ORIGINAL ARTICLE

Association between antidiabetic drugs and psoriasis risk in diabetic patients: Results from a nationwide nested case-control study in Taiwan

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Background: The risk of psoriasis in diabetic patients has rarely been explored.

Objectives: We sought to investigate the association between antidiabetic therapies and psoriasis.

Methods: The incidence of psoriasis was compared between a representative diabetic cohort and a matched nondiabetic cohort. We next conducted a nationwide cohort study with 1,659,727 diabetic patients using the National Health Insurance Research Database of Taiwan 1997 through 2011. Multivariate conditional logistic regression was used for nested case-control analyses.

Results: Incidence rates of psoriasis among diabetic patients and nondiabetic matched control subjects were 70.2 (95% confidence interval [CI] 59.5-80.9) and 42.3 (95% CI 39.5-45.5) per 100,000 person-years, respectively ($P < .0001$). Frequent insulin use was associated with higher risk of incident psoriasis (adjusted odds ratio 1.29, 95% CI 1.18-1.42) after adjusting for comorbidities, disease duration, and number of hospital visits. Among diabetic patients without history of insulin use, frequent use of thiazolidinedione was associated with lower risk of psoriasis (adjusted odds ratio 0.87, 95% CI 0.77-0.99).

Limitations: The National Health Insurance Research Database did not contain information regarding disease severity, diet, body mass index, lifestyle, or family history.

Conclusion: Among diabetic patients, regular insulin use is associated with psoriasis development. Frequent use of thiazolidinedione may be associated with modest reduction in psoriasis risk. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.08.042.)

Key words: diabetes mellitus; insulin; metformin; psoriasis; thiazolidinedione.

Meta-analyses and population-based cohort studies have demonstrated that psoriasis, especially severe disease, is associated with increased risk of new-onset diabetes.[1-3] Although the exact mechanism of the relationship between psoriasis and metabolic syndrome is complex, chronic inflammation in obesity appears to be a central component of these diseases.[4-7]

Metformin, a biguanide derivate, is the most widely prescribed drug for obese type 2 diabetes.

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It decreases the hepatic glucose output and acts as an insulin sensitizer, increasing glucose use by muscle and adipocytes.[8,9] Metformin activates adenosine 5′ monophosphate–activated protein kinase, which regulates cell functions such as cell proliferation, apoptosis, inflammation, and immune responses.[10]

Thiazolidinediones (TZD) are also commonly used to treat diabetes and have antiproliferative[11] and anti-inflammatory[12] effects on human cells via activation of nuclear peroxisome proliferator-activated receptor-γ.[13] Low proliferator-activated receptor-γ expression has been reported to be associated with psoriasis, especially among those with cardiovascular risk factors, metabolic syndrome, and extensive skin involvement.[14]

CAPSULE SUMMARY

- Mechanisms underlying the association between diabetes and psoriasis are complex.
- The current study demonstrated that severe diabetes is associated with an increased incidence of psoriasis.
- Frequent use of thiazolidinediones is associated with a modest reduction in psoriasis risk.

Early case reports have pointed to an association between oral hypoglycemic agents (OHAs) and psoriasis development.[15,16] However, a recent observational study[17] and meta-analyses[18-20] have suggested that TZD and metformin are associated with beneficial effects such as prevention of psoriasis or reduction in psoriasis severity. The aims of this study were to investigate the risk of incident psoriasis among diabetic patients and the effects of long-term antidiabetic drugs on the risk of psoriasis, using data from National Health Insurance claims published by the National Health Research Institute.

METHODS

Data sources

The National Health Insurance Research Database (NHIRD) has been used extensively in many epidemiologic studies in Taiwan.[21-24] It consists of detailed health care data from more than 25 million enrollees, representing more than 99% of Taiwan's entire population. The diagnostic codes are in the format of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). Personal information including body weight, height, family history, laboratory examination results, lifestyle, and habits, such as smoking and alcohol use, was not available from the NHIRD.

Longitudinal Health Insurance Dataset 2000

To compare the incidence rates of psoriasis between diabetic patients and nondiabetic general population, 2 age- and gender-matched groups of diabetic and reference subjects without history of psoriasis were randomly selected from the Longitudinal Health Insurance Dataset (LHID) 2000, a subset of the NHIRD. The LHID 2000 contains the entire original claims data from 1,000,000 individuals randomly sampled from the Registry of the NHIRD between 1996 and 2000. There were no significant differences in age or gender distributions between the LHID 2000 and original NHIRD groups.[25] All sampled individuals were followed up until the end of 2011.

Diabetic patients were defined as patients given a diagnosis of diabetes mellitus (*ICD-9-CM* code 250) who had received antidiabetic drugs for at least 90 days. Reference subjects were defined as those without diabetes and without history of antidiabetic drug use. Subjects with conflicting gender or uncertain birth date were not included. Information regarding medications was retrieved from the pharmacy prescription database. Reliability of the retrieved information was verified independently by 2 statisticians.

Nationwide diabetic cohort

All patients with a primary first-time diagnosis of diabetes mellitus who had received antidiabetic drugs for at least 90 days were identified (N = 1,727,289) from the NHIRD during the period 1997 through 2011. Patients with history of psoriasis or psoriatic arthritis (*ICD-9-CM* codes: 696.0, 696.1, 696.8) or who had received antipsoriatic treatment including phototherapy before the index date were excluded (N = 67,562). Finally, a total of 1,659,727 patients were included in the nationwide diabetic cohort.

Antidiabetic drugs included metformin, TZD, insulin, and other OHAs such as derivatives of sulfonylurea, meglitinide, α-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists. All sampled individuals were followed up between January 1, 1997, and December 31, 2011. This study was approved by the ethics review board of Taichung Veterans General Hospital, Taiwan.

Nested case-control study

To investigate the association between antidiabetic drug exposure patterns and risk of psoriasis, we conducted nested case-control analysis within