken without regard to meals, because the small differences in the absorption rate of TZDs with or without food are clinically irrelevant [24].

2.3. TZDs exert weight gain

In clinical trials, treatment with TZDs were associated with weight gain [25, 26]. Compared with the placebo group, the body weight of patients treated with pioglitazone was significantly increased after 12 weeks (1.68 ± 2.46 kg, p = 0.04) and after 24 weeks (3.88 ± 3.11 kg). In contrast, body weight in the placebo group decreased by 0.79 ± 3.336 kg, although the decrease was insignificant. Body weight continued to rise throughout the trial in the pioglitazone-treated group, and had not reached a plateau by the end of the study [27].

The recent studies on Wistar rats have demonstrated the effectiveness of pioglitazone and rosiglitazone in preventing weight loss and increasing survival in cancer cachexia [28, 29]. The rats were randomly assigned to two experimental groups: TC (tumor + saline-control) and TP5 (tumor + pioglitazone 5 mg). Body weight, food ingestion, and tumor growth were measured at baseline, and after removal of a tumor at days 7, 14, and 26. It was also enhanced by 40.7% and 56.3% body mass preservation on day 14 and 26, respectively, compared with the TC group. The pioglitazone treatment also reduced the final tumor mass (53.4%, $p < 0.05$) and anorexia, compared with the TC group during late-stage cachexia [28]. Rosiglitazone reduced average daily weight loss (2.33 g/day rosiglitazone versus 3.93 g/day placebo; $p < 0.05$) as a result of both fat and lean mass preservation. It decelerated white and brown tissue wasting. But had no effect on skeletal muscle mass and heart mass [29]. TZDs increase body weight largely due to increased fat pad mass, and alterations in adipocyte size and numbers. The zucker diabetic fatty rats were administered pioglitazone orally (20 mg/kg/day) for 4 weeks. Then, consumption and body weight were significantly greater than that of the control group [30].

Several studies compared the side effect on weight gain of TZDs, and sulfonylurea when combined with metformin [31-34]. In a randomized, double-blind study, Matthews compared the efficacy and safety of metformin and pioglitazone, with the established combination of metformin and gliclazide. Patients received either metformin at pre-study dose plus pioglitazone (15-45 mg daily), or metformin at pre-study dose plus gliclazide (80-320 mg daily). The body weight increased 1.5 kg in the metformin plus pioglitazone group, and 1.4 kg in the metformin plus gliclazide group. Both are not statistically significant compared to the baseline. By week 52, body weight in both groups appeared to have stabilized. The mean weight gain over 52 weeks was similar in both groups and plateaued by the end of the study [31]. Also, Charbonnel *et al*. and Seufert *et al*. compared adding pioglitazone (15-45 mg daily) with adding gliclazide (80-320 mg daily) to metformin (850-2550 mg daily) [32, 33]. Charbonnel *et al*. found weight increases of 2.5 kg in the pioglitazone, and 1.2 kg in the gliclazide add-on groups, but both are not statistically significant [32]. The study of Seufert *et al*. conducted for 2 years also had similar results. An increase of 2.3 kg in the mean weight when pioglitazone was added to metformin ($N = 317$) and 1.1 kg when gliclazide was added to metformin ($N = 313$) [33]. Also, Ceriello *et al*. compared the effect of pioglitazone and gliclazide on the weight gain. Then, there was no significant difference between the pioglitazone group and the gliclazide group. Similarly, no significant difference in weight gain between pioglitazone and gliciazide was observed when these two were used singularly or in cotherapy with metformin [34]. TZDs may cause more weight gain than sulfonylurea. But the weight gains caused by pioglitazone or gliclazide are not significantly different. The weight gain level is not similar in every case with TZDs treatment.

Unlike the metformin treatment, the thiazolidinediones treatment causes weight gain in both mono and combination therapy of type 2 diabetes mellitus. As reported by Ceriello *et al.*, in the pioglitazone versus metformin study, the mean weight change in the pioglitazone group (2.02 kg) was higher than in the metformin group (-2.6 kg) [34]. In the pioglitazone

plus sulfonylurea versus metformin plus sulfonylurea study, the mean weight change in the pioglitazone plus sulfonylurea group (2.6 kg) from baseline was different from that of the metformin plus sulfonylurea group (-1.5 kg) [34]. In a study conducted by Seufert *et al*., the results showed similar trend that the weight increased by 3.2 kg in the combination of pioglitazone with sulfonylurea (N = 319) and decreased by 1.7 kg in the metformin added to sulfonylurea group (N = 320) [33]. The above data suggest that metformin causes weight loss in many patients while pioglitazone exerts weight gain in most of the cases. Thus, the combination of pioglitazone with metformin may help to improve glycemic control and reduce the risks of changes in body weight.

2.4. The mechanism of TZDs on weight gain

Despite their potential to cause weight gain, TZDs improve glycemic control, and insulin sensitivity in type 2 diabetes mellitus patients [35]. Many studies attempt to clarify the mechanisms behind the paradoxical effect of TZDs: Improving insulin sensitivity while causing weight gain. TZDs improve insulin sensitivity and cause weight gain by increasing circulating adiponectin levels. Two distinct receptors, AdipoR1 and AdipoR2, are regulated by adiponectin concentrate. Pioglitazone increases insulin sensitivity via upregulation of AdipoR2-mediated AMPK-activated protein kinase phosphorylation in 3T3-L1 adipocytes. TZDs were found to directly bind and activate PPAR-γ. One activated PPAR-γ, adiponectin was induced in expression leading to inducing the expression of AdipoR2 [36]. AMPK, a key molecule in the adipoR-mediated signaling pathway, was activated under pioglitazone treatment. In 3T3-L1 adipocytes, pioglitazone increases insulin sensitivity by promoting GLUT4 expression via AdipoR2-mediated AMPK-activated protein kinase phosphorylation [13, 36].

