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EDITORIAL

Clinical effects of antidiabetic drugs on psoriasis: The perspective of evidence-based medicine

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Abstract

Psoriasis and diabetes shared common underlying pathophysiological mechanisms. Emerging data suggested that antidiabetic medications may improve the psoriasis severity in patients with diabetes mellitus. Several hypoglycemic agents including thiazolidinediones, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and biguanides have been reported to make a remarkable reduction in the Psoriasis Area and Severity Index score from baseline. This antipsoriatic effect could be mediated not only by the glucose-lowering action of these agents but also *via* inhibition of keratinocyte over proliferation, increase expression of differentiation markers, suppression the immune inflammatory pathway, and blocking the calcium channels and mitogen-activated protein kinase signaling pathways. On the other hand, there was no significant increase in adverse reactions associated with the treatment of pioglitazone or metformin. However, previous studies often had the relatively short duration of the trials, and did not have enough power to assess recurrence of psoriasis. Potential bias in the study and missing data could undermine the reliability of the results. Therefore, the appropriately randomized controlled studies with large sample sizes and long-term durations in various psoriasis patients are warranted for further support.

Key Words: Psoriasis; Hypoglycemic agents; Thiazolidinediones; Glucagon-like peptide-1 receptor agonists; Dipeptidyl peptidase-4 inhibitors; Biguanides; Antipsoriatic effect;

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Evidence-based medicine

Core Tip: Several hypoglycemic agents including thiazolidinediones, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and biguanides have been reported to make a remarkable reduction in the Psoriasis Area and Severity Index score from baseline. The antipsoriatic effect could be mediated not only by the glucose-lowering action of these agents but also *via* inhibition of keratinocyte overproliferation, increase expression of differentiation markers, suppression the immune inflammatory pathway, and blocking the calcium channels and mitogen-activated protein kinase signaling pathways. Potential bias in the study and missing data could undermine the reliability of the results. Therefore, the appropriately randomized controlled studies with large sample sizes and long-term durations in various psoriasis patients are warranted for further support.

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INTRODUCTION

Psoriasis is a relatively common disorder, though the prevalence varies among populations. An estimated 29.5 million adults worldwide suffered from psoriasis in 2017, equivalent to a lifetime prevalence of 0.59% (95% uncertainty interval 0.19% to 1.66%) diagnosed by physicians in the global adult population. The estimated prevalence of psoriasis was highest in high income countries such as Australasia (1.58%) and Western Europe (1.52%), and lowest in East Asia (0.11%). However, the highest number of adult populations with psoriasis lived in the United States, India, and China[1].

Psoriasis is an immune-mediated chronic inflammatory skin disease. The patients' quality of life was seriously affected by a variety of clinical manifestations including characteristic scaly, and itchy and reddish lesions of skin. Furthermore, psoriasis has also been identified as a systemic disorder that involves more than skin. Diabetes mellitus is one of common extra cutaneous disorders in individuals with psoriasis. Growing evidence supports that psoriasis and diabetes are comorbidities of each other and share common underlying pathophysiological mechanisms[2]. Type 1 diabetes is characterized by autoimmune destruction of the pancreatic beta cells. Type 2 diabetes is characterized by insulin resistance and a relative lack of insulin secretion from the beta cells. An altered adipose tissue microenvironment in obesity is responsible for insulin resistance and low-grade inflammation at either local or systemic level (*e.g.*, skin). That said, diabetes can relate with a wide spectrum of skin conditions, including but not limited to psoriasis, due to hyperglycemia-induced microvascular damage, altered immune functions, infections, genetic predisposition, *etc.* Inflammation can modulate the process of insulin resistance and beta cell damage, and play a critical role in the pathogenesis of type 1 and type 2 diabetes. Thus, antidiabetic drugs with anti-inflammatory properties may also have positive effects on treatment of psoriasis, which is the skin manifestation of an inflammatory response. Emerging data suggested that patients with psoriasis may also benefit significantly from antidiabetic medications due to the common immunological pathway and inflammatory signaling pathway[3-6].

As we know, psoriasis has no cure, so the main purpose of treatment is to control the disease rather than cure. There are many topical and systematic therapies for treatment of psoriatic skin manifestations. However, most of these treatments are expensive, unavailable or immune suppressive. Accumulating data support that hypoglycemic agents including thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and

biguanides, take beneficial effects on the treatment of psoriasis.

ANTIDIABETIC DRUGS ON PSORIASIS

TZDs

The peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist TZDs, like pioglitazone, are insulin sensitizers widely used for treatment of diabetes. In recent years, several double-blinded randomized controlled trial (RCT)s showed that TZDs are anti-inflammatory drugs with ameliorating effects on psoriasis[7-11]. In two meta-analysis of 6 RCTs in patients with psoriasis vulgaris, treatment with pioglitazone made a significant 75% or greater improvement in the Psoriasis Area and Severity Index score from baseline (PASI 75) response[5] and a remarkable reduction in the PASI score from baseline (weighted mean difference: 2.68)[6]; again, there was no increase in side effects associated with pioglitazone treatment such as elevated liver enzymes, weight gain, fatigue, and nausea. That suggested pioglitazone is an effective and safe drug in the treatment of patients with plaque psoriasis. We recently conducted a systemic review and meta-analysis including 10 randomized controlled studies to investigate a more comprehensive result among several kinds of antidiabetic drugs including GLP-1, analog TZDs and metformin for treatment of psoriasis[4]. Our study demonstrated that there was a significant increase in PASI 75 [risk difference = 0.42; 95%confidence interval (CI): 0.18-0.65] or a decrease in PASI score (mean difference = -3.82; 95%CI: -6.05 to -1.59) in psoriasis patients receiving pioglitazone than those intake placebo. But there was no significant effect for rosiglitazone and metformin. As for the different doses of pioglitazone in psoriasis, the daily 30 mg dose was significantly related to a greater therapeutic effect than that of the 15 mg dose per day with no significant change in the frequency of adverse reactions. This means that the amelioration from pioglitazone in psoriasis is dose-dependent[4,12].

