Increased risk of diabetes mellitus in relation to the severity of psoriasis, concomitant medication, and comorbidity: A nationwide population-based cohort study

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Background: The association between psoriasis and diabetes mellitus (DM) has been explored previously. However, no studies have been reported regarding the severity of psoriasis, comorbidities, and concomitant medications on the risks of DM in patients with psoriasis.

Objective: We sought to evaluate the impact of the severity of psoriasis, comorbidities, and concomitant medications on the risk of type 2 DM in patients with psoriasis.

Methods: We conducted a cohort study with 14,158 adults with psoriasis and adults without psoriasis using data from the Taiwan National Health Insurance Research Database. Cox regression models using time-varying covariates were used.

Results: After the comorbidities and concomitant medications were adjusted for, psoriasis was found to be independently associated with an increased risk of DM (severe: hazard ratio, 2.06 [95% confidence interval, 1.58-2.68] vs mild: hazard ratio, 1.28 [95% confidence interval, 1.05-1.55]). Other independent risk factors included age, Cushing disease, and the increased cumulative doses of the thiazide and methotrexate.

Limitation: The National Health Insurance Research Database did not have information regarding the Psoriasis Area and Severity Index, diet, obesity, body mass index, exercise status, and family history of diabetes.

Conclusion: Patients with psoriasis have a higher risk of developing DM. The risks vary depending on the severity of psoriasis, comorbidities, and concomitant medications. (J Am Acad Dermatol 2014;70:691-8.)

Key words: diabetes mellitus; methotrexate; National Health Insurance Research Database; psoriasis; severity; thiazide.

Psoriasis is a chronic immune-mediated inflammatory disease of the skin with a worldwide prevalence of 0.5% to 5.5%.[1] Approximately 2.6% to 13.6% of patients have extensive skin involvement or require systemic therapy.[2-4] A broad-ranging and increasing amount of literature has shown that psoriasis is associated with various conditions characterized by chronic inflammation, including hypertension,[5] myocardial infarction,[6] stroke,[7] metabolic syndrome,[8-11] and cardiovascular mortality.[12,13] In addition, mechanistic data suggest the presence of a link between psoriasis and diabetes mellitus (DM) underscored by T helper 1 (Th1) cytokines, which can promote insulin resistance, disordered metabolism (ie, metabolic syndrome), and inflammatory cytokines known to drive psoriasis.[14-16] An increased risk of DM has been reported both with psoriasis treatments

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such as methotrexate and cyclosporine,[17,18] and antihypertensive medications such as thiazide diuretics and beta-blockers,[19-21] which are widely used by patients with psoriasis, although their metabolic effects are weak. Further, several comorbidities such as Cushing disease and chronic pancreatitis are also known to promote DM.

Consequently, several studies have investigated the risk of incident DM in patients with psoriasis.[22-26] Two studies evaluated the effect of systemic treatment on DM.[27,28] However, the effect of comorbidities, concomitant medications, and disease severity along with time-to-event analysis and dose-related responses have not been considered in the estimation of treatment effects. Thus, the relationship between psoriasis and DM remains controversial.

CAPSULE SUMMARY

- Psoriasis is associated with an increased prevalence and incidence of diabetes mellitus.
- The risks of type 2 diabetes mellitus were modulated by the severity of psoriasis, comorbidities, and concomitant medication: thiazide and methotrexate.
- Patients with psoriasis and their physicians should be aware of the potential link with type 2 diabetes mellitus and concomitant medication.

We therefore aimed to examine the incidence of type 2 DM (T2DM) in patients with psoriasis and make comparisons with randomly selected subjects without a history of psoriasis. We also evaluated associations among the severity of psoriasis, concomitant medication, or comorbidities and the risk of T2DM.

METHODS

Data

The study protocol was approved by the institutional review board of Taipei City Hospital. A nationwide cohort study was conducted using data from the Longitudinal Health Insurance Database 2005, a subset of Taiwan's National Health Insurance Research Database (NHIRD), containing complete original claims data from 1 million randomly sampled individuals.[29] The National Health Insurance program was launched in 1995 to finance health care for all residents, and currently services more than 23 million people, representing approximately 99% of Taiwan's population. The NHIRD includes complete data on demographics, outpatient visits, hospitalizations, diagnostic codes, and prescriptions, as described in detail previously.[30] *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes were used to define diseases.

Study cohorts

We identified adult patients ($\geq$ 18 years) with a first-time diagnosis of psoriasis (*ICD-9* codes 696.0, 696.1) plus 2 or more diagnoses of psoriasis validated by a dermatologist or rheumatologist between January 1, 1999, and December 31, 2008. The initial diagnosis date was defined as the index date of entry into the psoriasis cohort. For the comparison cohort, patients without a history of psoriasis were randomly selected from the database and their visit date was assigned randomly as the index date. To ensure full access to their baseline characteristics, patients were required to be continuously enrolled in the NHIRD for 24 months before the index date (Fig 1).

Outcomes of interest

The study outcome was new-onset T2DM (*ICD-9* code 250, except 250.x1 and 250.x3). T2DM diagnoses were validated by confirming the prescription of compatible treatments in patient records. In each case, the initial diagnosis followed the index date. Patients with existing T2DM were excluded. Patients were followed up from the index date until the earliest date of the development of an outcome of interest, the date of death, or December 31, 2008.

Drug exposure

Of interest were exposures to drugs commonly used for the systemic treatment of psoriasis and antihypertensives. These included methotrexate, cyclosporine, thiazide diuretics, and beta-blockers. The pharmacy prescription database provided information on prescribed drug types (according to the Anatomic Therapeutic Chemical Classification System), dosage, prescription date, supply, and dispensation. Associations between the outcome of interest and changes in accumulated dosage were analyzed. Data were presented as the number of defined daily doses (DDDs), defined by an expert panel as the typical maintenance dose required when the drug is used for its main indication in an adult.[31] Cumulative drug exposure was calculated as the cumulative DDDs within a prespecified exposure time (induction period) preceding each new-onset T2DM and the cumulative DDDs from the first day of drug intake to new-onset T2DM. Cumulative DDDs was used as a time-varying continuous variable.[32] Biologics, which were not approved for psoriasis in Taiwan until late 2009, were not analyzed.