TZDs therapy has beneficial effects on glycemic control and insulin sensitivity. But it causes a weight gain side effect. Several studies showed that possible causes of weight gain with TZDs treatment are increased adipogenesis and fluid retention [35, 37]. Pioglitazone treatment leads to increasing circulating adiponectin, that reaches the hypothalamus in the central nervous system. Possibly, the increased adiponectin in the hypothalamus results in increased phosphorylation of hypothalamic AMPK via adipoR1 [38], this may lead to increased food intake, and eventually contributes to the increase in body weight with pioglitazone treatment. Conversely, inhibition of AMPK phosphorylation or AdipoR1 expression in the hypothalamus may cause the reversal of the obese phenotype shown by the rat group treated only with pioglitazone [38, 39].

Also, fluid retention associated with TZDs treatment can contribute to weight gain. Several studies showed that TZDs can cause early weight gain by enhancing tubular sodium and water reabsorption in the kidney, and increasing water retention in the body [40, 41]. It has been also suggested that TZDs stimulate Na(+) reabsorption in the collecting duct through activating epithelial Na(+) channel (ENaC) [40-42]. Furthermore, TZDs stimulate non-ENaC sodium channel or inhibition of chloride secretion to the tubular lumen. TZDs may increase sodium reabsorption in the proximal tubule by enhancing apical Na(+)/H(+) exchanger-3, basolateral Na(+)-HCO3 (-) cotransporter, and Na(+),K(+)-ATPase. In addition, TZDs-induced sodium retention through PPAR γ -induced nongenomic transactivation of the epidermal growth factor receptor and downstream extracellular signal-regulated kinases (ERK) [40].

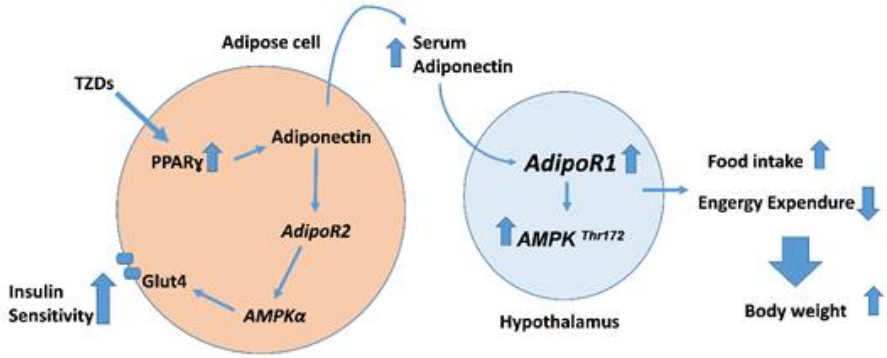

Figure 1. Schematic of the hypothetical mechanism in weight gain and insulin sensitivity in TZDs treatment. TZDs promote insulin sensitivity by AdipoR2-mediated AMPK phosphorylation in adipocytes. Circulating adiponectin stimulated by TZDs led to increasing phosphorylation of AMPK in the hypothalamus. This increased AdipoR1 expression and caused the reversal of weight gain.

3. CONCLUSIONS

We have overviewed TZDs and their side effects with a focus on the mechanisms of weight gain. The chain PPARγ/Adiponectin/AdipoR1/AMPK partially responsible for the weight gain in TZDs treatment was summarized in Figure 1. Another chain, PPARγ/Adiponectin/AdipoR2/AMPK, is the response to TZDs treatment to improve insulin sensitivity in adipocytes. Combining treatment of TZDs with metformin may reduce the risks of changes in body weight and control glycemic in diabetes mellitus patients. TZDs may cause weight gain in treatment now, but the development of next generation of TZDs or PPARγ agonists is expected to have fewer side effects.

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TÓM TẮT

VAI TRÒ CỦA THIAZOLIDINEDIONE
TRONG ĐIỀU TRỊ ĐÁI THÁO ĐƯỜNG TUÝP 2 VÀ HIỆN TƯỢNG TĂNG CÂN

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Đái tháo đường tuýp 2 là một bệnh lý nghiêm trọng đối với sức khỏe cộng đồng. Điều trị đái tháo đường tuýp 2 vẫn là một thách thức lớn. Thiazolidinediones (TZDs) là một trong những nhóm thuốc điều trị đái tháo đường được sử dụng rộng rãi để cải thiện tình trạng kháng insulin bằng cách kích hoạt thụ thể PPARγ, dẫn đến những thay đổi quan trọng trong quá trình phiên mã của một số gen điều hòa chuyển hóa glucose và chất béo. Tuy nhiên, bên cạnh vai trò hữu ích trong điều trị đái tháo đường tuýp 2, các TZD cũng gây ra những tác dụng không mong muốn như: tăng cân, phù, suy tim sung huyết và gãy xương. Các thuốc TZD gây tăng trọng lượng cơ thể vì chúng kích thích quá trình tạo các tế bào mô mỡ và tăng nhu cầu thức ăn. Trong bài báo này, chúng tôi sẽ giải thích về cơ chế làm tăng độ nhạy cảm insulin và tác dụng phụ gây tăng cân của các thuốc TZD trong điều trị đái tháo đường tuýp 2.

Từ khóa: Thiazolidinediones, tăng cân, đái tháo đường, insulin, PPARγ.