There are several pathophysiological mechanisms underlying the antipsoriatic effects of TZDs. First, as PPARγ-selective ligands, TZDs can suppress human keratinocyte over proliferation, increase the expression of epithetlin and intermediate filament related proteins, and then promote skin keratinocytes differentiation[13]. Second, TZDs may be beneficial to psoriasis by reducing the inflammatory response of psoriasis through PPAR-γ. In psoriatic patients, pioglitazone can reduce inflammatory cell infiltration into the skin and reduce the expression of inflammatory cytokines such as C-reactive protein, tumor necrosis factor (TNF) -α and interleukin (IL) 2, and thus inhibit the local immune inflammatory response[14]. Additionally, TZDs could intensify the histology of psoriatic skin *via* interfering the calcium channels and mitogen-activated protein kinase signaling pathways, but not related to the PPAR effect.

GLP-1-based therapies

GLP-1-based therapies such as GLP-1 receptor agonists and inhibitors of DPP-4 are effective hypoglycemic agents. GLP-1 is an incretin hormone that regulates glucose metabolism. DPP-4 is a GLP-1 degrading enzyme and exerts its physiological functions particular in lowering blood glucose *via* the action of GLP-1. Previous study indicated the mechanisms of GLP-1 receptor agonists that determine their antihyperglycemic and anti-inflammatory effects[15]. DPP-4 inhibitors can hinder the DDP-4 to attenuate the degradation of endogenous GLP-1 and prolong the action of GLP-1. A growing body of data shows that GLP-1-based therapies had anti-inflammatory effects in several organs, tissues, and cells through reducing inflammatory cytokine production and immunocyte infiltration. Previous studies on the pathogenesis of psoriasis have focused on keratinocyte excess proliferation, but recently immune system dysfunction has been identified as a critical event. GLP-1 analogues have been reported to alleviate the clinical and histopathology severity of psoriasis through interacting with innate immune system, particularly with invariant natural killer T cells[16-18].

A few case reports showed an interest in using GLP-1 RAs as a potentially option in treatment of psoriasis[18-20]. In a prospective case-series study, seven psoriatic patients with type 2 diabetes following 16–20 wk of GLP-1 RA therapy, alleviated their PASI, and reduced dermal γδT-cell counts, and decreased IL-17 expression levels[21]. Such positive effects on psoriasis severity scores was also observed in other prospective case studies of patients receiving GLP-1 RAs for shorter periods[22,23], but the finding was not confirmed in subjects without diabetes[24]. A RCT of 25 patients with psoriasis and type 2 diabetes showed liraglutide treatment for 12 wk led

to a reduction in the PASI score and the relative expression levels of inflammatory cytokines such as IL-23, IL-17, and TNF-α in the damaged skin tissues[17]. However, current studies were small sample size or poorly controlled or short-term follow-up, large-scale multi-center randomized controlled trials with a long duration follow-up are still needed for further verification.

Biguanides

Metformin, a synthetic biguanide, is one of the most popular oral glucose-lowering medications approved for treating type 2 diabetes. Metformin has insulin-sensitizing effect, anti-inflammatory effects and proliferation inhibition in keratinocytes by acting adenosine monophosphate-activated protein kinase. Similar to other antidiabetic drugs, metformin use was also found to decrease the risk of psoriasis in a large case-control cohort study[25]. Clinical findings demonstrated that metformin can significantly improve psoriasis severity by modulating the immune response[14]. A 17-year population-based real-world cohort study focused on the safety of metformin in psoriatic patients with type 2diabetes and found that metformin did not lead to increased mortality, severe psoriasis, and hospitalizations related to psoriasis. Further dose-response analysis confirmed that metformin is safe for psoriasis patients with diabetes[26]. However, there was only one RCT available for metformin as a potential option in the treatment of psoriasis patients with metabolic syndrome[11,27]. And the efficacy and safety of metformin in other psoriasis patients have not been determined. Further research in various psoriasis patients is clearly warranted to confirm the preliminary findings.

CONCLUSION

In conclusion, the current evidence demonstrates that pioglitazone but not rosiglitazone and metformin is effective in treating plaque psoriasis in diabetic patients. On the other hand, the antidiabetic agents do not appear to increase the incidence of adverse effects. However, the relatively short duration of the trials and no enough power to assess recurrence of psoriasis. Due to some biases such as loss to follow-up were observed in previous cohort studies, more RCTs in psoriasis patients with or without diabetes mellitus with a large sample and long observation time are needed for further support.

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